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Phases and phase transitions of the phosphatidylcholines

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Abstract

LIPIDAT (http://www.lipidat.chemistry.ohio-state.edu) is an Internet accessible, computerized relational database providing access to the wealth of information scattered throughout the literature concerning synthetic and biologically derived polar lipid polymorphic and mesomorphic phase behavior and molecular structures. Here, a review of the data subset referring to phosphatidylcholines is presented together with an analysis of these data. This subset represents ca. 60% of all LIPIDAT records. It includes data collected over a 43-year period and consists of 12,208 records obtained from 1573 articles in 106 different journals. An analysis of the data in the subset identifies trends in phosphatidylcholine phase behavior reflecting changes in lipid chain length, unsaturation (number, isomeric type and position of double bonds), asymmetry and branching, type of chain–glycerol linkage (ester, ether, amide), position of chain attachment to the glycerol backbone (1,2- vs. 1,3-) and head group modification. Also included is a summary of the data concerning the effect of pressure, pH, stereochemical purity, and different additives such as salts, saccharides, amino acids and alcohols, on phosphatidylcholine phase behavior. Information on the phase behavior of biologically derived phosphatidylcholines is also presented. This review includes 651 references.

Keywords: Membrane; Mesomorphism; Lipid bilayer; LIPIDAT database; Phospholipid; Polymorphism

Contents

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1. Introduction

Phosphatidylcholines (PC) represent the most abundant lipid class in mammalian membranes and a major membrane component in eukaryotic organisms. Phosphatidylcholines are also critical constituents of human lung surfactant, serum lipoproteins, and bile and represent the most widely used lipid in model membrane studies. The phase behavior of phosphatidylcholine/water systems is of interest in several disciplines because of the possible biological relevance of the different phases they form and the transitions they undergo. As a result, a sizable body of information concerning phosphatidylcholine phase behavior exists in the literature. Unfortunately, however, only episodic, less-than-comprehensive compendia have been published in this area. This same situation prevails for the other lipid classes. In response to the obvious and immediate need for a centralized compendium of such data, LIPIDAT, a lipid thermodynamic database, was established [1]. Its purpose is to collect, in one central location, all information on lipid mesomorphic and polymorphic transitions and miscibility. The database is considered comprehensive for glycerophospholipids, sphingolipids, glycoglycerolipids and biological membrane lipid extracts. A complete description of LIPIDAT has been presented previously [2,3]. Early versions of LIPIDAT were released in 1993 and 1994 [1,4,5]. Most recently, it has been established as a relational database for on-line access over the World Wide Web (http://www.lipidat.chemistry.ohio-state.edu).

Here we present an analysis of the phosphatidylcholine data subset in LIPIDAT that serves to highlight and to summarize what is known about phosphatidylcholine phase behavior and to identify deficits in our knowledge of this important lipid class. In preceding reviews, the phase behavior of the 1,2-dimyristoyl-*sn-glycero*-3-phosphocholine [6], the phosphatidylethanolamines [7], the glycoglycerolipids [8],

and the sphingolipids [9] was examined. The database has also proven useful in the evaluation of generalities concerning lipid phase behavior [10].

2. Bibliographic data

Version 2.0 of LIPIDAT consists of 15,400 records, each record of which contains 28 information fields [4]. The phosphatidylcholine subset represents 56% of the records in LIPIDAT 2.0. It includes data collected over a period extending from 1953 to 1993. Since LIPIDAT (Version 2.0) is current only through January 1993, for purposes of this article every effort has been made to also include in the discussion all relevant phosphatidylcholine literature references that have appeared since that date. The phosphatidylcholine subset in this updated version of LIPIDAT (Version 2.1), hereafter referred to simply as LIPIDAT, consists of 12,208 records obtained from 1573 scientific articles published in 106 different journals. Version 2.1 is in the process of being upgraded to Version 3.0 making the entire database contents current through January 1998. We expect to release this update in late 1998.

The annual frequency distribution for phosphatidylcholine records in LIPIDAT over the last 17 years is presented in Fig. 1. In this time period, the growth in annual output of phosphatidylcholine records is slower than that for the phosphatidylethanolamines [7]. By comparison with the phosphatidylethanolamines, lipids in the phosphatidylcholine class have a relatively simple mesophase behavior which is dominated by the lamellar phases (Fig. 2). It is not surprising then to find growth in the number of phosphatidylcholine records to have slowed after an initial bout of intensive research activity in the seventies [3,6]. A perusal of the data in LIPIDAT suggests that an increasing volume of work is being conducted on phosphatidylcholines in combination with other lipids and non-lipid additives with comparatively less emphasis of late on using phosphatidylcholines in isolation. Indeed, over the past decade, pure phosphatidylcholines represent less than half of the annual records in LIPIDAT (Fig. 1). Noteworthy, a shift in focus away from lipids in isolation to more complex, mixed lipid systems characterizes all lipid classes in LIPIDAT [3].

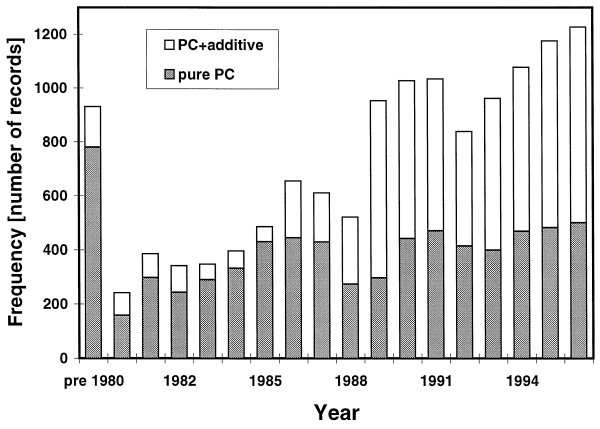

Fig. 1. Annual frequency of the phosphatidylcholine records in LIPIDAT in the period 1980–1996. Also included in the figure is frequency data for the pre-1980 period. Pure PC refers to records where phosphatidylcholine was used in isolation. PC + additive refers to measurements made on phosphatidylcholine in combination with another lipid and/or a non-lipid additive.

Over one hundred different journal titles are represented in the phosphatidylcholine subset of which eight account for more than 80% of the record entries (Fig. 3). More than 70% of the records derive collectively from *Biochimica et Biophysica Acta* (*BBA*, 27%), *Biochemistry* (23%), *Biophysical Journal* (*Biophys. J.*, 12%) and *Chemistry and Physics of Lipids* (*Chem. Phys. Lipids*, 9%).

3. Thermodynamic data

The thermodynamic properties of hydrated lipids depend on molecular structure (Fig. 4) and on the composition of the lipid dispersion. In what follows, we present a review of the thermodynamic data contained in LIPIDAT that addresses both of these influences for phosphatidylcholine containing systems. Under the rubric of molecular structure, we examine phosphatidylcholine phase behavior as affected by hydrocarbon chain length, unsaturation, asymmetry and branching, as well as the type of chain–glycerol linkage and the position of chain attachment to the glycerol backbone [31–385] (Fig. 4). Consideration is also given to head group modification [407–414,642]

[643–649], to stereochemical purity [470–487] [488,489] and to the morphology of the lipid aggregates (unilamellar and multilamellar vesicles). The manner in which the composition of the aqueous dispersing medium impacts on phosphatidylcholine phase behavior is considered from the point of view of pH, salts and small organic molecule additive effects. The effect of pressure on the phosphatidylcholine phase behavior is also reviewed.

4. Lipid molecular structure effects

4.1. Saturated diacyl phosphatidylcholines

The category of phosphatidylcholines containing two identical, saturated, linear fatty acyl chains consists of 5731 records. Record frequency within this group as a function of chain length is shown in Fig. 5. As has been found for all lipid classes in LIPI-

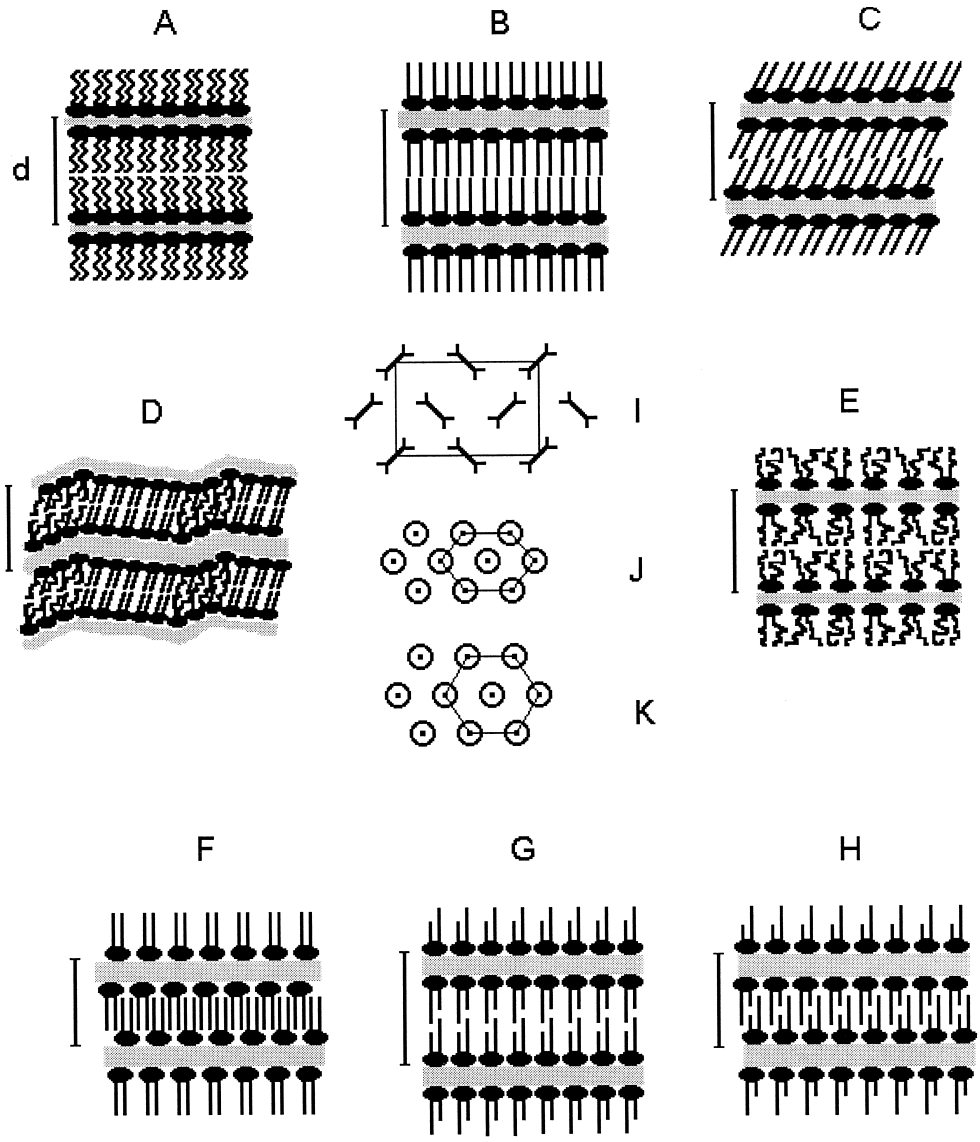

Fig. 2. Schematic of the various lamellar phases found in PC/water systems: (A) subgel, L_c; (B) gel (untilted chains), L_β; (C) gel (tilted chains), $L_{\beta'}$; (D) rippled gel, $P_{\beta'}$; (E) liquid crystalline, L_α; (F) fully interdigitated gel, L_β^{int}; (G) partially interdigitated gel; (H) mixed interdigitated gel. Cross-sectional view of the hydrocarbon chain arrangement in various chain packing modes (view is down the long axis of the chains): (I) orthorhombic; (J) quasi-hexagonal; (K) hexagonal.

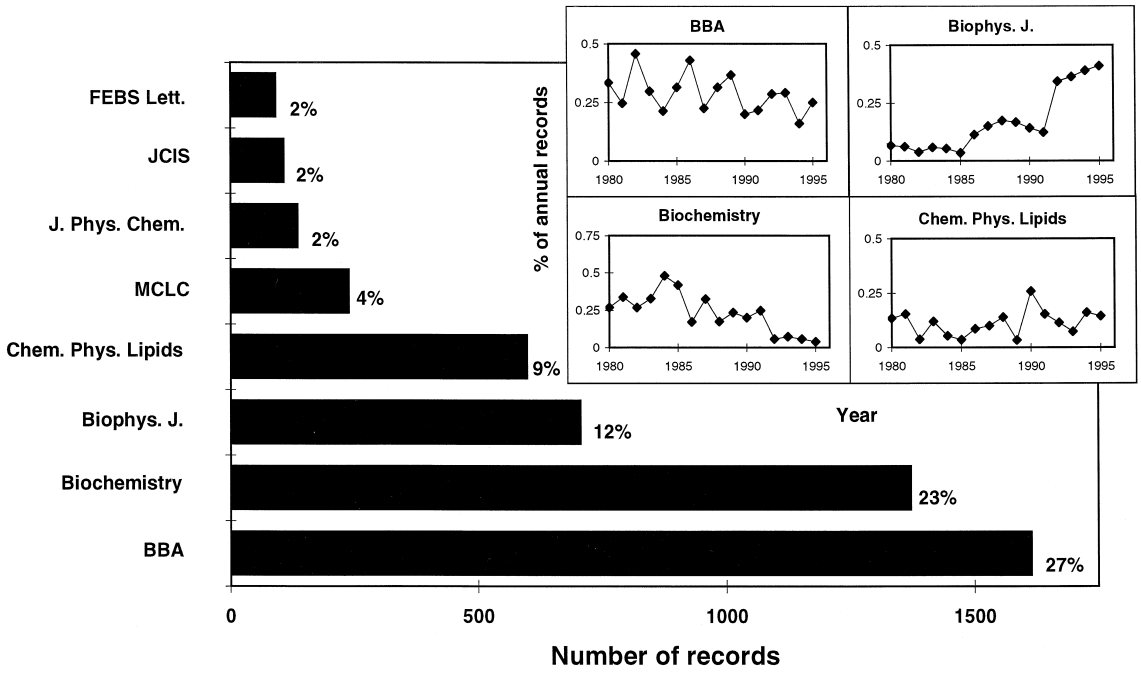

Fig. 3. Relative record contribution of the top eight journals to the phosphatidylcholine database subset (Biochim. Biophys. Acta, Biochimica et Biophysica Acta; MCLC, Molecular Crystals and Liquid Crystals; JCIS, Journal of Colloid and Interface Science). The annual record contributions from the top four journals are shown in the inset.

DAT, the even-chained species (lipids with an even number of carbon atoms per fatty acyl chain) predominate [7–9]. This perhaps reflects their frequency of occurrence in natural systems and, at a deeper level, fatty acid anabolism and catabolism involving two carbon units in the form of acetyl CoA [11]. Lipids bearing fatty acids with an odd number of carbon atoms occur in small amounts in terrestrial organisms. They are more common in marine organisms [11]. The bulk of the data in the saturated diacyl PC group is made up of even-chained species in the range of 12 to 22 carbon atoms. These, and especially 16:0/16:0 PC (lipid nomenclature is described in Appendix A), are the most extensively examined lipids in model membrane studies. In fact, close to 20% of all records in LIPIDAT deal with the phase behavior of 16:0/16:0 PC alone!

The transition temperature (T) and enthalpy change (ΔH) values for all lipids in this saturated diacyl phosphatidylcholines subset are shown in Table 1 complete with literature references. The table reports averages and standard deviations as appropriate. Included in the average are those values recorded at pH $\geq$ 3 and at salt concentrations $\leq$ 0.1 M since no significant effect of proton or salt concentration is observed in these ranges (see below). The averages also include measurements made in the heating and cooling directions, provided the transition temperature difference does not exceed 2°C. Exceptions to the rules of averaging just described do occur and these are identified in the text and tables as appropriate. Where irreversible or slowly reversible transitions were encountered, they are so indicated by a one sided arrow ($\rightarrow$). The lamellar subgel (L_c)-to-lamellar gel (L_β) transition is of this type and is represented as $L_c \rightarrow L_\beta$.

The saturated diacyl phosphatidylcholines having fatty acyl chains 15–22 carbon atoms long are characterized by a relatively rich polymorphism. For example, they undergo three phase transitions with increasing temperature in the 10 to 80°C range. Following low-temperature equilibration, they form the lamellar crystalline (subgel, L_c) phase with hydrocarbon chains tilted with respect to the bilayer normal [221] and the long axis of the head group oriented parallel to the bilayer plane [548,549]. The L_c phase

transforms to a lamellar gel phase ($L_{\beta'}$) with reduced chain tilt and increased hydration [221] upon heating. This low-temperature $L_c \rightarrow L_{\beta'}$, transition is referred to as a subtransition. At higher temperatures, an interconversion between two different gel phases takes place during the so-called pretransition—specifically, the $L_{\beta'}$ phase transforms to the rippled gel ($P_{\beta'}$) phase. Upon further heating, the $P_{\beta'}$ phase undergoes a highly cooperative transition to a lamellar liquid crystalline (L_α) phase (the so-called main or chain order/disorder transition). Using highly purified preparations of 16:0/16:0 PC and high-sensitivity DSC, the main transition was shown to have a half-width ($\Delta T_{1/2}$) of 0.067°C and a cooperative unit size of >1000 lipid molecules [550]. The subtransition is not rapidly reversible in that formation of the L_c phase requires low-temperature equilibration. The mechanism of L_c phase formation and its conversion to the $L_{\beta'}$ phase upon heating has been studied extensively [20,21,180,311,312,431,475,509,519] [522,556]. Two processes occur upon formation of the L_c phase from the $L_{\beta'}$ phase: dehydration of the

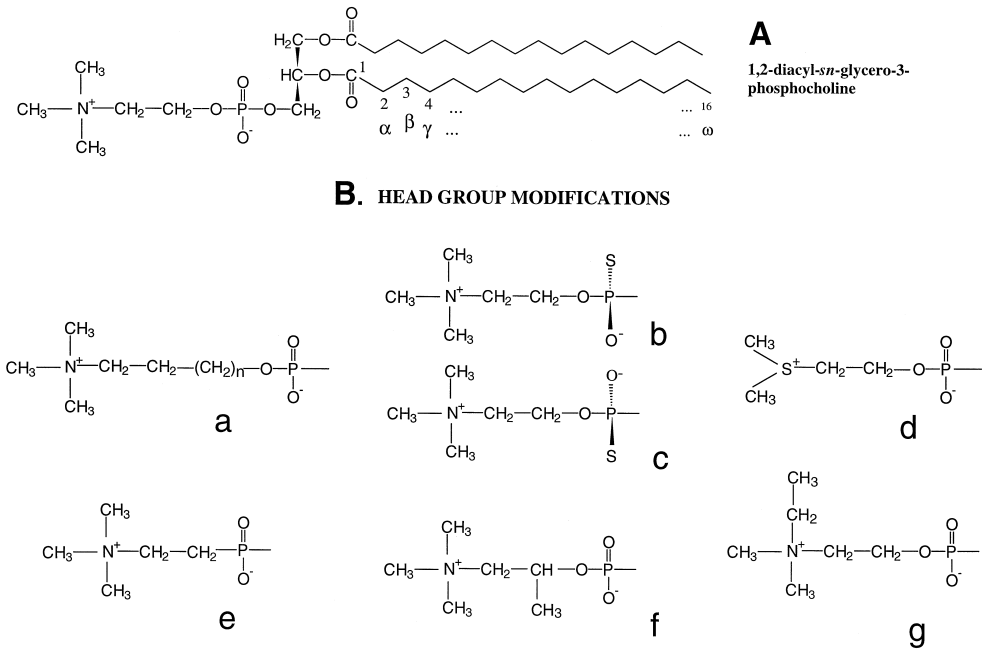

Fig. 4. Molecular structure of phosphatidylcholine and its modifications referred to in this paper. (A) Structural formula of 1,2-diacyl-*sn*-*glycero*-3-phosphocholine (L-(β,γ-diacyl-α-glycerophosphocholine)). The structure shown includes two identical, unbranched saturated hydrocarbon chains esterified at the C1 and C2 positions of the glycerol backbone with the head group covalently attached through a phosphodiester linkage at the C3 position of glycerol. It represents the default structure in the LIPIDAT nomenclature scheme and is denoted *n*:0/*n*:0 PC as described in Appendix A. Alternative schemes for labeling carbon atoms in the fatty acyl chain are shown. (B) Head group modifications: (a) additional methylene groups between the phosphate bridging oxygen and the quaternary ammonium nitrogen; (b) Rp-thiophosphocholine; (c) Sp-thiophosphocholine; (d) phosphosulfocholine; (e) phosphonocholine; (f) methyl group α to the phosphorus in the choline moiety; (g) ethyl group in place of one of the three choline methyl groups. (C) Chain-to-backbone linkage modifications (ω or methyl terminus is to the right hand side of the chain as drawn): (a) 1,2-dialkyl; (b) 1-acyl, 2-alkyl; (c) 2,3-diacyl; (d) 1,3-diacyl; (e) direct C–C linkage in place of the default ester linkage between the backbone and the hydrocarbon chains; (f) 1,2-diacylamido-1,2-deoxy; (g) 1,2-dialkyl-methylidene; (h) C1-methylated glycerol backbone; (j) C2-methylated glycerol backbone; (k) C3-methylated glycerol backbone; (m) 2,3-diacyl-cyclopentano, Inset: configurations of the six diastereoisomers of the dipalmitoyl cyclopentanophosphatidylcholine (R = 16:0 acyl chain): (1) 2-*cis*-16:0/3-*cis*-16:0-CPENT 1-*cis*-PC; (2) 2-*cis*-16:0/3-*trans*-16:0-CPENT 1-*cis*-PC; (3) 1-*cis*-16:0/2-*cis*-16:0-CPENT 3-*trans*-PC; (4) 2-*trans*-16:0/3-*cis*-16:0-CPENT 1-*cis*-PC; (5) 1-*cis*-16:0/3-*cis*-16:0-CPENT 2-*cis*-PC; (6) 1-*cis*-16:0/3-*cis*-16:0-CPENT 2-*trans*-PC; (D) Chain modifications: (a) chain asymmetry; (b) single *trans*-double bond; (c) single *cis*-double bond; (d) multiple double bonds; (e) triple bond; (f) methyl-isobranched; (g) ω-tertiary butyl (dimethyl-isobranched); (h) methyl-anteisobranched; (j) with methyl branching along the chain; (k) ethyl-anteisobranched; (m) short linear branching; (n) long linear branching; (p) branched branch; (q) ω-cyclohexyl-; (r) cyclohexyl-methyl-; (s) cyclopropyl-; (t) benzyl-; (u) thio-.

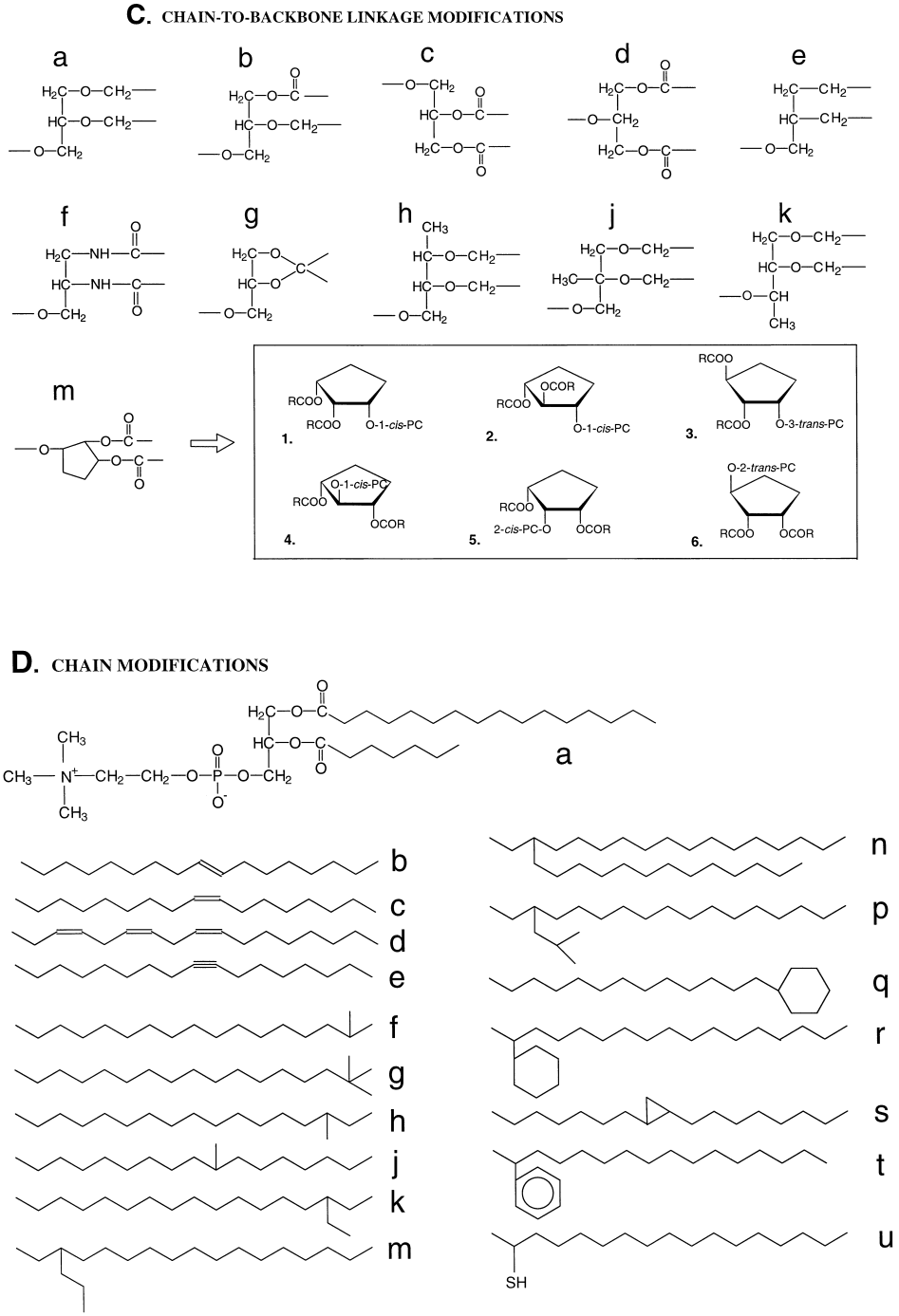

Fig. 4 (continued).

polar head group and rearrangement of the acyl chains from a quasi-hexagonal to a more ordered packing mode (with presumably orthorhombic hybrid subcell) [418,431,508]. Recently, it was shown for 16:0/16:0 PC and 18:0/18:0 PC that these two processes take place in discrete steps upon cooling [491]. The $L_{\beta'}$ phase first converts to the so-called sub-subgel (SGII) phase with well-ordered acyl chains but with the

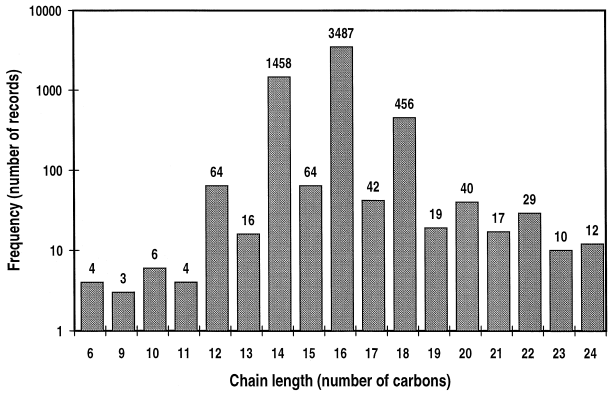

Fig. 5. Chain length-dependence of record frequency in the saturated diacyl phosphatidylcholine database subset of LIPIDAT. Note, this is a semilog plot.

same lamellar repeat period as the $L_{\beta'}$ phase. This conversion is rapidly reversible and presumably proceeds without significant change in hydration state. The SGII–$L_{\beta'}$ transition is referred to as the sub-subtransition [138]. The formation of the stable L_c phase, presumably involving the dehydration step, takes place from within the SGII phase upon equilibration. Thus, the formation of the SGII phase appears to be an intermediate step in the process of L_c phase formation which proceeds as follows: $L_{\beta'} \rightarrow$ SGII $\rightarrow$ L_c. Depending on sample history, the SGII $\rightarrow L_c$ transformation may include one or more metastable intermediates. Thus, the phase sequence SGII $\rightarrow$ $L^1_{c(mst)} \rightarrow L^2_{c(mst)} \rightarrow \ldots \rightarrow L_c$ gives rise to multiple subtransition endotherms in the corresponding calorimetric measurements [154,180,525]. The time required to convert fully from the metastable SGII to the stable L_c phase during low temperature incubation is chain length-dependent. Thus, for example, conversion times can vary from 30 min in the case of 10:0/10:0 PC [31] to more than 10 days for 16:0/16:0 PC [180] and ≥ 1.5 years in the case of the 21:0/21:0 PC and 22:0/22:0 PC [31].

Decreasing the chain length to < 15 carbon atoms progressively suppresses lamellar crystal polymorphism and simplifies the phase behavior considerably. Thus, for example, in the case of 14:0/14:0 PC, the L_c phase, once formed, converts directly into the $P_{\beta'}$ phase upon heating. The $L_c \rightarrow P_{\beta'}$ transition is not reversible. Rather, what happens upon cooling is that the $P_{\beta'}$ phase converts to the $L_{\beta'}$ phase. Subsequent heating–cooling cycles beginning in the $L_{\beta'}$ phase show a reversible $L_{\beta'}$–$P_{\beta'}$–L_α sequence. Further, the $L_{\beta'}$ phase is metastable over the entire temperature range in which it exists and converts to the stable dehydrated subgel phase L_c after equilibration at low-temperature. For the saturated diacyl phosphatidylcholines having fatty acyl chains 10–13 carbon atoms long, the $P_{\beta'}$ phase is absent in the heating sequence, following low-temperature equilibration. Thus, these short chained phosphatidylcholines undergo a direct $L_c \rightarrow L_\alpha$ transition upon heating. In the cooling direction, $P_{\beta'}$ and $L_{\beta'}$ phases form subsequently in 13:0/13:0 PC. Subsequent heating–cooling cycles beginning in the $L_{\beta'}$ phase show a reversible $L_{\beta'}$–$P_{\beta'}$–L_α sequence. For 12:0/12:0 PC, the $P_{\beta'}$–L_α transition has been shown recently to proceed via an intermediate lamellar liquid crystalline phase (L_x) which is described as being more ordered than the L_α phase [56,551]. The possible biological relevance of the L_x phase has been discussed [551]. For phosphatidylcholines with fatty acyl chains 23 and 24 carbon atoms long, formation of a subgel phase has not been reported. Although not observed experimentally, it is believed that long enough low-temperature storage (on the order of years) may induce the formation of an L_c phase in these long chain lipids [31]. For 24:0/24:0 PC, a complicated gel phase polymorphism different from that of the shorter-chain phosphatidylcholines has been reported recently [609,637]. Except for a gel phase with tilted hydrocarbon chains, an additional gel phase with almost perpendicular chains and orthorhombic chain arrangement forms at lower temperatures (< 40°C). At higher temperatures (> 45°C), another gel phase with hexagonally packed hydrocarbon chains, perpendicular to the bilayer plane, was detected. Gel phase coexistence is observed in extended temperature ranges. This phenomenon is ascribed to slow equilibration of the system [609].

The transition temperature data for the saturated diacyl phosphatidylcholines as a function of chain length are shown in Fig. 6A. With increasing chain length, both the pre- and main transition temperatures increase. These two transitions come together with the elimination of the $P_{\beta'}$ phase for phosphatidylcholine species with chain lengths > 22. The subtransition temperature also increases with increasing chain length, but at a lower rate than the pre- and main transitions. The subtransition T (chain length)

Table 1
Thermodynamic parameters of the phase transitions in fully hydrated saturated diacyl phosphatidylcholines

Lipid chains	$L_c \rightarrow L_\beta$		SGII–L_β		$L_c \rightarrow P_\beta$		$L_c \rightarrow L_\alpha$		L_β–P_β		P_β–L_α		References[e]
	T [°C]	ΔH [kcal/mol]	T [°C]	ΔH [kcal/mol]	T [°C]	ΔH [kcal/mol]	T [°C]	ΔH [kcal/mol]	T [°C]	ΔH [kcal/mol]	T [°C]	ΔH [kcal/mol]	
9:0/9:0											−55.2[a,b]		[33,625]
10:0/10:0							−5.7	18.3					[31]
11:0/11:0							−0.8	9.5			−13.9[b]		[31,364,625]
12:0/12:0							6.6 ± 0.6	13.4			−1.9 ± 1.4[c]	2.1 ± 1.1	[31,32,50–64,67,68,71,72,551]
											3.5 ± 1.2[d]	2.0 ± 2.4	
13:0/13:0					11.7 ± 1.4	2.8	14.4	12.3	0.1 ± 1.3	0.5	13.5 ± 0.8	3.9 ± 0.5	[31,33,45,51,56,60,71,76,77]
14:0/14:0			5.6	0.05	11.4 ± 4.9	3.8 ± 1.3			13.7 ± 2.2	1.2 ± 1.1	23.6 ± 1.5	6.0 ± 2.4	[31,33,45,47,50,51,55,56,60,65,71,77,81,84,85,96,97,101, 121,125,175,195,198,204,212,229,236,253,267,280,324, 328,333,378,388,410,418,429,491–510]
15:0/15:0	20.2 ± 3.0	6.3							22.0 ± 2.5	0.8 ± 0.4	33.7 ± 0.8	7.6 ± 0.7	[31,33,45,51,60,61,71,94–102]
16:0/16:0	18.8 ± 3.1	3.4 ± 1.1	7.1 ± 0.6	0.3 ± 0.05					34.4 ± 2.5	1.3 ± 1.0	41.3 ± 1.8	8.2 ± 1.4	[31,42,50,51,55,59,60,71,77,82,91,96,97,121,150,154, 161,162,175,181,204,234,251,324,346,373,410,431,436, 443,453,475,471,491,502,506,509,511–526]
17:0/17:0	21.6 ± 3.8	2.9 ± 1.6							42.7 ± 1.1	1.1 ± 0.1	48.6 ± 0.6[f]	9.8 ± 1.1	[31,33,45,51,57,60,71,73,78,96,97,101,103, 155,161–164,620]
18:0/18:0	26.3 ± 5.2	2.8 ± 2.0	14.8	0.8					49.1 ± 2.9	1.4 ± 0.4	54.5 ± 1.5[f]	10.4 ± 1.6	[31,50,51,55,60,61,71,77,81,85,96,97,161, 162,175,179,181,183,195,199,201,267–269,491,620]
19:0/19:0	30.0 ± 4.3	4.1 ± 4.0							57.2 ± 1.1	1.3	60.2 ± 1.1[f]	10.4 ± 1.23	[31] [45,51,60,70,71,97,101,620]
20:0/20:0	36.9 ± 1.3	2.5 ± 3.4							63.2 ± 0.8	1.5 ± 0.5	65.3 ± 1.5[f]	13.3 ± 2.5	[31,32,40,45,50,51,71,77,101,151,175,195,212, 231,313,342,343,620]
21:0/21:0	28.0	2.9							69.4 ± 0.9	1.4	70.7 ± 1.6	13.0 ± 1.1	[31,51,101]
22:0/22:0	32.1	4.3									73.6 ± 2.1[g]	15.8 ± 2.8	[31,32,45,50,51,77,212,216,262,263,267,269]
23:0/23:0									28.8 ± 1.2	1.5 ± 0.1	77.9 ± 1.6	18.0	[347]
24:0/24:0											80.3 ± 0.3[h]	15.4 ± 1.6	[50,77,609,610]

[a] Estimated transition temperature.
[b] Exact transition type not reported. Referred to as 'gel–liquid crystalline' transition.
[c] Transition from lamellar gel, P_β, phase to an intermediate lamellar phase, L_x [56,551].
[d] Transition from an intermediate lamellar phase, L_x, to lamellar liquid crystalline phase, L_α [56,551].
[e] For 14:0/14:0 PC and 16:0/16:0 PC, only a representative selection of references are included, since the total numbers of references are in the hundreds.
[f] A 'sub-main' transition takes place at 0.5–1°C below the main transition [620].
[g] The single heating endotherm registered is supposed to incorporate both L_β–P_β and P_β–L_α transitions [31].
[h] Additional lamellar gel–gel transitions at −40°C and −65°C [609].

function crosses the pre- and main transition lines at chain lengths of 14 and 12 carbons, respectively. Thus, in the case of 14:0/14:0 PC, a direct L_c–$P_{\beta'}$ transition is observed, while for 12:0/12:0 PC the $P_{\beta'}$–L_α transition proceeds in an unusual way, with the L_x phase as an intermediate [56,551].

Shown in Fig. 7 is a plot of the main transition temperatures of the saturated diacyl phosphatidylcholines vs. the reciprocal of chain length [96,636]. The chain length dependence of transition temperature is linear (regression coefficient $R^2 = 0.999$) and extrapolates to 430 K (157°C) at $n \rightarrow \infty$, a temperature close to the melting temperature of polyethylene.

The dependence of the enthalpy change for the sub-, pre-, and main transitions on saturated diacyl phosphatidylcholine chain length is shown in Fig. 6B. The main transition enthalpy depends on the chain length in a nearly linear way for chain lengths between 13 and 21 carbons indicating that the bulk of the heat of the transition derives from a chain order-to-disorder change in this chain length range. The slope of the ΔH (chain length) function in this chain length range is 0.56 kcal/mol per $-CH_2-$ group. The subtransition enthalpy change as a function of chain length has a negative slope, i.e., the enthalpy difference of the gel and subgel phases decreases with chain length, prompting the proposal that saturated diacyl phosphatidylcholines with long enough acyl chains are unlikely to form stable subgel phases [51]. This is indeed true for phosphatidylcholines with chain lengths $\geq$ 23 carbon atoms long (Table 1).

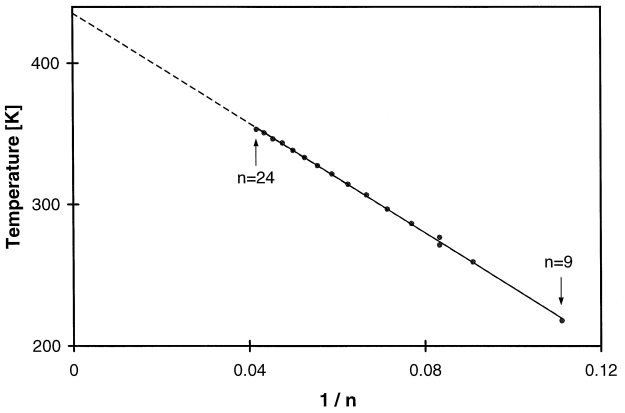

Fig. 7. Dependence of the main transition temperature (in degrees Kelvin) of the fully hydrated, saturated diacyl phosphatidylcholines on the reciprocal of hydrocarbon chain length (in number of carbon atoms, n).

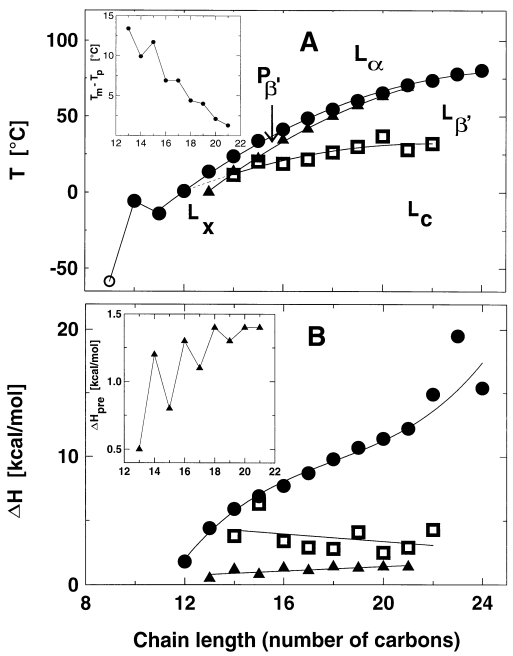

Fig. 6. Dependence of the transition temperature (A) and enthalpy change (B) on the fatty acyl chain length (in units of number of carbon atoms) of the fully hydrated, saturated diacyl phosphatidylcholines: (□) subtransition; (▲) pretransition; (●) main transition (measured values); (○) main transition (calculated value). Insets: (A) difference between the temperature of the main transition and the pretransition; (B) expanded view of the pretransition enthalpy change data.

A large variation is observed in the values of the temperature and enthalpy of the subtransition (Table 1, Fig. 6). This is attributed to the high thermal history dependent behavior of these parameters. For example, the temperatures reported for the 16:0/16:0 PC subtransition vary from 7.0°C [175] to 28.0°C [552], while the corresponding enthalpy values range from 1.9 kcal/mol [553] to 7.0 kcal/mol [82]. Indeed, subtransition enthalpy values in excess of those of the main transition have been measured (R. Koynova, unpublished observation).

An odd–even alternation in the chain length dependencies exists for both the temperature and the enthalpy (Fig. 6B, inset) of the pretransition. The alternation is clearly evident when the difference, $T_m - T_{pre}$, is plotted vs. acyl chain length (Fig. 6A, inset). A similar alternation in the phase behavior and

in the thermodynamic transition parameters is observed in homologous series of paraffinic compounds. The saturated diacyl-α-glyceromonoglucosides represent one such example [8]. Odd–even alternation is generally associated with differences in the way the chains arrange themselves in a crystalline lattice [12]. In the case of the pretransition of saturated diacyl phosphatidylcholines, it has been attributed to differences in chain tilt with respect to the bilayer normal [60].

Early studies of the $P_{\beta'}$–L_{α} transition in 16:0/16:0 PC suggested that it was a rapidly and perfectly reversible two-state transition. This was based on calorimetry measurements which showed the chain melting transition to be extremely sharp and with minor temperature hysteresis [550]. More recent, time-resolved X-ray diffraction measurements demonstrate that cooling from the L_{α} phase does not restore the original $P_{\beta'}$ phase. Rather, a long-lived metastable $P_{\beta'}^{mst}$ phase is formed [509,628] which differs from $P_{\beta'}$ in its ripple structure [554]. The enthalpy of the $P_{\beta'}^{mst}$–L_{α} transition is ~5% lower than that of the $P_{\beta'}$–L_{α} transition [509]. These structure measurements also showed a lack of a detectable coexistence of the $P_{\beta'}$ and L_{α} phases during the $P_{\beta'}$–L_{α} transition. Rather, a disordering in bilayer stacking and a partial loss of correlation in the lamellar structure takes place in a narrow temperature range of ~0.1°C at the transition midpoint [509]. The relaxation kinetics for the $P_{\beta'} \rightarrow L_{\alpha}$ transition is slow (relaxation time 120 s for 14:0/14:0 PC and 260 s for 16:0/16:0 PC) as recently demonstrated [632] and probably reflects a slow rearrangement of bilayer stacking from the rippled gel to the lamellar liquid crystalline phase.

The data reviewed above all refer to multilamellar vesicles (MLV). For unilamellar vesicles of 16:0/16:0 PC, the phase transition parameters depend on vesicle size. Vesicles with diameters below ~35 nm undergo a chain melting transition at 37–37.5°C. For larger sized vesicles (35–70 nm), the transition temperature increases from 37°C to 41°C as vesicle size increases. Larger vesicles (diameters > 70 nm) undergo the transition at ′41°C, essentially independent of size [605,606]. Also, the chain melting transition of small unilamellar vesicles (SUV) with diameters below 30–50 nm is considerably broader than that observed for MLV (cf. $\Delta T_{1/2}$ = 3.5°C for SUV vs. ~0.1°C for MLV). Further, the enthalpy change of the transition in SUVs is smaller than that in MLVs (Table 2). The difference is attributed to a sensitivity of the enthalpy level of the gel phase lipid to vesicle size [605]. In a recent study, the high curvature of the SUV surface has been regarded to act in a similar way to an external field that drives the transition from first order (as it is in MLVs) to critical and then to supercritical [613].

For saturated diacyl phosphatidylcholines having fatty acyl chains 14 and 16 carbon atoms long, the phase behavior of the D-enantiomers, 2–14:0/3–14:0 PC and 2–16:0/3–16:0 PC, is identical to that of the L-enantiomers, 1–14:0/2–14:0 PC and 1–16:0/2–

Table 2
Thermodynamic parameters of the phase transitions undergone by saturated diacyl phosphatidylcholines in different liposome preparations

Lipid chains	Liposome preparation[b]	Pretransition		Main transition		References[a]
		T [°C]	ΔH [kcal/mol]	T [°C]	ΔH [kcal/mol]	
14:0/14:0	MLV	13.7 ± 2.2	1.2 ± 1.1	23.6 ± 1.5	6.0 ± 2.4	Table 1
	SUV			22.2 ± 2.0	4.1 ± 0.9	[183,215,504,528–531]
16:0/16:0	MLV	34.4 ± 2.5	1.3 ± 1.0	41.3 ± 1.8	8.2 ± 1.4	Table 1
	LUV	33.8	0.60 ± 0.12	41.4 ± 0.1	7.5 ± 0.5	[605]
	SUV	28.0	0.13 ± 0.03	37.8 ± 1.0	5.9 ± 1.3	[183,196,245,409,532–537,605]
18:0/18:0	MLV	49.1 ± 2.9	1.4 ± 0.4	54.5 ± 1.5	10.4 ± 1.6	Table 1
	SUV			51.8 ± 1.1	9.0	[183,196,215]

[a] Because of the large number of references available for 14:0/14:0 PC and 16:0/16:0 PC, a limited few are included here.
[b] SUV, small unilamellar vesicles (diameter < 100 nm); LUV, large unilamellar vesicles (diameter 100 nm) [607,608]; MLV, multilamellar vesicles.

Table 3
Thermodynamic parameters of the phase transitions in different positional isomers and racemic mixtures of saturated diacyl phosphatidylcholines

Lipid chains and backbone	Gel–gel		Gel–liquid crystal		References
	T [°C]	ΔH [kcal/mol]	T [°C]	ΔH [kcal/mol]	
1–14:0/2–14:0[a]	13.7 ± 2.2	1.2 ± 1.1	23.6 ± 1.5	6.0 ± 2.4	Table 1
1–16:0/2–16:0[a]	34.4 ± 2.5	1.3 ± 1.0	41.3 ± 1.8	8.2 ± 1.4	Table 1
2–14:0/3–14:0	15.0[d]	1.0	23.9	5.6	[333]
2–16:0/3–16:0	35.8[d]		41.2 ± 0.5		[110,143,338]
rac-14:0/14:0[b]	13.2[d]	0.3	23.9	5.7	[333]
rac-16:0/16:0[c]	32.1 ± 1.3[d]	1.2 ± 0.7	41.6 ± 0.8	10.5 ± 2.6	[338,471,474,475]
1–14:0/3–14:0	15.0[e]	4.3	19.0	6.1	[85]
1–16:0/3–16:0	24.8 ± 2.4[f]	5.6 ± 2.3	36.1 ± 3.6	8.8 ± 0.8	[85,138–144]

[a]According to the nomenclature used in LIPIDAT, the descriptions 1–14:0/2–14:0 and 1–16:0/2–16:0 are identical to 14:0/14:0 and 16:0/16:0, respectively (see Appendix A).
[b]Racemic mixture of 1–16:0/2–16:0 and 2–16:0/3–16:0 PC.
[c]Racemic mixture of 1–16:0/2–16:0 and 2–16:0/3–16:0 PC.
[d]$L_{\beta'}$–$P_{\beta'}$.
[e]L_c–P_β.
[f]L_c–L_β^{int}.

16:0 PC, respectively [1] (Table 3). The temperature and enthalpy of the main transition for the racemic mixture is the same as that for the pure enantiomers. Differences exist, however, in the gel phase polymorphism of the racemic mixtures versus the pure enantiomers. To begin with, the pretransition temperature of the racemic mixture *rac*-14:0/14:0 PC and *rac*-16:0/16:0 PC is approximately 2°C lower than for the pure L- and D-enantiomers [333,338,475]. In the case of 14:0/14:0 PC, the enthalpy of the pretransition in the racemic mixture is less than that of the pure enantiomers [333]. The formation of the subgel L_c phase and the metastable intermediate subgel SGII phase is hindered in the case of *rac*-16:0/16:0 PC [471,475].

Exchanging adducts at the C2 and C3 positions of the glycerol backbone of 14:0/14:0 PC and 16:0/16:0 PC has a profound effect on the phase properties of the corresponding lipids. To begin with, the normal $L_{\beta'}$ phase does not form as a stable phase in these 1,3-diacyl phosphatidylcholines [35,138]. In the case of 1–16:0/3–16:0 PC [2], an interdigitated lamellar gel phase forms in the temperature interval between the subgel and the lamellar liquid crystalline phases. In addition, the gel–liquid crystalline transition temperature is lower while the transition from the L_c phase is higher for the 1,3- compared to the 1,2-isomers (Table 3).

4.2. Saturated dialkyl phosphatidylcholines

This subset includes 96 records, 83 of which refer to O-16:0/O-16:0 PC. Dialkyl and alkyl–acyl phospholipids are found in plasma and subcellular organelle membranes [13,14]. The average transition temperatures and associated enthalpy changes recorded for this group of ether lipids are listed in Table 4. Unless otherwise noted, the same averaging criteria were implemented with this subgroup as was used with the diacyl phosphatidylcholines above.

As observed with the saturated diacyl phosphatidylcholines, the chain order/disorder transition

[1] The LILIDAT nomenclature used in this article and outlined in Appendix A identifies 1–14:0/2–14:0 PC and 1–16:0/2–16:0 PC as 14:0 PC and 16:0/16:0 PC, respectively.

[2] According to the nomenclature used in LIPIDAT, the descriptor 1–16:0/3–16:0 PC is identical to 16:0/3–16:0 PC (see Appendix A).

Table 4
Thermodynamic parameters of the phase transitions in fully hydrated, saturated dialkyl and alkyl–acyl phosphatidylcholines

Lipid chains and backbone	L_c–L_β^{int}		L_β^{int}–$P_{\beta'}$		$P_{\beta'}$–L_α		References
	T [°C]	ΔH [kcal/mol]	T [°C]	ΔH [kcal/mol]	T [°C]	ΔH [kcal/mol]	
Dialkyl							
O-14:0/O-14:0					27.2 ± 1.1	5.92 ± 1.5	[224,259,361,363,364]
O-16:0/O-16:0	4.9 ± 0.5	0.4	32.5 ± 2.3	1.3 ± 0.3	43.4 ± 1.3	8.8 ± 0.8	[144,148,195,229,247,259, 273,363,369,371–383,611]
O-18:0/O-18:0					56.5 ± 1.5	10.7 ± 1.9	[224,259,380]
Alkyl–acyl							
O-16:0/16:0			35.0 ± 4.2	-1	41.0 ± 1.9	9.2 ± 1.3	[365–367,611]
Acyl–alkyl							
16:0/O-16:0					44.5	8.6	[611]

temperature increases with chain length. Comparison between ether- and ester-linked phosphatidylcholines shows that the ether analogues exhibit slightly higher temperatures for the lamellar gel–lamellar liquid crystalline phase transition. The same trend was observed with ether vs. ester linked phosphatidylethanolamines [7] and glucoglycerolipids [8]. The effect was attributed to the more hydrophilic character of the ester as opposed to the ether linkage.

For lack of appropriate data, a detailed comparison of phase behavior is possible only for the dialkyl and diacyl phosphatidylcholines with hydrocarbon chains 16 carbon atoms long. In general, fully hydrated O-16:0/O-16:0 PC and 16:0/16:0 PC exhibit a similar thermotropic behavior with the subgel, gel, rippled gel, and liquid crystalline lamellar phases emerging sequentially upon heating. The most notable difference between the two lipid species is in the structure of the gel and subgel phases. In the case of O-16:0/O-16:0 PC, the hydrocarbon chains are fully interdigitated in the subgel and gel phases [374,466,555]. It is postulated that an interaction between opposing polar layers rather than between hydrocarbon chains is responsible for interdigitation. This notion is supported by the observation that interdigitation does not occur in unilamellar vesicles containing the dialkyl PC [374]. Since chain interdigitation increases the area per molecule in the plane of the bilayer, hydrogen bond formation between neighboring lipid head groups within a given monolayer is less likely. Accordingly, this packing mode is considered energetically more favorable in ether as opposed to ester lipids which contain the carboxyl oxygen, an excellent hydrogen bond acceptor. In contrast to the phosphatidylcholines, chain interdigitation is not observed in the dialkyl phosphatidylethanolamines [7].

It is worth noting that gel phase chain interdigitation in O-16:0/O-16:0 PC only occurs above a certain hydration limit, specifically, > 30 wt.% water [466,555]. At lower hydration levels, a non-interdigitated L_β phase, similar to that in 16:0/16:0 PC, is observed.

The enthalpy change associated with the chain order/disorder transition is quite similar for the dialkyl and diacyl phosphatidylcholines when lipids with the same chain length are compared (Tables 1 and 4). This supports the contention that the bulk of the enthalpy change derives from the chain 'melting' process and is less sensitive to the details of how the chains are anchored to the glycerol backbone.

4.3. Saturated acyl / alkyl phosphatidylcholines

Since changing the chain linkage type from ester to ether produces a major structural alteration in the fully hydrated lamellar gel phase of O-16:0/O-16:0 PC and 16:0/16:0 PC, it is of interest to know what happens when the lipid incorporates both ester- and ether-linked chains. Such mixed-linkage species which includes the plasmalogen–phosphatidylcholines and phosphatidylethanolamines, platelet activating factor, etc., are of great biological relevance in

signal transduction. To date, we have only two examples in LIPIDAT of a phosphatidylcholine containing both an ester- and an ether-linked chain where the chain length is the same. The lipids in question are O-16:0/16:0 PC and 16:0/O-16:0 PC [365–367,611] and the corresponding transition temperatures and enthalpies are included in Table 4. Comparing the data for 16:0/16:0 PC in Table 1 and for O-16:0/O-16:0 PC in Table 4 with those for the mixed-linkage lipids we find that the presence of a single ether linkage at the *sn*-1 position is sufficient to induce formation of the chain-interdigitated gel phase and in a hydration-dependent way, as was observed with O-16:0/O-16:0 PC.

4.4. Amide phosphatidylcholines

Changing the chain linkage type from ester to amide (Fig. 4C-f) in NH-14:0/NH-14:0 PC results in a lowering of the chain melting transition temperature from 23.6°C to 18°C and increase of ΔH value from 6.0 to 10.7 kcal/mol (Ref. [641], Table 5). An additional transition of low cooperativity is observed with this amide at 23°C ($\Delta H = 3$ kcal/mol). The latter is attributed to a 'melting' of the hydrogen bonding belt formed by the amide groups [641].

A mixed-linkage lipid with an ester bond at the *sn*-1 position and an amide bond at the *sn*-2 position, 18:0/NH-18:0 PC, displays a pretransition at 51.7°C ($\Delta H = 1.3$ kcal/mol) and gel–liquid crystalline transition at 52.8°C ($\Delta H = 3.9$ kcal/mol, Ref. [640], Table 5). Thus, replacing the ester bond at the *sn*-2 position with an amide linkage has little effect on the main transition temperature but lowers, by a factor of three, the associated enthalpy change for the C18 lipid (compare data in Table 1 for 18:0/18:0 PC).

4.5. Cyclopentanoid phosphatidylcholines

Analogues of the glycerophosphocholines with the glycerol moiety replaced by cyclopentane-1,2,3 triol (Fig. 4C-m) have been utilised to examine the effect

Table 5
Thermodynamic parameters of the lamellar gel–liquid crystalline transition in fully hydrated, saturated phosphatidylcholines with modified backbones

Lipid	T [°C]	ΔH [kcal/mol]	References
Amide (Fig. 4C-f)			
NH-14:0/NH-14:0 PC	18.0	10.7	[641]
18:0/NH-18:0 PC	52.8	3.9	[640]
Methylidene (Fig. 4C-g)			
15:0/15:0-METH PC	17.9	4.8	[378]
Cyclopentanoid (Fig. 4C-m)			
2-*cis*-16:0/3-*cis*-16:0-CPENT 1-*cis*-PC (Fig. 4C-m1)	38	10.0	[650]
2-*cis*-16:0/3-*trans*-16:0-CPENT 1-*cis*-PC (Fig. 4C-m2)	36	8.9	[650]
1-*cis*-16:0/2-*cis*-16:0-CPENT 3-*trans*-PC (Fig. 4C-m3)	45	18.0	[650]
2-*trans*-16:0/3-*cis*-16:0-CPENT 1-*cis*-PC (Fig. 4C-m4)	46	19.0	[650,413]
1-*cis*-16:0/3-*cis*-16:0-CPENT 2-*cis*-PC (Fig. 4C-m5)	44	7.8	[650]
1-*cis*-16:0/3-*cis*-16:0-CPENT 2-*trans*-PC (Fig. 4C-m6)	42	9.9	[650]
Other backbone modifications			
C-17:0/C-18:0 PC (Fig. 4C-e)[a]	27	8.1	[259]
2-O-16:0/3-O-16:0–CH(CH_3)–CH–CH_2 PC (Fig. 4C-h)[b]	38.1 ± 0.3		[377]
O-16:0/O-16:0–CH_2–C(CH_3)–CH_2 PC (Fig. 4C-j)[c]	40.1 ± 0.4		[377]
O-16:0/O-16:0–CH_2–CH–CH(CH_3) PC (Fig. 4C-k)[d]	41.8 ± 0.2		[377]

[a][(2-octadecyleicosyl)phosphoryl]choline. A phosphatidylcholine analogue with C–C linkages in place of the usual ester or ether linkages between the backbone and the hydrocarbon chains.
[b]Methyl group substituted at position 1 of the glycerol backbone.
[c]Methyl group substituted at position 2 of the glycerol backbone.
[d]Methyl group substituted at position 3 of the glycerol backbone.

on the phosphatidylcholine phase behavior of chemical modifications in the polar/apolar interfacial region [413,650]. The six diastereoisomers of the dipalmitoyl cyclopentanophosphatidylcholine studied (Fig. 4C-m, inset) exhibit a chain melting transition temperature that is within ± 5°C of that for the 'control' 16:0/16:0 PC (Table 5). For four of these compounds, the associated enthalpy change is comparable to that of 16:0/16:0 PC. In the other two, ΔH is considerably higher (Ref. [650], Table 5) and is attributed to a direct lamellar crystalline–lamellar liquid crystalline phase change [413].

4.6. Methylidene phosphatidylcholine

15:0/15:0-METH PC is a phosphatidylcholine where the glycerol backbone has been replaced by a methylidene moiety (Fig. 4C-g). It represents another example of a backbone-modified glycerophosphocholine [378]. Aqueous dispersions of 15:0/15:0-METH PC exhibit a gel–liquid crystalline phase transition temperature, enthalpy change and cooperativity that are considerably lower than those for the corresponding diacyl and dialkyl glycerophosphocholines (Table 5). This may reflect a limited conformational flexibility in parts of the hydrocarbon chains next to the backbone that is imposed by the methylidene moiety.

4.7. Other backbone modifications

[(2-octadecyleicosyl)phosphoryl)choline (C-17:0/C-18:0 PC) represents an analog of the dialkyl phosphatidylcholine, O-17:0/O-18:0 PC, where the ether linkages have been replaced by direct C–C bonds between the backbone and the hydrocarbon chains (Fig. 4C-e). An aqueous dispersion of C-17:0/C-18:0 PC undergoes a chain melting transition at a considerably lower temperature than the corresponding glycerophosphocholine (compare data in Tables 3 and 5).

Another structural modification of the glycerol backbone involves substituting methyl groups for hydrogens at the C1, C2, or C3 position of the glycerol (Fig. 4C-h,j,k) in O-16:0/O-16:0 PC. These modifications are designated O-16:0/O-16:0–$CH(CH_3)$–CH–CH_2 PC, O-16:0/O-16:0–CH_2–$C(CH_3)$–CH_2 PC, and O-16:0/O-16:0–CH_2–CH–$CH(CH_3)$ PC, respectively, and in all cases the chain melting transition temperature is lower than the corresponding unmodified PC (Ref. [377], Table 5). The results show that methylation at C1 or C3 of glycerol eliminates chain interdigitation in the lamellar gel phase of the type seen in O-16:0/O-16:0 PC, while methylation at the C2 position allows for its retention [377].

4.8. Unsaturated phosphatidylcholines

The data for the chain melting transition temperature, half-width and enthalpy for phosphatidylcholines with one or two unsaturated hydrocarbon chains are included in Table 6. The same criteria for calculating averages was used here as applied above for the saturated diacyl phosphatidylcholines.

The data in Table 6 show that introducing a single site of unsaturation of the *cis* type on the *sn*-2 chain only and in both chains of an 18-carbon phosphatidylcholine can have the effect of lowering the chain melting transition temperature by 50°C and 75°C, respectively. In contrast, when the double bond is of the trans type, the effect is considerably lessened. Thus, in the case of 18:0/18:0 PC, the gel–liquid crystalline transition temperature is 54°C. The same transition occurs at -18.3°C in 18:1c9/18:1c9 PC, at 6.9°C in 18:0/18:1c9 PC, and at 12°C in 18:1t9/18:1t9 PC (Table 6). Further, T_m and ΔH depend critically on the position of the *cis*-double bond (Fig. 8). Specifically, T_m and ΔH are minimized when the double bond is located near the geometric center of the hydrocarbon chain, and progressively increase as the double bond migrates toward either end of the chain. These dependencies apply when the double bond is present in the *sn*-2 chain only or in both chains of phosphatidylcholine (Fig. 8). The molecular origin of the stability variation with double bond position along the hydrocarbon chain is thought to be associated with a maximum local perturbation of the van der Waals chain–chain interaction when the chain is separated into two relatively small segments as a result of localizing the double bond at the center of the chain. In contrast, when the double bond is positioned close to either end of the chain, the relatively long saturated seg-

Table 6
Thermodynamic parameters of the lamellar gel–liquid crystalline phase transition in fully hydrated olefinic (double bond) and acetylenic (triple bond) phosphatidylcholines

Lipid chains and backbone	T [°C]	ΔH [kcal/mol]	$\Delta T_{1/2}$ [°C]	References
Diacyl (identical chains)				
16:1t9/16:1t9	−4.0			[150]
16:2c2,4/16:2c2,4	1.0			[159]
17:1c9/17:1c9	−27.6			[163]
18:1c2/18:1c2	41.0	9.6		[298]
18:1c3/18:1c3	35.0	8.7		[298]
18:1c4/18:1c4	23.0	8.2		[298]
18:1c5/18:1c5	11.0	7.8		[298]
18:1c6/18:1c6	1.0	7.8		[298]
18:1c7/18:1c7	−8.0	7.6		[298]
18:1c8/18:1c8	−13.0	7.5		[298]
18:1c9/18:1c9	−18.3 ± 3.6	9.0 ± 2.8		[45,53,57,62,116,120,126,150,151, 178,179,214,227,261,262,298–312]
18:1c10/18:1c10	−21.0	7.6		[298]
18:1c11/18:1c11	−20.5 ± 2.1	7.8		[150,152,298]
18:1c12/18:1c12	−8.0	7.9		[298]
18:1c13/18:1c13	1.0	8.2		[298]
18:1c14/18:1c14	7.0	8.6		[298]
18:1c15/18:1c15	24.0	8.9		[298]
18:1c16/18:1c16	35.0	9.6		[298]
18:1c17/18:1c17	45.0			[298]
18:1t6/18:1t6	23.0			[64]
18:1t9/18:1t9	11.9 ± 1.0[a]	7.8 ± 1.4		[57,58,62,64,121,126,150,151, 175,227,230,275,311,315–328]
18:1t11/18:1t11	13.2			[150]
18:2c2,4/18:2c2,4	18.7 ± 2.8	9.5		[159,277]
18:2c9,12/18:2c9,12	−55.1 ± 2.8	1.7 ± 0.4		[45,116,330,331,623]
18:2y2,4/18:2y2,4	16.0			[136]
18:2y4,6/18:2y4,6	26.3 ± 3.3	10.2 ± 0.3		[332]
18:3c9,12,15/18:3c9,12,15	−61.5 ± 2.1	1.0		[116,330]
19:1c10/19:1c10	−8.6	9.9		[300]
20:1c11/20:1c11	−4.3	11.4		[300]
20:2y10,12/20:2y10,12	22.0	5.0		[344]
20:4c5,8,11,14/20:4c5,8, 11,14	−69.5 ± 0.7	0.8 ± 0.2		[330,331]
21:1c12/21:1c12	6.5	11.1		[300]
22:1c13/22:1c13	12.1 ± 1.6	15.1		[64,300]
22:1t13/22:1t13	41.0			[64]
22:2c5,9/22:2c5,9	7.0 ± 4.2			[329]
22:6c4,8,12,15,18,21 /22:6c4,8,12,15,18,21	−67.4 ± 1.4	0.6 ± 0.2		[331]
23:1c14/23:1c14	20.9	13.7		[300]
23:2y11,13/23:2y11,13	43.1	23.0	1.3	[351]
24:1c15/24:1c15	25.9 ± 2.5	16.8 ± 2.3	2.0	[64,108,174,300]
24:1c5/24:1c5	59.0	15.0	3.0	[174]
24:1c9/24:1c9	34.0	13.4	4.0	[174]
24:2c5,9/24:2c5,9	31.0			[329]
25:2y10,12/252:y10,12	49.0 ± 1.2	11.8 ± 2.4		[263,344,352]
26:2c5,9/26:2c5,9	42.0	12.2		[329,353]
26:2c5t9/26:2c5t9	49.0	7.3		[353]
26:2c6,9/26:2c6,9	45.0	14.7		[354]

Table 6 (continued)

Lipid chains and backbone	T [°C]	ΔH [kcal/mol]	$\Delta T_{1/2}$ [°C]	References
Diacyl (identical chains)				
26:2y10,12/26:2y10,12	53.7 ± 3.8			[233,355]
27:2y/27:2y	57.8	28.0		[356]
27:2y10,12/27:2y10,12	60.7 ± 1.2			[295,344,357,358]
27:2y11,13/27:2y11,13	56.0 ± 0.1	25.0		[357,358]
27:2y12,14/27:2y12,14	60.7 ± 0.4			[357,358]
27:2y13,15/27:2y13,15	57.7 ± 0.4			[357,358]
27:2y17,19/27:2y17,19	61.85 ± 0.2			[357,358]
27:2y6,8/27:2y6,8	65.7 ± 0.8			[357,358]
27:2y7,9/27:2y7,9	55.4 ± 0.1			[357,358]
27:2y8,10/27:2y8,10	58.8 ± 0.2			[357,358]
27:2y9,11/27:2y9,11	54.8 ± 0.1			[357,358]
Diacyl mixed-chain				
14:0/24:1c15	22.5	7.3 ± 0.5	1.1	[557]
16:0/16:1c9	30.0			[66]
16:0/18:1c6	17.7 ± 1.5	6.1 ± 0.4	1.7 ± 0.3	[110–112,557]
16:0/18:1c9	−2.5 ± 2.4	5.8 ± 1.0	6.0	[34,113–132]
16:0/18:2c6,9	−15.0			[134]
16:0/18:2c9,12	−19.6 ± 0.4	2.9 ± 0.4		[116,135]
16:0/18:2y2,4	28.0			[136]
16:0/20:4c5,8, 11,14	−22.5		15.0	[129]
16:0/22:1c13	11.5/12.0/12.6	6.9 ± 0.5		[557]
16:0/22:6c4,7,10,13,16,19	−3.0		20.0	[129]
16:0/24:1c15	27.6	7.6 ± 0.4	0.3	[557]
18:0/11:1e10	13.3	0.6		[170]
18:0/16:1c9		6.5		[174]
18:0/18:1c6	24.8	7.1 ± 0.5	0.4	[557,625]
18:0/18:1c7	16.7	6.8 ± 0.4	0.3	[557,625]
18:0/18:1c9	6.9 ± 2.9	5.8 ± 0.7	0.8	[34,113,119,126,197, 219,230,216,283–290, 538,557,586,625]
18:0/18:1c11	3.8	6.0 ± 0.7	0.8	[557,625]
18:0/18:1c12	9.1	6.6 ± 0.3	0.9	[557,625]
18:0/18:1c13	15.9	6.8 ± 0.4	1.1	[557,625]
18:0/18:1c16	43.0			[298]
18:0/18:2c9,12	−14.4 ± 4.1	3.3 ± 1.1		[135,291–293,586]
18:0/18:3c6,9,12	−11.0 ± 0.7	3.7 ± 0.4		[538]
18:0/18:3c9,12,15	−12.3 ± 1.2	6.6		[291,293,586]
18:0/20:1c11	13.2	6.8 ± 0.3	0.9	[557]
18:0/20:1c13	18.5	7.1 ± 0.4	0.6	[625]
18:0/20:2c11,14	−5.4 ± 0.3	2.9 ± 0.3		[538]
18:0/20:3c8,11,14	−9.3 ± 0.7	4.3 ± 0.4		[538]
18:0/20:4c5,8,11,14	−12.9 ± 0.4	5.0 ± 0.5		[293,538,586]
18:0/20:5c5,8,11,14,17	−10.4 ± 0.1	5.5 ± 0.1		[538,586]
18:0/22:1c13	19.6	7.2 ± 0.5	0.6	[557,625]
18:0/22:4c7,10,13,16	−8.5 ± 0.1	4.8 ± 0.2		[538]
18:0/22:5c4,7,10,13,16	−6.4 ± 0.2	4.4 ± 0.6		[538]
18:0/22:5c7,10,13,16,19	−9.1 ± 0.4	4.3 ± 0.1		[538]
18:0/22:6c4,7,10,13,16,19	−3.8 ± 1.8	6.1 ± 0.4		[538,586]
18:0/23:2y10,12	23.0			[295]
18:0/18:24:1c15	31.8	8.2 ± 0.6	0.6	[557]
18:1c9/16:0	−8.9 ± 0.7	4.3 ± 0.5		[34,113,120]

Table 6 (continued)

Lipid chains and backbone	T [°C]	ΔH [kcal/mol]	$\Delta T_{1/2}$ [°C]	References
Diacyl mixed-chain				
18:1c9/18:0	9.4 ± 2.2	6.6 ± 0.2		[34,108,113,261,286,299]
18:1c9/20:0	16.0 ± 0.2	7.0 ± 0.1		[34,313]
20:0/18:1c6	27.8 ± 1.0	7.5 ± 0.4	1.4	[557,625]
20:0/18:1c7	20.9	7.1 ± 0.5	0.6	[625]
20:0/18:1c9	11.5 ± 0.5	5.6 ± 1.5	1.0	[34,313,557,625]
20:0/18:1c11	7.2/8.5	6.6 ± 0.5		[625]
20:0/18:1c12	10.2	6.5 ± 0.5	0.9	[625]
20:0/18:1c13	15.9	6.8 ± 0.5	0.8	[625]
20:0/20:1c5	44.9	8.2 ± 0.5	0.5	[625]
20:0/20:1c8	30.7	7.8 ± 0.4	0.3	[625]
20:0/20:1c11	20.5 ± 1.3	6.5 ± 1.0	0.6	[342,557,625]
20:0/20:1c13	22.8	7.3 ± 0.5	0.6	[625]
20:0/20:2c11,14	5.4 ± 1.7	6.0		[342]
20:0/20:3c11,14,17	1.8 ± 1.4	7.0		[342]
20:0/20:4c5,8,11,14	−7.5 ± 2.2	3.5 ± 0.7		[342]
20:0/22:1c13	29.2	8.0 ± 0.3	1.0	[557,625]
20:0/24:1c15	36.6	8.5 ± 0.4	0.6	[557]
22:0/18:1c6	29.8 ± 1.0	8.0 ± 0.5	1.9	[557,625]
22:0/18:1c7	23.7	7.6 ± 0.6	0.4	[625]
22:0/18:1c9	15.1	7.7 ± 0.3	1.0	[557,625]
22:0/18:1c11	11.5	7.1 ± 0.4	0.4	[625]
22:0/18:1c12	13.2	7.4 ± 0.5	0.3	[625]
22:0/18:1c13	14.6/16.3	7.4 ± 0.7		[625]
22:0/20:1c11	22.9	8.1 ± 0.4	0.4	[557]
22:0/20:1c13	23.5/24.0	8.0 ± 0.6		[625]
22:0/22:1c13	32.8	8.3 ± 0.4	0.7	[557,625]
22:0/24:1c15	41.7	9.1 ± 0.5	0.5	[557]
24:0/18:1c6	30.7	8.6 ± 0.5	1.9	[557]
24:0/18:1c9	20.7	8.2 ± 0.6	0.9	[557]
24:0/20:1c11	24.5	8.5 ± 0.4	0.5	[557]
Acyl–alkyl, alkyl–acyl				
18:1c9/O-16:0	−5.0			[122]
O-16:0/18:1c9	9.4 ± 0.1			[369]
Dialkyl				
O-16:0/O-18:1c9	16.7 ± 0.4			[369]
O-18:2y2,4/O-18:0	39.0			[136]

ment on the one side of the double bond packs tightly with neighboring chains and so increases gel phase stability and the chain melting transition temperature and enthalpy change [557].

When two or three sites of *cis*-unsaturation are introduced into both acyl chains, the chain melting transition temperature is lowered by an impressive 109°C and 116°C, respectively, in the case of 18:2c9,12/18:2c9,12 PC and 18:3c9,12,15/18:3c9,12,15 PC. These data show that additional double bonds have progressively less of an effect in lowering T_m (Fig. 9).

4.9. Mixed-chain saturated phosphatidylcholines

This lipid class is a subject of increasing scientific interest. More than 800 entries belong to this data subset of LIPIDAT, 80% of which have been produced in the last 10 years. Having established a reasonable understanding of the phase behavior of the

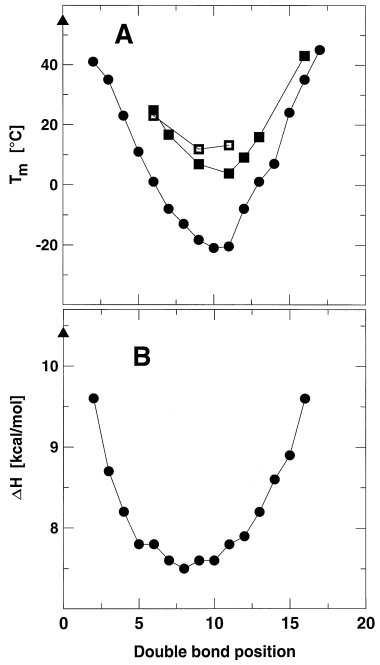

Fig. 8. Dependence of the chain melting transition temperature (A) and enthalpy change (B) on the position of the double bond in the fatty acyl chain of the fully hydrated diacyl phosphatidylcholines: (●) 18:1cX/18:1cX PC; (□) 18:0/18:1cX PC; (□) 18:1tX/18:1tX PC (X denotes the position of the double bond). The transition temperature and enthalpy change of fully hydrated 18:0/18:0 PC are included for comparison (▲).

simpler identical-chain phosphatidylcholines, it is not unreasonable to proceed and to tackle the more biologically relevant lipids which typically have different hydrocarbon chains at the *sn*-1 and *sn*-2 positions. Based on a sizable volume of experimental data referring to the phase transitions in mixed-chain phosphatidylcholines, empirical equations have been derived that allow for accurate prediction of the transition temperatures of related phosphatidylcholines of defined structure [15,33,39,45]. Data pertaining to the chain melting transition of the diacyl phosphatidylcholines, both experimental and empirically estimated, are presented in Table 7.

In discussing mixed-chain lipids, it has proven useful to describe them in terms of a normalized chain-length inequivalence parameter, $\Delta C/\mathrm{CL}$ [16]. Here, ΔC $(=|n_1 - n_2 + 1.5|)$ is the effective chain-length difference and n_1 and n_2 are the number of carbons in the chains at the *sn*-1 and *sn*-2 positions of the glycerol backbone, respectively. The constant 1.5 is employed to take account of the effective *sn*-2 chain length shortening due to a bend in the chain between the β and γ methylene units (Fig. 4A). CL is the effective length of the longer of the two chains and is defined as $\mathrm{CL} = n_1 - 1$, if *sn*-1 has the longer chain, and $\mathrm{CL} = n_2 - 2.5$, if the *sn*-2 has the longer chain.

Phase behavior as a function of $\Delta C/\mathrm{CL}$ for the asymmetric and symmetric phosphatidylcholines is presented in Fig. 10. Two sets of curves are shown. One refers to a phosphatidylcholine series with a fixed molecular weight where the sum of the number of carbons per chain is constant ($n_1 + n_2 = 30$; $n_1 + n_2 = 32$; $n_1 + n_2 = 34$). The other refers to phosphatidylcholines with a constant chain length difference ($n_1 - n_2 = 0$; $n_1 - n_2 = 6$; $n_1 - n_2 = -12$). For the first series in which the chain length sum is constant, the chain order/disorder transition temperature decreases monotonically when the chain length inequivalence $\Delta C/\mathrm{CL}$ is increased to about 0.4. This decrease in melting temperature is believed to originate from the progressive perturbation of the chain–chain lateral interaction in the gel state caused by the

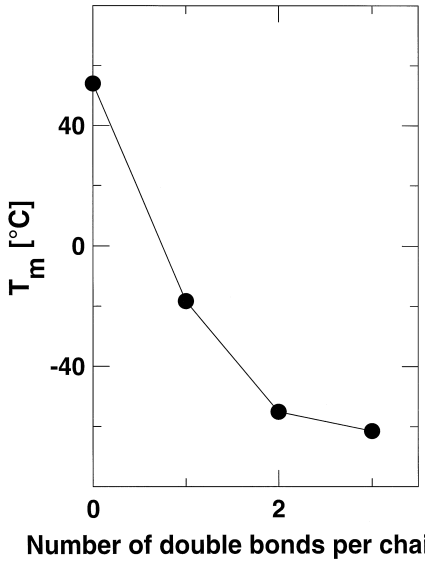

Fig. 9. Dependence of the chain melting transition temperature on the number of double bonds per chain in the 18-carbon, fully hydrated diacyl phosphatidylcholines: 18:0/18:0 PC, 18:1c9/18:1c9 PC, 18:2c9,12/18:2c9,12 PC and 18:3c9,12,15/18:3c9,12,15 PC.

Table 7
Thermodynamic parameters of the lamellar gel–liquid crystalline phase transition in fully hydrated, saturated diacyl phosphatidylcholines with varying degrees of acyl chain length asymmetry[a]

Number of carbon atoms in the *sn*-1 acyl chain (n_1) \ Number of carbon atoms in the *sn*-2 acyl chain (n_2)	2	4	6	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
6														-5.2 1.7								
8													*2.9*	10.1±0.2 7.1±0.6	17.1 10.2±0.2	21.3 12.2±0.9	24.3 10.7±0.4					
9					*-55.2*	*-40.0*	*-27.4*	*-21.8*	*-17.2*	*-13.5*	*-10.3*		*1.6*	10.9 8.3±0.6	19.6 11.3±0.9	24.9 10.9±0.7	29.3 11.2±0.3	32.0 11.5±0.4	33.7 11.4±0.3			
10					*-47.8*	*-32.7*	-20.3	-10.4	*-6.0*	*-2.4*	*0.6*	*3.0*	*5.1*	12.0±0.2 6.5±0.1	19.9 7.1±0.5	27.2±0.4 9.2±0.7	32.7 11.3±0.3	37.6±0.3 11.9±0.7	40.0 13.2±0.5	42.2 13.3±0.2	43.1 13.1±0.6	
11					*-42.0*	*-27.0*	*-14.5*	*-4.1*	*3.7*	*7.3*	*10.4*	*12.1*	13.9 4.9	*16.0*	17.8 4.4	25.7 8.4±0.2	32.6 9.4±0.4	38.6 12.6±0.2	43.5 12.4±0.3	47.7 13.4±0.7	49.5 13.7±0.5	*50.1*
12						*-22.5*	*-10.0*	-1.9; 3.5 4.1±2.4	*9.5*	*15.7*	*18.5*	21.7	*22.6*	23.4 5.2	*25.4*	25.6 5.2±0.5		37.9±0.3 12.2±1.0	44.0 13.4±0.4	48.7 13.8±0.5	*52.4*	55.2 14.7±0.3
13					*-33.6*	*-18.9*	*-6.4*	*4.2*	13.5±0.8 3.9±0.5	*21.0*	25.8 6.0	*28.1*	30.5 6.9	*31.5*	32.6 7.2	33.1	34.1 5.5	*35.0*		*47.5*	53.3 14.7±0.4	*57.0*
14					*-16.4*	*-15.9*	*-3.5*	*7.1*	*16.3*	23.6±1.5 6.0±2.4	30.7	35.3±1.2 7.9±0.6	*36.5*	38.8±0.4 7.4±0.5	*39.2*	39.8 7.1	*40.9*	*41.4*	*41.9*	43.3		55.5 15.1±0.5
15					*-4.5*	*-6.8*	*-1.2*	*9.4*	18.8 5.3	*26.6*	33.7±0.8 7.6±0.7	39.5	41.7 10.1	*43.8*	44.8 8.7	*46.0*	46.1	*47.3*	*47.7*	*48.0*	*48.2*	
16					3.6 6.1	5.4±0.5 6.6±0.1		11.3 4.5	*20.4*	27.8±0.6 6.5±0.6	*35.6*	41.3±1.8 8.2±1.4	46.2	49.0±0.3 9.2±0.1	*50.3*	*51.3*	*52.1*	52.8	*53.1*	53.2	*53.5*	53.3
17					7.4 4.4±0.5	13.6 8.4±0.5	12.8 6.9±0.5		21.2 5.2	*30.0*	37.7 7.4	42.8±0.4	49.0 9.7	*53.7*	*55.1*	*56.1*	*56.9*	*57.5*	57.9	*58.2*	*58.4*	*58.5*
18	18.5 5.0	14.0 4.0	8.2 3.6	0.3 6.3	11.0 8.2±0.5	18.9±0.3 9.7±0.3	21.4 9.1±0.5	17.3 8.4±0.8	*22.9*	30.2±1.0 5.2±0.2	38.1	44.2±0.3 8.0±0.2	*50.4*	54.5±1.5 10.4±1.6	*59.6*	*60.4*	*61.3*	*61.9*	*62.4*	62.7	*62.9*	63.9
19					13.2 8.3±0.2	22.7 8.3±0.5	28.7 11.0±0.6	27.7 9.6±0.4	23.8 5.0	*31.8*	39.0 6.4	*45.8*	*51.5*	*56.6*	60.2±1.6 10.4±1.2	*64.9*	*65.2*	*65.9*	*66.5*	*66.8*	*67.1*	*67.2*
20						26.2±0.1 10.7±0.5	32.7±0.5 11.1±0.6	34.0±0.4 11.5±0.6	30.2 11.6±0.5	33.2 4.7	*39.9*	*46.4*	*52.3*	*57.5*	*62.1*	65.3±1.5 13.3±2.5	*69.7*	*69.6*	*70.2*	*70.6*	*70.9*	70.7
21					20.1 8.1	27.0 11.5±0.4	35.4 12.2±0.4	39.6 11.8±0.3	39.4 12.0±0.5		*40.3*	*46.9*	*52.8*	*58.2*	*62.9*	*67.1*	70.7±1.6 13.0±1.1	*74.1*	*73.5*	*74.0*	*74.3*	*74.5*
22						29.4 12.3	37.5 12.2±0.4	43.2±0.3 13.2±0.8	44.4±0.3 14.1±0.7	41.6±0.3 12.5±0.9		*47.2*	*53.2*	*58.6*	*63.4*	*67.7*	*71.6*	73.6±2.1 15.8±2.8	*78.0*	*77.1*	*77.5*	77.8
23							*38.9*	*45.9*	*49.4*	*48.9*		*47.3*	*53.4*	*58.8*	*63.7*	*68.2*	*72.1*	*75.7*	77.9±1.6 18.0	*81.6*	*80.4*	*80.7*
24								*48.1*	*52.3*	*53.1*	*49.7*		*52.7*	*58.9*	*63.9*	*68.4*	*72.5*	*76.2*	*79.4*	80.3±0.3 15.4±1.6	*85.0*	*83.5*
25								*49.0*	*54.9*	*57.4*	*56.7*		*53.7*	*57.6*	*63.9*	*68.5*	*72.7*	*76.4*	*79.8*	*82.9*	*85.6*	*88.0*
26									*57.0*	*60.1*	*60.2*	*56.7*		*58.4*	*62.1*	*68.5*	*72.7*	*76.5*	*80.0*	*83.2*	*86.0*	*88.6*

[a]Data from Refs. [33,36–42,73,81,84,87,168,169,547,556,558,624]. The upper and lower numbers in a given cell represent transition temperature in °C and transition enthalpy in kcal/mol, respectively. Transition temperatures in italics were calculated by linear extrapolation/interpolation from measured values [33,39,556,624].

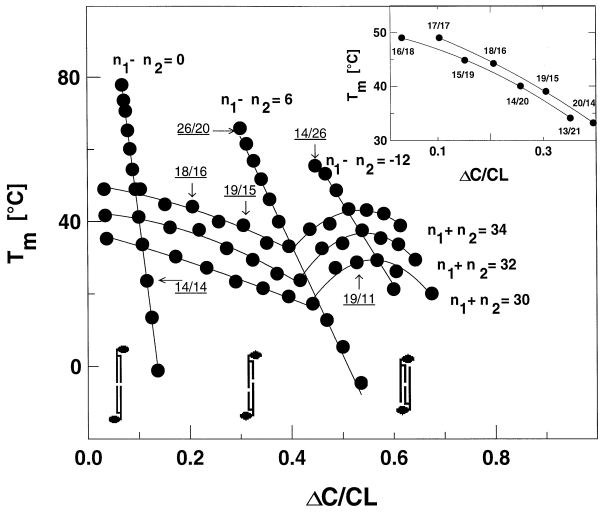

Fig. 10. Dependence of the transition temperature on chain length inequivalence ($\Delta C/\mathrm{CL}$) in fully hydrated, saturated diacyl phosphatidylcholines. Fatty acyl chain lengths in number of carbon atoms at the *sn*-1 and *sn*-2 positions of the glycerol backbone are indicated as n_1 and n_2, respectively. A schematic representation of the lipid bilayer in the non-interdigitated, partially interdigitated and mixed interdigitated gel phases formed at low temperatures at $\Delta C/\mathrm{CL}$ values of 0, < 0.4 and > 0.42, respectively, is included. Inset: expanded view of the $n_1 + n_2 = 34$ data set showing that the transition temperatures of asymmetric phosphatidylcholines with chains reversed lie on separate lines.

bulkier methyl ends of the lipid acyl chains [558]. As $\Delta C/\mathrm{CL}$ and chain length asymmetry increases, there is a greater tendency for the acyl chains to engage in what is referred to as partial interdigitation ( ), resulting in progressively larger overlapping regions of the terminal methyl ends with the adjacent methylene groups of the lipid acyl chains in the bilayer. When $\Delta C/\mathrm{CL}$ goes above ca. 0.42, the packing perturbation becomes so overwhelming that the asymmetric phosphatidylcholine molecules adopt a new packing arrangement referred to as mixed interdigitation ( ). This rearrangement reverses the trend of T_m vs. $\Delta C/\mathrm{CL}$, which now increases with chain length asymmetry (Fig. 10). Upon further increase in $\Delta C/\mathrm{CL}$ to values of ~ 0.56–0.60, the sum of the effective chain lengths of the two opposing shorter acyl chains matches exactly the effective chain length of the longer acyl chain, thus, permitting maximum chain–chain van der Waals contact in the mixed interdigitated gel state bilayer thereby maximizing T_m. A further increase in chain inequivalence creates obvious packing problems in this mixed interdigitated phase with a concomitant decrease in T_m. Of note is the observation that the chain-melting enthalpy (ΔH) changes with chain inequivalence in approximately the same way as T_m [558].

An empirical relationship has been derived relating T_m to the lipid molecule structural parameters, ΔC and CL that applies in the range $0.07 < \Delta C/\mathrm{CL} < 0.4$ [33] as follows:

$$T_m = 154.2 + 2.0(\Delta C) - 142.8(\Delta C/CL) - 1512.5(1/CL).$$

Using this equation, the transition temperatures of a number of asymmetric phosphatidylcholines have been predicted with remarkably high accuracy (deviation between experimental and calculated T_m values ≤ 1°C) [33]. Further, since the T_m vs. $\Delta C/\mathrm{CL}$ lines for asymmetric phosphatidylcholines with chains reversed are found to lie on slightly displaced lines (Fig. 10, inset), refinements to the general equation have been made [556,625].

An empirical description of the order/disorder transition temperatures of the highly asymmetric phosphatidylcholines with $0.43 < \Delta C/\mathrm{CL} < 0.63$ in the mixed interdigitated gel phase requires the introduction of an additional structure parameter δ. δ is defined as 'the difference between the value of the apparent chain length of the longer acyl chain, CL, and the sum of two shorter acyl chains plus the van der Waals contact distance between the two opposing methyl ends $[2(\mathrm{CL} - \Delta C) + 1.7]$' [39]. Thus, the value of δ is zero for species where the effective length of the longer acyl chain exactly matches the sum of the effective lengths of the two shorter chains. Empirical equations with high predictive power relating T_m of highly asymmetric phosphatidylcholines to ΔC and δ have been derived [39].

Recently, the cooling behavior of a series of highly asymmetric, mixed-chain diacyl phosphatidylcholines has been reported and identified as enigmatic [547]. Upon heating, the aqueous dispersions invariably display a single highly cooperative endotherm, while the cooling calorimetric scan depends on the thermal history of the sample in the gel state before heating. With prolonged, low-temperature equilibration in the gel phase, cooling from the L_α phase is characterized

Table 8
Thermodynamic parameters of the heating and cooling phase transitions—in fully hydrated, highly asymmetric phosphatidylcholines[a]

Lipid chains and backbone	Heating		First cooling[b]				Subsequent coolings[c]	
	T [°C]	ΔH [kcal/mol]	T_1 [°C]	ΔH_1 [kcal/mol]	T_2 [°C]	ΔH_2 [kcal/mol]	T [°C]	ΔH [kcal/mol]
10:0/18:0	12.1	6.4	10.4	5.8	11.2	0.6	10.3	6.4
10:0/20:0	27.6	9.9	23.4	6.4	26.3	3.5	23.1	9.9
10:0/22:0	37.9	13.0	31.8	10.7	36.5	2.3	31.8	13.0
12:0/22:0	38.2	11.2	33.6	8.3	37.0	2.8	33.6	11.2
16:0/10:0	5.9	6.7	1.9	3.3	4.4	3.4	1.9	6.7
18:0/10:0	19.3	10.1	14.9	9.6	18.2	0.5	14.9	10.1
18:0/12:0	17.4	8.9	15.3	7.8	16.1	1.1	15.3	8.9
20:0/10:0	26.3	10.6	21.3	7.5	25.1	3.1	21.2	10.6
20:0/12:0	34.1	12.2	28.6	7.3	32.6	4.9	28.4	12.2
22:0/10:0	29.4	12.3	25.6	6.3	27.7	6.0	25.5	12.3
22:0/12:0	43.5	13.4	37.3	6.2	42.7	7.2	36.9	13.4
22:0/14:0	41.9	11.2	37.1	5.9	40.6	5.3	37.0	11.2

[a]Data from Ref. [547].
[b]Low-temperature incubation (overnight at −20°C or for several weeks at 0–4°C) before preceding heating.
[c]Without low-temperature incubation before preceding heating (see text for details).

by two distinct exotherms separated by 1–5°C. In contrast, a single exotherm is observed when prolonged low-temperature incubation in the gel phase was not performed. The total enthalpy of the two cooling exotherms equals that of the single heating endotherm and the single cooling exotherm when observed (Table 8). IR spectroscopic and X-ray diffraction studies do not reveal anything other than coexisting gel and L_α phases in the temperature interval between the two cooling exotherms. The

Table 9
Thermodynamic parameters of the phase transitions in fully hydrated, mixed-chain dialkyl, alkyl–acyl, 1,3-diacyl, 1-acyl-2-acylamido-2-deoxy, and 1-alkyl-2-acylamido-2-deoxy phosphatidylcholines

Lipid chains and backbone	Transition type	T [°C]	ΔH [kcal/mol]	References
O-20:0/O-12:0	mxd int gel–L_α	34.8	11.2	[360]
O-12:0/O-20:0	L_β–mxd int gel	9.0[a]	0.3	[360]
	mxd int gel–L_α	25.2	4.7	
O-16:0/2:0	lamellar gel–micellar	0.0		[370]
O-18:0/2:0	fully int multilamellar gel–bilayer vesicle gel	10.4 ± 1.4		[384,385]
	bilayer vesicle gel–micellar	19.1 ± 1.6		[384,385]
14:0/3–18:0	lamellar subgel–P_β	16.0	5.9	[85]
	P_β–L_α	30.0	7.1	[85]
16:0/3–18:0	lamellar subgel–P_β	26.0	7.3	[85]
	P_β–L_α	46.0	10.4	[85]
18:0/3–14:0	gel–liquid crystal	29.9 ± 1.6		[296]
O-18:0/NH-16:0	gel–gel[b]	39.8	4.9	[640]
	gel–gel[b]	44.4	7.3	[640]
	gel–gel[b]	46.5	4.4	[640]
	gel–gel[b]	47.3	5.5	[640]
	gel–liquid crystal[b]	47.8	5.8	[640]
18:0/NH-18:0	'pretransition'	51.7	1.3	[640]
	gel–liquid crystal	52.8	3.9	[640]

[a]A low-enthalpy 'subtransition' appears at 7.7°C after low-temperature incubation at −4°C for 39 days [360].
[b]Complex transition curve represented as a sum of five components is recorded calorimetrically [640].

Table 10
Thermodynamic parameters of the phase transitions in fully hydrated, branched-chain phosphatidylcholines

Lipid chains and backbone	Low temperature lamellar gel–intermediate gel		Lamellar gel–liquid crystal		References
	T [°C]	ΔH [kcal/mol]	T [°C]	ΔH [kcal/mol]	
Methyl-isobranched					
11:1me10/11:1me10			−18.8[a]	7.8	[48,150]
12:1me11/12:1me11			−9.5[b]	13.1	[48,150]
13:1me12/13:1me12			7.6[c]	11.6	[48,150]
14:1me13/14:1me13	6.7	−3	7.0	−3	[48,92,150]
15:1me14/15:1me14			22.7 ± 1.3[d]	14.0 ± 0.3	[48,92,106,150,154]
16:1me15/16:1me15	16.5 ± 3.7	4.1 ± 1.9	27.5 ± 0.5	7.9 ± 0.5	[48,80,92,106,150,155,156]
17:1me16/17:1me16	36.3 ± 1.2	8.0	37.0 ± 0.2	10.0	[48,80,92,106,150]
18:1me17/18:1me17	27.7 ± 2.2[e]	5.7 ± 2.5	43.5 ± 0.5	10.9\ + − 1.1	[48,80,92,106,150]
19:1me18/19:1me18	43.5 ± 0.6	9.0 ± 0.6	50.2 ± 1.0	12.3 ± 1.1	[48,92,106,156]
20:1me19/20:1me19	31.0 ± 4.2[e]	5.0 ± 2.0	55.5 ± 0.6	14.4\ + − 0.6	[48,92]
21:1me20/21:1me20	47.9	10.0	60.4	16.0	[48]
ω-Tertiary butyl					
12:2me11,11/12:2me11,11			−35.9[f]	3.3	[75]
13:2me12,12/13:2me12,12			−9.7[f]	7.0	[75]
14:2me13,13/14:2me13,13			−7.5[f]	5.3	[75]
15:2me14,14/15:2me14,14			9.9[f]	9.6	[75]
16:2me15,15/16:2me15,15			13.4[f]	8.3	[75]
17:2me16,16/17:2me16,16			23.6[f]	14.0	[75]
18:2me17,17/18:2me17,17			28.9[f]	10.6	[75]
19:2me18,18/19:2me18,18			35.6[f]	13.8	[75]
20:2me19,19/20:2me19,19			40.2[f]	11.6	[75]
Methyl-anteisobranched					
13:1me11/13:1me11			−30.7	0.13	[90]
14:1me12/14:1me12			−13.9	2.8	[90,91]
15:1me13/15:1me13	−5.0	6.9	−0.4	2.7	[90]
16:1me14/16:1me14	4.8	4.5	9.2	5.4	[90,91,155]
17:1me15/17:1me15	6.9[g]	1.6[g]	18.9	6.4	[90,314]
18:1me16/18:1me16	15.6	2.9	29.5	7.9	[90,91,314]
19:1me17/19:1me17			36.7	10.5	[90]
20:1me18/20:1me18	24.3	4.0	43.4	12.3	[90]
21:1me19/21:1me19			48.7	13.8	[90]
16:0/18:1me16			34.6	10.2	[133]
Other methyl-branched					
14:1me2/14:1me2	−3.3	1.3	3.5	5.4	[93]
14:1me3/14:1me3	−5.8	0.6	−4.2	3.7	[93]
14:1me4/14:1me4			−22.8	2.3	[93]
16:1me1/16:1me1			28.0		[153]
16:1me2/16:1me2	23.3	0.5	28.3 ± 0.3[h]	8.4 ± 0.3	[93,546]
16:1me2/3–16:1me2	31.4	0.8	35.9	9.4	[93]
16:1me3/16:1me3	16.1	0.4	19.8	6.8	[93]
16:1me4/16:1me4	2.5	0.4	6.8	5.3	[93]
16:1me5/16:1me5	−3.8	0.2	−3.0	3.4	[93]
16:1me6/16:1me6			−21.4	1.9	[93]
18:1me2/18:1me2	42.5	0.6	45.8	10.4	[93]
18:1me3/18:1me3			39.1	9.9	[93]
18:1me4/18:1me4	28.2	0.5	29.5	8.4	[93]

Table 10 (continued)

Lipid chains and backbone	Low temperature lamellar gel–intermediate gel		Lamellar gel–liquid crystal		References
	T [°C]	ΔH [kcal/mol]	T [°C]	ΔH [kcal/mol]	
Other methyl-branched					
20:1me2/20:1me2			57.5	13.8	[93]
16:1me3/O-16:0	−3.0	0.4	29.8	6.9	[157]
Ethyl-branched					
16:1et2/16:1et2	25.4	0.4	30.4 ± 0.6[h]	9.0 ± 0.4	[93,546]
16:1et2/3-16:1et2	28.9	0.9	33.1	9.1	[93]
Long linear branched					
14:1(4:0)2/14:1(4:0)2			0.9[h]	5.8	[546]
16:1(3:0)2/16:1(3:0)2	24.2	0.4	30.4 ± 1.4[i]	9.1 ± 0.3	[93,546]
16:1(4:0)2/16:1(4:0)2	21.1	0.6	25.6 ± 1.3[j]	8.6 ± 0.4	[93,546]
16:1(5:0)2/16:1(5:0)2	12.1[k]	1.5	16.4 ± 0.6[k]	7.5 ± 0.1	[93,546]
16:1(6:0)2/16:1(6:0)2	−7.8	1.9	3.0	8.9	[93]
16:1(8:0)2/16:1(8:0)2			−18.8	8.2	[93]
16:1(10:0)2/16:1(10:0)2	−23.8	1.0	−15.3	7.3	[93]
16:1(14:0)2/16:1(14:0)2	−6.9	0.8	14.8	8.7	[93]
18:1(4:0)2/18:1(4:0)2			42.4	10.5	[546]
O-16:0/16:1(14:0)2	0.5		40.5	9.2	[149]
O-16:0/18:1(16:0)2			52.4	11.4	[612]
16:1(n:0)2 / O-16:0 PC					
16:1me2/O-16:0			33.3	8.1	[145,148]
16:1et2/O-16:0			31.9	7.9	[145,148]
16:1(3:0)2/O-16:0			31.2	7.7	[145,148]
16:1(4:0)2/O-16:0			29.7	7.2	[145,148]
16:1(5:0)2/O-16:0			26.5	7.0	[145,148]
16:1(6:0)2/O-16:0			25.2	6.9	[145,148]
16:1(8:0)2/O-16:0			12.9	6.0	[145,148]
16:1(10:0)2/O-16:0			11.4	5.2	[145,148]
16:1(12:0)2/O-16:0			33.2	9.3	[145,148]
16:1(14:0)2/O-16:0	−2.0		42.8	9.8	[145,148,149]
PC with branched branches					
16:1(3:1me2)2/16:1(3:1me2)2			26.3[m]	7.9	[546]
16:1(4:1me2)2/16:1(4:1me2)2			17.5[n]	7.1	[546]
16:1(4:1me3)2/16:1(4:1me3)2			18.5[p]	7.1	[546]
16:1(4:2me3)2/16:1(4:2me3)2			14.6[q]	7.9	[546]
16:1(4:1et2)2/16:1(4:1et2)2			9.8[r]	5.4	[546]

authors relate this behavior to the ability of the subject phosphatidylcholines to form the mixed interdigitated gel phase. They ascribe the thermal history dependent behavior to possible alteration in the size and/or structure of microdomains in the L_α phase [547]. Thus, it has been proposed that both exothermic peaks represent phase transitions from L_α to the mixed interdigitated gel phase but that they arise from different domains of L_α phase. It has been reported recently that low-temperature incubation produces morphological changes in certain mixed interdigitated lipid aggregates which are subsequently reflected in a differential solidification upon cooling from the liquid crystalline phase [626]. This kind of thermotropic behavior upon cooling is interesting, since it infers an ability of the lipid system to 'remember' its gel phase thermal prehistory after equilibration in the high temperature liquid crystalline

phase. A similar thermotropic behavior has been observed in hydrated 16:0/16:0 phosphatidylethanolamine (PE), which does not form the mixed interdigitated gel phase [559].

In Table 9, the phase transition parameters of mixed-chain 1,2-dialkyl, 1,2-alkyl-acyl, and 2,3-diacyl phosphatidylcholines are summarized. O-20:0/O-12:0 PC and its positional isomer O-12:0/O-20:0 PC both form the mixed interdigitated gel phase [360]. Thus, it has been concluded that the conformational inequivalence at the *sn*-1 and *sn*-2 positions is less pronounced in the ether-linked phosphatidylcholines as compared to the ester analogues, since 20:0/12:0 PC, but not 12:0/20:0 PC, forms the mixed interdigitated gel phase. The two platelet-activating factors, O-16:0/2:0 PC and O-18:0/2:0 PC, are shown to form micellar solutions upon chain-melting [370,384,385]. Since pure phosphatidylcholines are known for their ability to have a distinct preference for lamellar phases, this is a noteworthy example of a phosphatidylcholine that, under appropriate conditions, is in a non-lamellar state. Such behavior is related to the extreme shortness of the chain at the *sn*-2 position. The corresponding phosphatidylcholine is more akin in structure and thermotropic properties to the single chain lysolipids [633].

4.10. Chain-modified phosphatidylcholines

This subgroup includes the different kinds of branched-chain phosphatidylcholines (mono- and dimethyl-isobranched, methyl- and ethyl-anteiso-branched, etc.) and also phosphatidylcholines with ω-cyclohexyl, cyclopropyl, benzyl, and thio-functional groups in the chains. The relevant data for the linear branched phosphatidylcholines are summarized in Table 10, while data for other chain-modified phosphatidylcholines are included in Table 11.

The chain modified phosphatidylcholines are conveniently discussed in the context of an 'effective' chain length defined as the total number of carbon atoms in the main chain. For lipids with unbranched chains, the effective chain length is the total number of carbon atoms in the chain. For branched-chain lipids, the effective chain length equals the total number of carbon atoms in the chain overall minus those present in the branch or branches.

A comparison of the gel–liquid crystal phase transition temperatures for the methyl-isobranched, methyl-anteisobranched and the ω-tertiary-butyl phosphatidylcholines with those for the unbranched saturated diacyl phosphatidylcholines having the same effective chain length is presented in Fig. 11A. These data show clearly that chain modification lowers the

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Notes for Table 10:

[a] Considered to be a direct low-temperature gel–liquid crystal transition; a single exothermal at -40°C upon cooling is ascribed to a liquid crystalline–intermediate gel transition [48].

[b] Considered to be a direct low-temperature gel–liquid crystal transition; a single exotherm at -19.5°C upon cooling is ascribed to a liquid crystalline–intermediate gel transition [48].

[c] Considered to be a direct low-temperature gel–liquid crystal transition; a single exotherm at -5.2°C upon cooling is ascribed to a liquid crystalline–intermediate gel transition [48].

[d] Considered to be a direct low-temperature gel–liquid crystal transition; a single exotherm at 19.5°C upon cooling is ascribed to a liquid crystalline–intermediate gel transition [48].

[e] Transition observed only after prolonged incubation at low temperature.

[f] Transition from L_c-like gel phase to liquid crystalline phase.

[g] Dispersion in 50% (v/v) ethylene glycol in water.

[h] Predominantly lamellar at $T < 70$°C; predominantly cubic at $T > 80$°C [546].

[i] Predominantly lamellar with some cubic structures at $T > T_m$ [546].

[j] Predominantly lamellar at $T < 65$°C; predominantly cubic at $T > 85$°C [546].

[k] Subtransition at 4.6°C with ΔH strongly dependent on low-temperature storage, and a post-transition at 31.8°C ($\Delta H = 0.2$ kcal/mol) [93]; predominantly lamellar at $T < 25$°C, cubic at $30° < T < 45$°C, $H_{\|}$ at $T > 60$°C [546].

[m] Lamellar at $T < 60$°C; cubic at $T \sim 85$°C [546].

[n] Lamellar at $T < 25$°C, cubic (1a3d) at $25° > T > 50$°C, cubic (Pn3m) at $T > 70$°C [546].

[p] Predominantly lamellar at $T_m < 30$°C; cubic at $T > 40$°C; $H_{\|}$ when rapidly heated to 85°C [546].

[q] Lamellar only at $T < T_m$; cubic at $T = 15$°C; $H_{\|}$ at $T > 20$°C [546].

[r] Predominantly lamellar at $T_m < 20$°C; cubic at $20° < T < 30$°C; $H_{\|}$ at $T > 40$°C [546].

Table 11
Thermodynamic parameters of the phase transitions in fully hydrated phosphatidylcholines with cyclohexyl, cyclopropyl, benzyl, or thio-functional groups in the hydrocarbon chains

Lipid chains and backbone	Gel–gel	Gel–liquid crystal		References
	T [°C]	T [°C]	ΔH [kcal/mol]	
Cyclohexyl				
9:1ch9/9:1ch9		−6.8	4.4	[43]
10:1ch10/10:1ch10	−16.0, −11.0	−10.8	1.2	[43]
11:1ch11/11:1ch11		18.3	11.7	[43]
12:1ch12/12:1ch12	13.6, 14.5, 15.5, 15.8	16.0	6.3	[43]
13:1ch13/13:1ch13		34.3 ± 0.6	12.2 ± 1.4	[43,47,79,80]
14:1ch14/14:1ch14	26.0, 29.0, 33.0	34.1 ± 0.7	8.2 ± 0.6	[43,79,80,89]
15:1ch15/15:1ch15		46.3 ± 0.6	16.7 ± 0.7	[43,80]
16:1ch16/16:1ch16	43.2, 48.0	48.5	8.7	[43]
17:1ch17/17:1ch17		57.6	≥ 18[a]	[43]
18:1ch18/18:1ch18	55.3, 60.2	60.6	≥ 11[a]	[43]
Cyclohexyl methyl				
14:1ch-me2/14:1ch-me2		−36.1[c]		[546]
16:1ch-me2/16:1ch-me2		6.4[d]	7.9	[546]
18:1ch-me2/16:1ch-me2		24.5[d]	10.5	[546]
Cyclopropyl				
16:0/18:1cp(c)9		−10 – −20		[545]
17:1cp(c)9/17:1cp(c)9		−19.9		[49]
17:1cp(t)9/17:1cp(t)9		−0.3		[49]
19:1cp(c)9/19:1cp(c)9		−0.5		[49]
19:1cp(t)9/19:1cp(t)9		16.3		[49]
19:1cp(c)11/19:1cp(c)11		−3.5		[49]
19:1cp(t)11/19:1cp(t)11		14.0		[49]
19:1cp9/19:1cp9		−7.0		[152]
19:1cp11/19:1cp11		−7.0		[152]
Benzyl				
12:1benz2/12:1benz2		< −50[e]		[546]
14:1benz2/14:1benz2		−9.4[I]	5.6	[546]
16:1benz2/16:1benz2		18.5[g]	7.7	[546]
Thio				
16:1sh2/16:1sh2		26.0	5.1	[158]
16:1sh2/16:1sh2 (polymerized)		29.0[b]	1.7	[158]

[a]Because hydrolysis occurred during data collection, these values obtained from the first calorimetric run should be considered as minimum values [43].
[b]Transition type not specified.
[c]$H_{\|}$ at all temperatures measured (0–85°C) [546].
[d]Lamellar at $T < T_m$, $H_{\|}$ at $T > T_m$ [546].
[e]Lamellar at $T < 65$°C, predominantly cubic at $T > 80$°C [546].
[f]Predominantly lamellar at $T < 60$°C with some cubic structures at higher temperatures [546].
[g]Lamellar at all temperatures measured (0–85°C) [546].

transition temperature and that the degree to which they are lowered depends on the kind of branching and on the effective chain length. In addition, the T_m values of the phosphatidylcholines with branching at the penultimate carbon atom of the chains (iso-branched, ω-tertiary-butyl) show quite pronounced alternation for odd and even chain length lipids, while unbranched and anteisobranched species do not

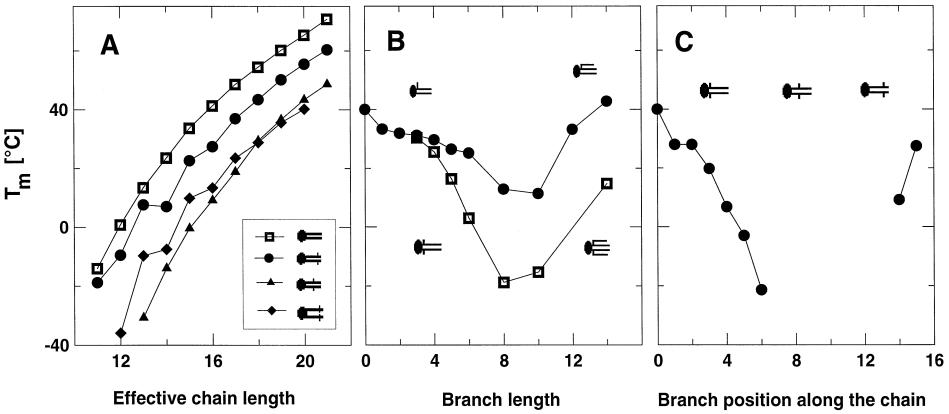

Fig. 11. Dependence of the chain melting transition temperature on (A) the effective chain length in unbranched (□), methyl-isobranched (●), ω-tertiary butyl (♦), and methyl-anteisobranched phosphatidylcholines (▲); (B) branch length at the C2 position of the hydrocarbon chain in 16:1(*n*:0)2/16:1(*n*:0)2 PC (□) and 16:1(*n*:0)2/O-16:0 PC (●); and (C) the position of the methyl branch in 16:1me(*n*)/16:1me(*n*) PC. Lipid notation is discussed in Appendix A. 16:1(*n*:0)2 indicates a fatty acyl chain 16 carbon atoms long with a single [1] modification at carbon number 2. In this case, it is a fully saturated alkyl branch of chain length *n*.

(an odd–even alternation is observed also for the ΔH values of the ω-tertiary-butyl species—see Table 10). The tendency of T_m and ΔH to show alternation has been correlated with chain tilting in the gel phase of the different kinds of branched and unbranched phosphatidylcholines [150].

In Fig. 11B, the transition temperature T_m is plotted as a function of branch length n at the α-carbon of the fatty acyl chains in 16:1(*n*:0)2/16:1(*n*:0)2 PC and 16:1(*n*:0)2/O-16:0 PC (notation is described in Appendix A and legend to Fig. 11). Introducing a single methyl group ($n = 1$) at this position on the chains reduces T_m by more than 10°C. This presumably is a result of a change in the packing mode of the lipids in the $L_{\beta'}$ and $P_{\beta'}$ gel phases to that of the interdigitated ( ) type [93,145]. Elongation of the branches by one, two, or three $-CH_2-$ units (short-chain branched species, $n \leq 4$ continues to lower T_m but the effect is relatively small. The chain-melting transition for these phosphatidylcholines is of the L_{β}^{int}–L_{α} type. A further increase in branch length (long-chain branched species, $n > 4$) has a biphasic effect on T_m with an initial decrease to a minimum value at about $n = 9$ (Fig. 11B). As branch length increases to $n > 9$, T_m increases which is attributed to a restoration of the non-interdigitated packing of chains in the gel phase ( ) [93,546].

The position of the methyl branch along the length of the acyl chains in 16:1me(*n*)/16:1me(*n*) PC also influences T_m in a biphasic manner (Fig. 11C). The origins of the stability variation is probably similar to that observed for variations in double bond position along the hydrocarbon chain as discussed above.

Recently, a noteworthy relationship between molecular structure and the phase behavior of branched chain phosphatidylcholines has been reported. Specifically, acyl chain modifications in the vicinity of the ester carbonyl induces non-lamellar phase formation in the generally lamellar phase-preferring phosphatidylcholines (Tables 10 and 11). Thus, substitution of moderately sized hydrophobic groups (methyl, ethyl, propyl, butyl, pentyl, isobutyl, isopentyl, sec pentyl, cyclohexyl methyl, etc.) at C2 (or Cα) of the fatty acyl chains of saturated diacyl phosphatidylcholines with chains 14-, 16-, and 18-carbon atom long has been shown to destabilize the lamellar phases and to promote formation of cubic and hexagonal phases [546]. Interestingly, increasing the effective chain length results in a stabilization of the lamellar phases and a suppression of the non-lamellar forming tendency.

As noted, a reduction in the gel–liquid crystal phase transition temperature relative to that of the unbranched saturated phosphatidylcholines occurs when sites of unsaturation are introduced into the acyl chains of phosphatidylcholines. Thus, for a given effective chain length, any modification imposed on the basic unbranched, saturated fatty acyl chains ef-

fects a decrease in T_m. Data accumulated to date suggest the following order in the propensity of different modifications to lower the transition temperature for phosphatidylcholines with an effective chain length of 18 carbons: unbranched saturated (highest transition temperature) < ω-cyclohexyl < methyl-anteisobranched < dimethyl-isobranched < methyl-iso-branched < *trans*-monounsaturated < *cis*-mono-unsaturated < *cis*-diunsaturated < *cis*-triunsaturated (lowest transition temperature). However, we note that the order of effectiveness may change with chain length. At this juncture, there is insufficient data available to evaluate this possibility reliably. Nonetheless, this type of information on chain modification effects should prove useful in rational lipid design for application in natural and reconstituted systems. Thus, by carefully engineering the length of the chain and its modification, a lipid with defined mesomorphism can be produced to order.

4.11. Head group-modified phosphatidylcholines

As a lipid class, the phosphatidylcholines are defined based on the nature of the α-glycero-phosphocholine backbone/head group combination. Thus, any modification to the head group gives rise to another lipid class. Nonetheless, we consider it appropriate to address phosphatidylcholine head group

Table 12
Thermodynamic parameters of the lamellar gel–liquid crystalline phase transition in fully hydrated, head group-modified phosphatidylcholine analogues

Lipid[a]		T [°C]	ΔH [kcal/mol]	References
Chains and backbone	Head group			
16:0/16:0	$P(CH_2)C$ (Fig. 4B-a, $n=1$)	38.2 ± 2.5	7.0	[407–409]
16:0/16:0	$P(CH_2)_2C$ (Fig. 4B-a, $n=2$)	37.0 ± 3.7	10.3	[407–409]
16:0/16:0	$P(CH_2)_3C$ (Fig. 4B-a, $n=3$)	39.9 ± 3.1	11.3	[407–409]
16:0/16:0	$P(CH_2)_4C$ (Fig. 4B-a, $n=4$)	39.2 ± 4.4	11.3	[407–409,411]
16:0/16:0	$P(CH_2)_5C$ (Fig. 4B-a, $n=5$)	40.8 ± 3.0	13.0	[407–409]
16:0/16:0	$P(CH_2)_6C$ (Fig. 4B-a, $n=6$)	40.7 ± 2.5	10.0	[407–409]
16:0/16:0	$P(CH_2)_7C$ (Fig. 4B-a, $n=7$)	40.7 ± 3.3	12.5	[407–409,412]
16:0/16:0	$P(CH_2)_8C$ (Fig. 4B-a, $n=8$)	39.3 ± 3.6	8.8	[407,409,412]
16:0/16:0	$P(CH_2)_9C$ (Fig. 4B-a, $n=9$)	36.6 ± 3.4	12.4	[407,409]
16:0/16:0	$P(CH_2)_{14}C$ (Fig. 4B-a, $n=14$)	46.3 ± 1.4	16.5	[407]
O-16:0/O-16:0	$P(CH_2)C$ (Fig. 4B-a, $n=1$)	43.5 ± 0.7		[414]
O-16:0/O-16:0	$P(CH_2)_4C$ (Fig. 4B-a, $n=4$)	45.0		[411]
2-16:0/3-16:0-CPENT	$P(CH_2)C$ (Fig. 4B-a, $n=1$)	49	18	[638]
2-16:0/3-16:0-CPENT	$P(CH_2)_2C$ (Fig. 4B-a, $n=2$)	38	7.5	[638,639]
2-16:0/3-16:0-CPENT	$P(CH_2)_3C$ (Fig. 4B-a, $n=3$)	38	6	[638]
2-16:0/3-16:0-CPENT	$P(CH_2)_4C$ (Fig. 4B-a, $n=4$)	41	7.5	[638]
2-16:0/3-16:0-CPENT	$P(CH_2)_5C$ (Fig. 4B-a, $n=5$)	43	5.5	[638]
2-16:0/3-16:0-CPENT	$P(CH_2)_6C$ (Fig. 4B-a, $n=6$)	43	8	[638]
2-16:0/3-16:0-CPENT	$P(CH_2)_7C$ (Fig. 4B-a, $n=7$)	42	6.5	[638]
14:0/14:0	PC:1(N × S) (Fig. 4B-d)	26.5		[179,643]
16:0/16:0	PC:1(N × S) (Fig. 4B-d)	44.5 ± 0.5		[179,642,643]
18:0/18:0	PC:1(N × S) (Fig. 4B-d)	60.5		[179,643]
18:1c9/18:1c9	PC:1(N × S) (Fig. 4B-d)	−24.5		[179,643]
16:0/16:0	(Rp)-PC:1(O × S) (Fig. 4B-b)	44.9	7.4	[498,644–646]
16:0/16:0	(Sp)-PC:1(O × S) (Fig. 4B-c)	45.0	7.1	[498,644–646]
16:0/16:0	(Rp + Sp)-PC:1(O × S)	44.8	6.8	[498,644–646,648]
16:0/16:0	PC:1(O × Se)	44.0		[651]
O-16:0/O-16:0	PC:1(-O) (Fig. 4B-e)	45.0	8.3	[649]
C-17:0/C-18:0	PC:1(me)C1 (Fig. 4B-f)	44.8	9.3	[259]
C-17:0/C-18:0	PC:1(et)N (Fig. 4B-g)	44.3	9.4	[259]

[a] Notation is described in Appendix A. See also Fig. 4.

modifications in this article so as to illustrate the sensitivity of mesophase behavior to changes in the chemical structure of this part of the lipid molecule.

Some of the modifications to the phosphatidylcholine head group studied to date include the addition of $-CH_2-$ groups between the bridging oxygen and the quaternary ammonium nitrogen of choline [407–414,638,639]. A summary of the relevant data is presented in Table 12. The phase behavior of a related class of lipids, the mono- and di-*N*-methylated phosphoethanolamine derivatives, which might be regarded as demethylated phosphatidylcholine analogues, have been reviewed previously [7].

Successive additions of $-CH_2-$ groups between the phosphate and quaternary ammonium in the head group of 16:0/16:0 PC (Fig. 4B-a) results in a non-monotonous change in the temperature and enthalpy of the gel–liquid crystalline phase transition (Fig. 12). This, together with data presented above, suggest that this part of the molecule does not participate directly in the melting process. An odd–even alternation in T_m and ΔH is observed as the number of methylenes separating the oxygen and nitrogen in choline increases from 2 to 11. It is proposed that the elongated head groups form a two-dimensional quasi-crystalline structure [407]. Interestingly, the T_m (and also ΔH) values for the 16:0/16:0 PC analogues with odd and even numbers of $-CH_2-$ groups in the head group lie on separate smooth curves (dashed lines in Fig. 12A). Such odd–even alternation is reminiscent of that seen before in several systems, most notably the saturated hydrocarbons [12].

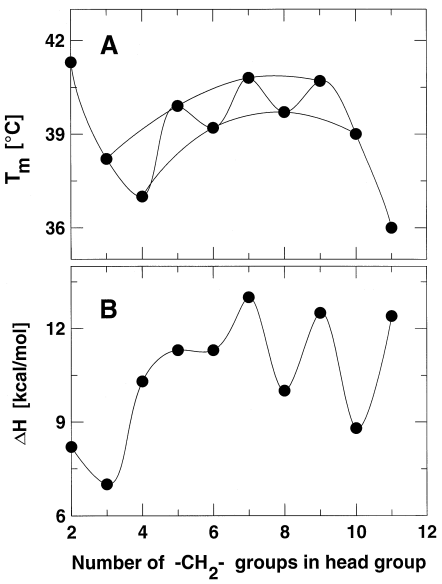

Fig. 12. Dependence of the chain melting transition temperature (A) and enthalpy change (B) on the number of methylene groups between the phosphate bridging oxygen and the quaternary ammonium nitrogen in the head group of 16:0/16:0 PC-analogues.

Thiophosphocholine represents another modification to the phosphocholine head group which involves the substitution of one of the unesterified phosphoryl oxygen atoms by a sulfur atom. Such a modification creates a chiral center at phosphorus (designated Rp or Sp) in addition to that at C2 in the glycerol backbone. The two different diastereomers of the thiophosphatidylcholines, (Rp)-PC:1(O × S) and (Sp)-PC:1(O × S), are shown in Fig. 4B-b,c. The two diastereomers, as well as a 1:1 mixture of the two, (Rp + Sp)-PC:1(O × S), differ in their gel phase polymorphism [498,644–647]. Both 16:0/16:0 (Sp)-PC:1(O × S) and 16:0/16:0 (Rp + Sp)-PC:1(O × S) display pretransitions at 43.7 and 43.8°C, respectively, and subtransitions at 22 and 21.7°C, respectively, similar to 16:0/16:0 PC. The 16:0/16:0 (Rp)-PC:1(O × S) compound displays either a direct lamellar subgel–liquid crystalline transition at 45.9°C (13.4 kcal/mol), when equilibrated at low temperature, or a lamellar gel–liquid crystalline transition at 44.9°C (7.4 kcal/mol), when not equilibrated (Ref. [645], Table 12).

Aqueous dispersions of a selenophosphocholine, 16:0/16:0 PC:1(O × Se), display a lamellar gel–lamellar liquid crystalline phase transition at 44°C ($\Delta T_{1/2} = 2$°C) (Table 12), just 2°C above that of the control compound, 16:0/16:0 PC [651].

Phosphatidylsulfocholines are phosphatidylcholine analogues with the trimethylammonium group replaced by a dimethylsulfonium moiety (Fig. 4B-d). The phosphatidylsulfocholines represent a major membrane component in certain marine diatoms [179]. A summary of the relevant data is included in Table 12. The chain melting transition temperatures of 14:0/14:0 PC:1(N × S), 16:0/16:0 PC:1(N × S) and 18:0/18:0 PC:1(N × S) are 4–5°C higher than the corresponding phosphatidylcholines. A pretransition is observed with 14:0/14:0 PC:1(N × S) at 24°C. No such pretransition is observed with either 16:0/16:0 PC:1(N × S) or 18:0/18:0 PC:1(N × S) [643]. In this

regard, therefore, the phosphatidylsulfocholines can be regarded as exhibiting phase behavior intermediate between that of the phosphatidylcholines and the phosphatidylethanolamines [643].

Aqueous dispersions of a phosphonocholine analogue of O-16:0/O-16:0 PC, O-16:0/O-16:0 PC:1(-O) (Fig. 4B-e), display a lamellar gel–liquid crystalline phase transition at a slightly elevated transition temperature (Table 12), and an enthalpy change and volume change (3.1%) close to that of the control compound, O-16:0/O-16:0 PC [649].

4.12. Phosphatidylcholine extracts from biological sources

In addition to the single, synthetic or natural and purified lipid species, lipid extracts from a variety of biological sources have been studied from the point of view of mesophase behavior [386–406]. The phosphatidylcholine extract subgroup in LIPIDAT consists of 88 records of which egg (whole and yolk) phosphatidylcholine makes up three quarters of the entries. The rest derive from chick embryo (liver, brain, and lung), soybean, and the rod outer segment of the retina. The average transition temperatures and enthalpy change values are listed in Table 13. The data show that most of the natural phosphatidylcholines have chain melting transition temperatures at or below 0°C. One exception is phosphatidylcholine from chick embryo lung which has a T_m of 21°C. This is not unexpected given that this particular lipid has a high content ($>40\%$) of 16:0/16:0 PC [386].

Table 13
Thermodynamic parameters of the gel–liquid crystalline phase transition in fully hydrated natural phosphatidylcholine extracts

Lipid	T [°C]	ΔH [kcal/mol]	References
Chick brain	-12.5	0.8	[386]
Chick liver	-23.0	2.1	[386]
Chick lung	21.0	1.7	[386]
Egg (whole)	1.8 ± 18.4		[66,260,387–398]
Egg yolk	-5.8 ± 6.5		[178,304,400,401]
Rod outer segment	19.6 ± 7.3		[405]
Soybean, hydrogenated	52		[398]

The hydrogenated soybean phosphatidylcholine transition temperature at 52°C is close to that of 18:0/18:0 PC (54.5°C, Table 1), reflecting the high percentage of 18-carbon phosphatidylcholines in soybean phosphatidylcholine [398].

All of the natural phosphatidylcholine extracts represent complex mixtures of individual lipid species which share a common α-glycerophosphocholine backbone and head group moiety. The variety exists at the level of the acyl chain component. For example, the major fatty acids in egg phosphatidylcholine are 16:0 (32%), 18:1 (30%), 18:2 (17%), 18:0 (16%), 20:4 (3%), and 16:1 (1%) [19]. One long term objective of the LIPIDAT database analysis project is to establish the underlying principles of lipid phase behavior as these relate to molecular structure and composition. With the principles and rules in hand, it should be possible to predict the mesophase properties of such a complex mixture as egg phosphatidylcholine from a knowledge of the identity and relative amounts of its constituent lipid species.

5. Aqueous medium additive effects

5.1. pH

The only physiologically relevant titrable group in the phosphatidylcholine molecule is the phosphate oxygen (Fig. 4). The phase stability of phosphatidylcholine is sensitive to its degree of protonation since it, in turn, determines the magnitude of the charge at the lipid/water interface. The phosphate oxygen titrates under very acid conditions, with a pK_a of ca. 1–2 (Ref. [17], see below). Accordingly, we find a wide pH range, certainly extending above pH 3, in which the protonation state of the lipid and, thus, its mesophase behavior, does not change appreciably. As noted, it is in this pH range that the various average transition temperatures and enthalpy change values were calculated. Below this pH, however, protonation occurs with the attendant changes in mesophase behavior (Table 14). The corresponding titration curves for the chain melting transition of the saturated diacyl and dialkyl phosphatidylcholines are shown in Fig. 13. An increase of 9–12°C in the transition temperature of the different phosphatidylcholine species oc-

curs upon acid titration below pH 3 (Table 14). The apparent pK value (pK_a) of the phosphate oxygen is a matter of some controversy with estimates of <1 [28], <1.5 [29], <2 [30], and <3 [27] having been reported. Unfortunately, a precise determination of this pK_a from the pH dependence of T_m is hardly possible since the increase in T_m upon acid titration does not level out even at pH ~ 0 (Fig. 13). In a recent study of the effect of pH on the increment in T_m of 16:0/16:0 PC induced by the incorporation of protonated stearylamine, a pK_a of 1.3 for the phosphate oxygen was obtained [534].

Table 14
Effect of pH on the lamellar gel–liquid crystalline phase transition temperature of fully hydrated phosphatidylcholines and a phosphatidylcholine head group analogue

Lipid		pH	T [°C]	References
Chains and backbone	Head group			
14:0/14:0	PC	0	36.0	[363]
		1	32.0	[30]
		1.7	27.0	[30]
		2.2	26.0	[30]
		3.2	25.0	[30]
		6	24.0	[30]
		8	23.0	[363]
		11	23.6	[490]
		12	23.5 ± 0.5	[30,362]
		13	23.5 ± 0.5	[30,363]
16:0/16:0	PC	0	50.0	[363]
		1	49.0 ± 1.0	[30,379]
		1.5	46.0	[30]
		2	43.5	[30]
		2.7	42.0	[527]
		3	42.5	[30]
		3.7	42.2	[30]
		7	42.0	[30]
		8	42.0	[363]
		11	41.8	[30]
		13	42.0	[363]
18:0/18:0	PC	1	64.0	[245]
		7	55.0	[245]
		13	55.0	[245]
18:0/18:0	$P(CH_2)_2C$[a]	1	63.0	[245]
		7	54.0	[245]
		13	54.0	[245]
O-14:0/O-14:0	PC	0	39.0	[363]
		8	28.5	[363]
		13	28.5	[363]
O-16:0/O-16:0	PC	0	54.0	[363]
		8	43.5	[363]
		13	43.5	[363]

[a] Notation is described in Appendix A.

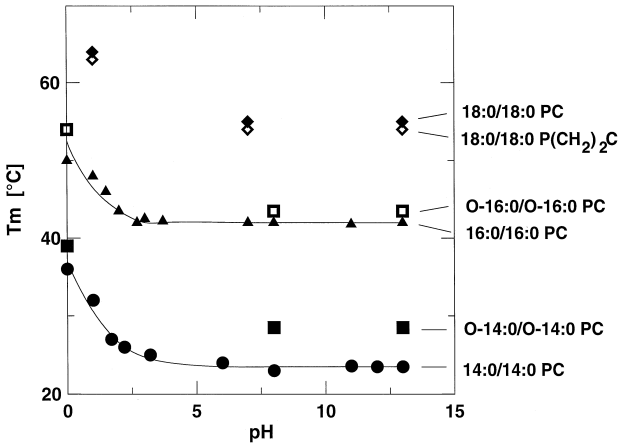

Fig. 13. pH-dependence of the lamellar gel–liquid crystalline phase transition temperature in fully hydrated, saturated diacyl and dialkyl phosphatidylcholines and a phosphatidylcholine head group analogue: (●) 14:0/14:0 PC; (■) O-14:0/O-14:0 PC; (▲) 16:0/16:0 PC; (□) O-16:0/O-16:0 PC; (◇) 18:0/18:0 $P(CH_2)_2C$ (this modification corresponds to two additional methylene units in the head group between the phosphate oxygen and the quaternary ammonium nitrogen); (◆) 18:0/18:0 PC.

The observed effect of phosphatidylcholine phosphate group protonation on the transition temperature is not consistent with current concepts of membrane electrostatics. Purely electrostatic considerations suppose that the mutual repulsion of like charged polar groups would favor a lateral expansion in the plane of the membrane, thereby destabilizing the more ordered low-temperature gel phase. Consequently, the gel–liquid crystalline phase transition temperature is expected to decrease as the head group is rendered net positively charged upon acid titration [18]. This is quite the opposite to what is actually observed in the case of phosphatidylcholine (Fig. 13). A possible explanation involves favorable hydrogen bond formation of the PO...HOP type that develops upon acid titration and that more than compensates for the unfavorable like charge repulsion that should accompany phosphate group protonation.

5.2. Salts

In this section, we address the effects of various salt additives on phosphatidylcholine mesophase be-

Table 15
Thermodynamic parameters of the phase transitions in fully hydrated phosphatidylcholines in the presence of different salts

Lipid chains and backbone	Salt	Pretransition		Main transition		References
		T [°C]	ΔH [kcal/mol]	T [°C]	ΔH [kcal/mol]	
12:0/12:0	–	−16.0		0.0		[71]
	3 M NaCl	−10.0		1.0		[71]
	6 M NaCl	0.0		4.0		[71]
14:0/14:0	–	14.1	1.2	23.6 ± 1.5	6.0 ± 2.4	[587], Table 1
	1 M GuSCN			19.8		[587]
	1 M KSCN			21.1[a]	7.23	[176]
	1 M NaI			21.2		[587]
	1 M LiCl	14.1		22.8		[587]
	1 M GuCl	8.2		23.2		[587]
	1 M NaBr	11.0		23.6		[587]
	1 M TlAc	14.2		23.8		[587]
	1 M CsCl	13.6		23.9		[587]
	1 M KCN	13.9		24.1		[587]
	1 M NaCNO	14.5		24.1		[587]
	1 M KCl	15.5		24.3		[587]
	1 M $(CH_3)_4N^+Cl$	16.1		24.3		[587]
	1 M RbCl	15.1		24.5		[587]
	1 M NaAc	17.5		24.5		[587]
	1 M PbAc	14.6		24.6		[587]
	1 M $CdCl_2$	16.9		24.6		[587]
	1 M NaCl	16.1		24.7		[587]
	1 M $CuSO_4$	18.3		24.8		[587]
	1 M NaF	16.8		25.1		[587]
	1 M $AgNO_3$	17.3		25.6		[587]
	1 M $MgCl_2$	19.6		25.7		[587]
	1 M NH_4Cl	17.1		26.2		[587]
	1 M $CaCl_2$			28.6		[587]
	3 M NaCl	17.5		24.0		[71]
	6 M NaCl	21.0		25.0		[71]
16:0/16:0		34.4 ± 2.5	1.3 ± 1.0	41.3 ± 1.8	8.2 ± 1.4	Table 1
	1 M $(C_2H_5)_4N^+Br$			35.0		[593]
	1 M $(CH_3)_4N^+Cl$			37.0		[593]
	1 M $NaClO_4$			39.0		[622]
	1 M NaSCN			39.5		[622]
	1 M NaI			40.0		[622]
	1 M KI			40.0	8.2	[595]
	1 M CdOAc			40.4	10.0	[595]
	1 M $CsNO_3$			40.5	10.3	[598]
	1 M $NaNO_3$			40.5	9.7	[598]
	1 M $LiNO_3$			40.8	10.3	[598]
	1 M KNO_3			40.9	9.1	[598]
	1 M KSCN			41.0 ± 2.0[a]	9.6 ± 0.8	[176,594,595, 599,614]
	1 M $SrCl_2$			41.2	6.8	[595]
	1 M RbCl			41.4	8.9	[598]
	1 M NaCl	36.4 ± 1.2	0.88 ± 0.4	41.9 ± 0.8	7.7 ± 2.2	[593,594,596,598]
	1 M $LaCl_3$			42.0	7.7	[595]
	1 M CsCl	35.2 ± 1.5	0.88 ± 0.4	42.2 ± 1.0	8.6 ± 1.0	[589,590,598, 594,596]
	1 M LiCl	38.9 ± 0.5	0.94	42.2 ± 1.9	7.2 ± 0.8	[594–596,598,600]

Table 15 (continued)

Lipid chains and backbone	Salt	Pretransition		Main transition		References
		T [°C]	ΔH [kcal/mol]	T [°C]	ΔH [kcal/mol]	
	1 M $CdSO_4$			42.4	7.6	[595]
	1 M NH_4Cl	36.9 ± 3.0	0.51 ± 0.06	42.4 ± 1.1	7.2 ± 0.8	[594,596]
	1 M KBr	34.0 ± 2.0	0.72	42.4 ± 1.3	6.5	[594,599]
16:0/16:0	1 M KCl	35.1 ± 1.0	0.6 ± 0.05	42.4 ± 1.3	7.4 ± 1.3	[594–596,598,599]
	1 M $Cd(NO_3)_2$			42.6, 44.0	4.68, 2.3	[595]
	1 M CdI_2	38.5	0.64	43.0	3.8	[595]
	1 M $MgCl_2$			43.1	7.0	[595]
	1 M $BaCl_2$	37.6 ± 2.1	0.61 ± 0.04	43.1 ± 1.0	6.8 ± 1.0	[594–596]
	1 M KOAc	36.6	1.1	43.2 ± 1.8	7.7 ± 1.0	[594–596]
	1 M $CaCl_2$			44.8	7.5	[595]
	1 M $FeCl_3$			48.8	7.4	[595]
	1 M Ca^{2+}			53.0		[597]
	1 M $CdCl_2$			57.0	9.5	[595]
16:0/16:0		34.4 ± 2.5	1.3 ± 1.0	41.3 ± 1.8	8.2 ± 1.4	Table 1
	3 M $RbNO_3$			40.9	10.9	[598]
	3 M $NaNO_3$			41.1		[598]
	3 M $LiNO_3$			41.3		[598]
	3 M KNO_3			41.4	10.9	[598]
	3 M $NaClO_4$			41.4		[598]
	3 M RbCl	39.0		42.9	9.4	[598]
	3 M KCl	39.3		42.9	9.8	[598]
	3 M CsCl	39.5		43.0	9.8	[598]
	3 M LiCl			43.1	9.8	[598]
	3 M NaCl	38.0		43.7 ± 0.7	8.7 ± 0.8	[71,589,590,598]
	3 M KI			43.7	9.3	[595]
	3 M $LaCl_3$			47.2	5.6	[595]
	3 M $CaCl_2$			64.9	11.3	[595]
	6 M RbCl				9.3	[598]
	6 M NaCl				9.5	[598]
	7 M RbCl				8.3	[598]
	7 M CsCl				10.0	[598]
	7 M LiCl				10.2	[598]
	8 M LiCl				10.7	[598]
	8 M CsCl				10.8	[598]
	9 M LiCl				10.7	[598]
	10 M LiCl				9.5	[598]
	10 M CsCl				11.5	[598]
	11 M LiCl				9.1	[598]
18:0/18:0		50.0	1.4 ± 0.4	54.0	10.4 ± 1.6	[71], Table 1
	0.6 M $NaClO_4$			52.0		[207]
	1 M KSCN	53.3[a]	2.05	56.1[b]	8.23	[176]
	3 M NaCl	52.0		57.0		[71]
	6 M NaCl	54.0		58.0		[71]
18:119/18:119				10.0		[316]
	1 M $MnCl_2$			14.0		[316]
	2 M $MnCl_2$			21.0		[316]
	3 M $MnCl_2$			22.0		[316]

[a] L_c–L_β^{int} transition [176].
[b] L_β^{int}–L_α transition [176].

Table 16
Temperature of the gel–liquid crystalline transition in small unilamellar vesicles of 16:0/16:0 PC in the presence of different salts (data from Ref. [589])

Salt	T_m [°C]
None	37.0
CsCl	
1 M	35.5
2 M	34.5
3 M	33.5
LiCl	
1 M	36.0
2 M	34.0
3 M	33.5
NaCl	
1 M	35.5
2 M	34.5
3 M	33.0
KCl	
1 M	35.5
2 M	34.0
3 M	[a]

[a]Transition too broad to determine T_m.

havior at concentrations above 0.1 M. Below this concentration limit, most salt effects are relatively insignificant. A representative selection of the phosphatidylcholine subgroup that has been studied under conditions of high salt concentration is included in Table 15. Generally, two kinds of salts can be distinguished depending on whether they increase or decrease the pretransition and the chain melting transition temperatures. A systematic study of the effect of monovalent ions on the phase behavior of 16:0/16:0 PC established that all alkali chloride salts increase the temperature of the pretransition and the main transition, with a gross correlation between the effect and the $(\text{charge})^2/\text{radius}$ value of the cations. In contrast, alkali nitrates and perchlorates do not have a significant effect on the transition temperatures of 16:0/16:0 PC [598]. The disparate effects of the different salts on lipid mesophase behavior have been interpreted as a manifestation of the so-called Hofmeister effect [22,603,627]. This relates to the differential ability of solutes to modify water structure [602]. In turn, this impacts on the aqueous/lipid interface which, depending on the character of the solute, can alter the relative stabilities of the various lyotropic mesophases [7,22,602,603,627]. On the basis of the available data, no systematic effect of salts on phase transition enthalpy has been identified. A recent investigation has shown that the cooperative unit of the chain melting transition of 16:0/16:0 PC increases from 109 to 149 as NaCl concentration is raised from 0 to 3 M [590]. Further, 1 M KSCN has been reported to produce chain interdigitation in the gel phase of 16:0/16:0 PC [599].

While sodium chloride increases the transition temperature of 16:0/16:0 PC multilayers at the rate of 0.6–0.7°C M^{-1}, the reverse effect is observed with sonicated unilamellar vesicles of the same lipid [589,590]. Thus, 3 M NaCl decreased the T_m of 16:0/16:0 PC SUVs from ca. 38°C to 33°C [589]. A similar effect is seen for other chloride salts, with the magnitude of the effect decreasing in the following order: $Cs^+ < Li^+ < Na^+ < K^+$ (Table 16). These data have been discussed in terms of ion-induced perturbations of either electrostatic interactions or of the hydrogen bond network in the polar head group region of the lipid bilayer. The different radii of curvature in multilamellar as opposed to small unil-

Table 17
Thermodynamic parameters of the gel–liquid crystalline phase transition in fully hydrated 16:0/16:0 PC dispersed in 0.20 M saccharide solutions (data from Ref. [591])

Saccharide	T [°C]	ΔH [kcal/mol]
None	41.7 ± 0.1	7.22 ± 0.17
Monosaccharides		
Arabinose	41.6 ± 0.1	6.61 ± 0.40
Ribose	41.6 ± 0.1	5.57 ± 0.36
Xylose	41.7 ± 0.1	5.86 ± 0.37
Glucose	41.8 ± 0.1	5.07 ± 0.32
Fructose	41.7 ± 0.1	6.19 ± 0.32
Galactose	41.8 ± 0.1	4.87 ± 0.06
Mannose	41.7 ± 0.1	4.93 ± 0.39
Rhamnose	41.6 ± 0.1	5.66 ± 0.23
Disaccharides		
Sucrose	41.8 ± 0.1	4.46 ± 0.02
Lactose	41.8 ± 0.1	6.77 ± 0.56
Trisaccharides		
Raffinose	41.8 ± 0.1	5.05 ± 0.19

Table 18
Thermodynamic parameters of the gel–liquid crystalline phase transition in fully hydrated 16:0/16:0 PC in the presence of amino acids at 1:9 (mol/mol) amino acid/lipid ratio (data from Ref. [592])

Amino acid	T [°C]	ΔT [°C]	ΔH [kcal/mol]	$\Delta\Delta H$ [kcal/mol]
None	41.7		9.62	
Lysine	40.7	−1.0	6.74	−2.88
Tryptophan	40.7	−1.0	7.95	−1.67
Arginine	40.8	−0.9	9.53	−0.09
Tyrosine	40.9	−0.8	9.11	−0.51
Valine	41.1	−0.6	9.55	−0.07
Threonine	41.2	−0.5	9.46	−0.16
Glycine	41.2	−0.5	9.58	−0.04
Cysteine	41.3	−0.4	9.62	0.00
Ornithine	41.4	−0.3	9.41	−0.21
Histidine	41.4	−0.3	9.51	−0.11
Serine	41.5	−0.2	9.62	0.00
Alanine	41.6	−0.1	9.60	−0.02
Proline	41.7	0.0	10.02	0.40
Asparagine	41.7	0.0	9.60	−0.02
Phenylalanine	41.8	0.1	9.37	−0.25
Glutamic acid	42.5	0.8	–	

amellar vesicles is considered to play a role in the differential response of these two aggregate types to added salt [589,590].

5.3. Saccharides, amino acids

Systematic studies of how saccharides and amino acids modulate the chain melting transition parameters of phosphatidylcholines are few. Interest in these additives stems from their possible use as cryo- and lyoprotectants. One such study concerns 16:0/16:0 PC [591,592] and the relevant data are summarized in Tables 17 and 18, respectively. Saccharides at a concentration of 0.2 M do not produce a measurable change in the transition temperature, but do decrease the transition enthalpy (Table 17). Of the 16 amino acids studied, only lysine and tryptophan have any significant effect. Both increase the transition temperature by 1°C when included at the level of 10 mol% (1 amino acid per 9 lipid molecules) and decrease the enthalpy by more than 10% (Table 18). Detailed

Table 19
Change in the thermodynamic parameters of the phase transitions in fully hydrated 16:0/16:0 PC induced by increasing concentration trehalose, sucrose, and proline[a]

Additive trehalose	Subtransition		Pretransition		Main transition		References
	ΔT [°C]	$\Delta\Delta H$ [kcal/mol]	ΔT [°C]	$\Delta\Delta H$ [kcal/mol]	ΔT [°C]	$\Delta\Delta H$ [kcal/mol]	
Trehalose							
Trehalose/lipid ratio, [mol/mol]							
0.074	0.2	0.12	0.2	0.1	0.1	−0.23	[453]
0.148	0.2	0.39	0.3	0	0.2	0.24	[453]
0.296	0.3	0.34	0.5	0	0.3	−0.31	[453]
0.444	0.4	−0.26	0.6	0	0.4	−0.45	[453]
0.592	0.4	0.20	0.9	−0.1	0.4	−0.33	[453]
0.740	0.8	0.84	1.6	0.1	0.7	0.34	[453]
Sucrose							
1.0 M	0.4		3.0		1.4		[22,627]
1.5 M	0.4		5.0		2.0		[22,627]
2.0 M	0.4		6.6		2.7		[22,627]
2.5 M	0.4		9.5		3.5		[22,627]
Proline							
1 M	2.2		2.2		0.6		[458,627]
3 M	5.6		6.8		1.9		[458,627]
5 M	10.2		[b]		6.8[b]		[458,627]

[a] Differences are calculated as values observed with additive minus values observed without additive.
[b] Direct L_β–L_α transition [458].

studies of 16:0/16:0 PC transition parameter changes at different concentrations of the disaccharides trehalose and sucrose, and the imino acid proline show that the pretransition and main transition temperatures increase in all cases, and that the former is the more sensitive of the transitions to added solutes (Table 19).

5.4. Alcohols

Data concerning the influence of a variety of low- and high-molecular weight organic additives such as alcohols, polyols, alkanes, ethyleneglycol, polyethyleneglycols, stearylamine, methylsulfoxides, etc., on the phase behavior of hydrated phosphatidylcholines are presented in numerous studies, the majority of which are included in LIPIDAT. A detailed description of each is beyond of the scope of this review. Here, we examine the effect of ethanol on the phase behavior of hydrated 16:0/16:0 PC (Fig. 14). Interest in ethanol effects on lipid membranes arises because of its high solubility in apolar solvents and in water, it is an important component in the diet of certain individuals, and because of its powers of inebriation and addiction.

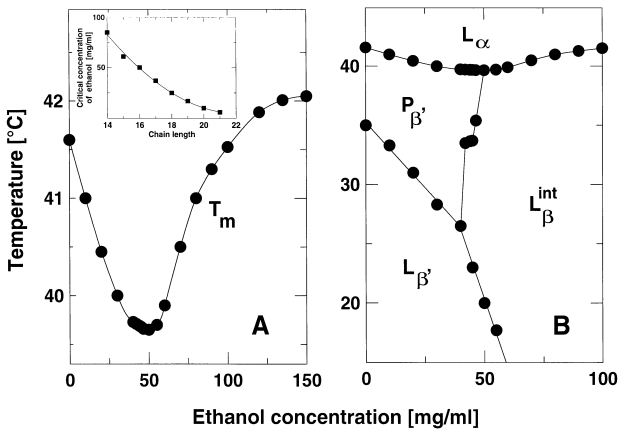

Fig. 14. Dependence of the phase behavior of hydrated 16:0/16:0 PC on ethanol concentration in the dispersing medium: (A) chain melting transition temperature as a function of ethanol concentration (data from Ref. [601]). Inset, threshold ethanol concentration required for interdigitated gel phase formation (see text) as a function of chain length (in units of number of carbon atoms per chain) for saturated diacyl phosphatidylcholines (data from Ref. [101]); (B) temperature-composition phase diagram for the 16:0/16:0 PC/aqueous ethanol system (data from Ref. [601]).

Table 20
Minimum alcohol concentration that induces complete interdigitation of the gel phase in fully hydrated 16:0/16:0 PC

Alcohol	Concentration [mM]	References
Methanol	2750 ± 350	[615,629]
Ethanol	1100 ± 100	[615]
1-Propanol	365 ± 50	[615,629,631]
1-Butanol	150 ± 42	[615,630]
2-Butanol	130 ± 20	[615]
1-Pentanol	48 ± 18	[615]
2-Pentanol	75 ± 10	[615]
3-Pentanol	70 ± 10	[615]
1-Hexanol	30 ± 28	[615]
2-Hexanol	42 ± 10	[615]
3-Hexanol	42 ± 25	[615]
1,2-Pentanediol	240 ± 100	[615]
1,2-Hexanediol	100	[615]

Ethanol has a biphasic effect on the main phase transition temperature of 16:0/16:0 PC multilamellar arrays. At low concentrations (< 50 mg/ml), increasing the ethanol concentration induces an almost linear decrease in T_m. This effect is attributed to a preferential partitioning of ethanol into the liquid crystalline rather than the low-temperature gel phase [101]. At higher ethanol concentrations (> 50 mg/ml), there is a reversal of the effect, and T_m increases to ~ 42°C, which is slightly above the T_m of 16:0/16:0 PC observed in the absence of ethanol. The effect is nonlinear and saturates at ethanol concentrations of ca. 150 mg/ml. A further increase in ethanol concentration results in a steady decrease in T_m [634]. The minimum in T_m at 50 mg/ml corresponds to a triple point in the temperature/composition phase diagram (Fig. 14B). At temperatures just below the triple point, the $P_{\beta'}$ phase is observed at low ethanol concentrations and is replaced by an interdigitated gel phase L_β^{int} at high ethanol concentrations [604]. Thus, an L_β^{int}–L_α transition is observed at ethanol concentrations in the 60–100 mg/ml range. Similar biphasic curves of T_m vs. ethanol concentration have been observed for other saturated diacyl phosphatidylcholines with chains ranging from 14–21 carbon atoms long [101]. The minimum ethanol concentration needed for interdigitated gel phase formation decreases with chain lengths (inset in Fig. 14A).

Other short-chain alcohols have been shown to induce chain interdigitation in the gel phase of phos-

phatidylcholines. The minimum concentration of these assorted alcohols required to induce complete interdigitation in the gel phase of 16:0/16:0 PC is given in Table 20.

Alcohols are able to induce interdigitation not only in multilamellar but also in unilamellar vesicles of 16:0/16:0 PC [616–618]. The alcohol concentration necessary for chain interdigitation increases as vesicle size decreases [616,617].

According to a recently proposed structural model for alcohol induced interdigitation in phosphatidylcholine, two alcohol molecules pack methyl end-to-

Table 21
Thermodynamic parameters of the phase transitions in dry and partially hydrated phosphatidylcholines

Lipid chains and backbone	Water content	Transition type	T [°C]	ΔH [kcal/mol]	References
12:0/12:0	4.7% (w/w)	L_c–L_α	44.5		[415]
14:0/14:0	monohydrate	L_c–L_α	61.0		[235]
	dry	L_c–L_α	87.5		[235]
	dry	melting (l.c.–isotropic)	236.0		[47]
16:0/16:0	trihydrate	gel–l.c.	66.3 ± 1.5		[417,449,450]
	dihydrate	gel–l.c.	75.6 ± 3.8		[235,357,444,455–459]
	monohydrate	powder–aggregated crystal	100		[432]
		aggregated crystal–isotropic	130		[432]
		isotropic–spherulites	170		[432]
	dry	gel–l.c.	99.3 ± 3.3		[235,434,444,455,456,621]
		melting (l.c.–isotropic)	235		[47]
18:0/18:0	monohydrate	L_c–L_α	83.3 ± 2.9	7	[235,258,425]
	dry	L_c–L_α	101		[235]
23:0/23:0	dry	L_c–centered rectangular + $H_{\|}$	112	12.4	[350]
O-14:0/O-14:0	10% (w/w)	gel–l.c.	53.0		[421]
O-16:0/O-16:0	4.8% (w/w)	L_β–L_α	74.2	5.6	[376]
	10% (w/w)	L_β–L_α	62.0	6.8	[376]
8:0/18:0	20% (w/w)	mxd int gel–L_α	11.1	6.8	[36]
O-16:0/16:0	12% (w/w)	L_β–L_α	44.0		[365]
16:0/18:1c9	dry	gel–l.c.	68		[116,130]
16:0/18:2c9,12	dry	gel–l.c.	37		[116]
18:1c9/18:1c9	dihydrate	gel–l.c.	46.0 ± 2.0		[45,116]
	dry	gel–l.c.	62.5		[45]
18:2c9,12:18:2c9,12	dihydrate	gel–l.c.	25.5 ± 2.1		[45,116]
	dry	gel–l.c.	48.0		[45]
18:3c9,12,15/18:3c9,12,15	dihydrate	gel–l.c.	20.0		[45]
	dry	gel–l.c.	44.0		[45]
23:2y10,12/23:2y10,12	dry	L_c–primitive rectangular + L_α	52.7	22.9	[350]
27:2y17,19/27:2y17,19	dry	*n*	63.7	29	[357]
27:2y6,8/27:2y6,8	dry	*n*	74.8	30	[357]
11:1ch1/11:1ch1	dry	melting (l.c.–isotropic)	230.0		[47]
13:1ch1/13:1ch1	dry	melting (l.c.–isotropic)	230.0		[47]
2-18:0-lyso	10% (w/w)	*n*	62.2	6.8	[341]
	20% (w/w)	*n*	51.5	6.4	[341]
	30% (w/w)	*n*	43	6.4	[341]
Egg	dry	L_c–L_α	38.5 ± 0.7		[444,468]
		L_α–cubic	84		[468]
		cubic–neat	110		[468]
		melting (l.c.–isotropic)	231		[468]
Soybean	dry	crystal melting	212		[469]
	2–7% (w/w)	*n*–cubic	57.5		[469]
		cubic–$H_{\|}$	128		[469]
		$H_{\|}$–isotropic fluid	235		[469]

methyl end with the two hydrocarbon chains of a single phosphatidylcholine molecule. This model produces a polar/apolar interface composed of phosphatidylcholine backbones and head groups and alcohol hydroxyl groups [619].

6. Dry and partially hydrated phosphatidylcholines

Data concerning the phase transitions in dry and partially hydrated phosphatidylcholines [415–469] are reported in Table 21. A high-temperature melting transition to the fluid isotropic phase is reported for most of the dry species. In addition, the majority of dry PCs undergo either a crystal polymorphic change or a gel–liquid crystal transition below the melting temperature (Table 21).

Data concerning the phase behavior of phosphatidylcholines at different levels of hydration up to and above full hydration are included in the numerous published temperature/composition phase diagrams of phosphatidylcholine/water systems. They

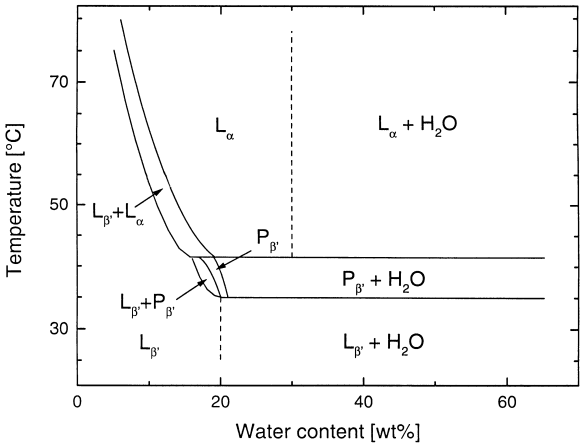

Fig. 15. Schematic temperature/composition phase diagram of the 16:0/16:0 PC/water binary system (data from Refs. [438,443,451,455,576]).

Table 22
Index to published temperature–composition phase diagrams of phosphatidylcholine/water and phosphatidylcholine/non-aqueous lyotrope mixtures

Lipid	Lyotrope	References
8:0/8:0 PC	H_2O	[579–581]
8:0/18:0 PC	H_2O	[36][a]
10:0/18:0 PC	H_2O	[36][a]
12:0/12:0 PC	H_2O	[566]
14:0/14:0 PC	H_2O	[418,422,565–567,569,571,573–575]
16:0/16:0 PC	H_2O	[436,442,445,451,452,455,562–564,566,568,570,576,635]
DL-16:0/16:0 PC	H_2O	[443]
16:0/18:1c9 PC	H_2O	[116][a]
16:0/18:2c9,12 PC	H_2O	[116][a]
18:0/18:0 PC	H_2O	[566]
18:1c9/18:1c9 PC	H_2O	[560,578][a]
18:2c9,12/18:2c9,12 PC	H_2O	[116][a]
18:3c9,12,15/18:3c9,12,15 PC	H_2O	[116][a]
Diacyl PC (n = 12–19 C atoms)	H_2O	[577]
Egg (whole) PC	H_2O	[468,571,572,575]
Egg yolk PC	H_2O	[561]
O-16:0/16:0 PC	H_2O	[367][a]
O-16:0/O-16:0 PC	H_2O	[374,466][a]
14:0/14:0 PC	D_2O	[569]
16:0/16:0 PC trihydrate	glycerol	[450]
18:1c9/18:1c9 PC	formamide	[560]
18:1c9/18:1c9 PC	methylformamide	[560]
18:1c9/18:1c9 PC	dimethylformamide	[560]

[a]Not a bona fide phase diagram, with defined phases and phase boundaries. Diagram presents transition midpoint temperature as a function of composition.

Table 23
Effect of pressure on the phase transition temperatures of fully hydrated phosphatidylcholines

Lipid chains and backbone	Pressure [bar]	Transition type	T [°C]	References
14:0/14:0	150	$P_{\beta'}-L_{\alpha}$	27.0	[540]
	200	$P_{\beta'}-L_{\alpha}$	31.0	[543]
	210	$P_{\beta'}-L_{\alpha}$	30.0	[544]
	400	$L_{\beta'}-P_{\beta'}$	19.0	[542]
		$P_{\beta'}-L_{\alpha}$	35.0	[543]
	600	$P_{\beta'}-L_{\alpha}$	38.0	[543]
	650	$P_{\beta'}-L_{\alpha}$	40.0	[544]
	700	$P_{\beta'}-L_{\alpha}$	40.0	[121]
	760	$P_{\beta'}-L_{\alpha}$	43.0	[390]
	800	$P_{\beta'}-L_{\alpha}$	43.0	[543]
	1000	$L_{\beta'}-P_{\beta'}$	24.0	[542]
		$P_{\beta'}-L_{\alpha}$	45.0	[543]
	1100	$P_{\beta'}-L_{\alpha}$	50.0	[544]
	1500	$P_{\beta'}-L_{\alpha}$	60.0	[544]
	1800	$L_{\beta'}-P_{\beta'}$	30.0	[542]
		$P_{\beta'}-L_{\alpha}$	60.0	[121]
	3100	GIII–$L_{\beta'}$	29.0	[542]
		$L_{\beta'}-P_{\beta'}$	40.0	[542]
		$P_{\beta'}-L_{\alpha}$	81.0	[542]
	4000	GIII–$P_{\beta'}$	50.0	[542]
16:0/16:0	25.2	$P_{\beta'}-L_{\alpha}$	42.0	[539]
	44.6	$P_{\beta'}-L_{\alpha}$	42.4	[539]
	69.9	$P_{\beta'}-L_{\alpha}$	43.1	[539]
	100.3	$P_{\beta'}-L_{\alpha}$	44.1	[539]
	150	$P_{\beta'}-L_{\alpha}$	45.0	[540]
	300	$L_{\beta}-P_{\beta'}$	36.5	[542]
		$P_{\beta'}-L_{\alpha}$	48.0	[541]
	760	$L_{\beta}-P_{\beta'}$	40.0	[542]
		$P_{\beta'}-L_{\alpha}$	60.0	[390]
	900	$L_{\beta}-P_{\beta'}$	42.0	[542]
		$P_{\beta'}-L_{\alpha}$	63.0	[121]
	1900	GIII–$L_{\beta'}$	30.0	[542]
		$L_{\beta}^{int}-P_{\beta'}$	66.0	[542]
		$P_{\beta'}-L_{\alpha}$	81.0	[542]
	2000	$L_{\beta'}-L_{\beta}^{int}$	51.0	[542]
	2050	$P_{\beta'}-L_{\alpha}$	85.0	[541]
	2250	$L_{\beta'}-L_{\beta}^{int}$	45.0	[121]
	3760	$L_{\beta}^{int}-L_{\alpha}$	110.0	[541]
O-16:0/O-16:0	500	$L_{\beta}^{int}-P_{\beta'}$	50.0	[638]
		$P_{\beta'}-L_{\alpha}$	58.0	[638]
	1000	$L_{\beta}^{int}-P_{\beta'}$	65.0	[638]
		$P_{\beta'}-L_{\alpha}$	68.0	[638]
	1300	$L_{\beta}^{int}-L_{\alpha}$	74.5	[638]
	1750	$L_{\beta}^{int}-L_{\alpha}$	82.5	[638]
16:0/18:1c9	700	$L_{\beta}-L_{\alpha}$	10.0	[121]
	2000	$L_{\beta}-L_{\alpha}$	38.0	[121]
18:119/18:119	1250	$L_{\beta}-L_{\alpha}$	34.0	[121]

refer both to pure synthetic phosphatidylcholines and to phosphatidylcholine extracts from biological sources. An index to the published phase diagrams for these systems is given in Table 22. For completeness, references to phase diagrams of phosphatidylcholine/non-aqueous solvent (such as glycerol, formamide, etc.) systems are also included in the table. A generic temperature/composition phase diagram of the 16:0/16:0 PC/water system based on data from Refs. [438,443,451,455,576] is shown on Fig. 15. A detailed description of phosphatidylcholine phase miscibility is beyond the scope of this review and of LIPIDAT. It is, however, within the purview of LIPIDAG—a phase diagram database [2,3]. In LIPIDAG, data are presented in the form of temperature–composition and temperature–pressure phase diagrams. LIPIDAG encompasses lipid/water and lipid/lipid phase diagrams prepared dry and in the presence of excess aqueous phase. Binary, multicomponent and theoretical phase diagrams are included in the compendium.

7. Pressure effects

The phase transitions in aqueous dispersions of phosphatidylcholines have been studied extensively as a function of temperature and lipid concentration. The effect of one other thermodynamic parameter–pressure, has been somewhat less well studied, however. What has been reported in this area is summa-

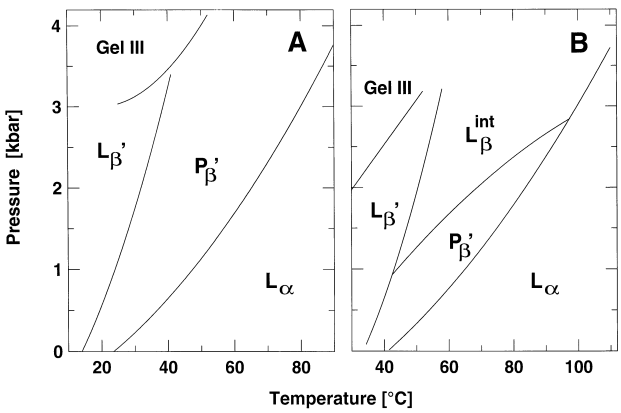

Fig. 16. Pressure/temperature phase diagrams of hydrated 14:0/14:0 PC (A) and 16:0/16:0 PC (B) (data from Ref. [542]).

Table 24
A summary of the phases and phase transitions in hydrated phosphatidylcholines

Phase transition type[a]	Phosphatidylcholine species	Transition temperature [°C]	Reference source
Lamellar gel–lamellar liquid crystal [L_β–L_α]	olefinic (double bond) and acetylenic	−70–66	Table 6
	n:1me(*n*-1)/*n*:1me(*n*-1), *n* = 14, 16–21	7–60	Table 10
	n:1me(*n*-2)/*n*:1me(*n*-2), *n* = 13–21	−30–49	Table 10
	16:1(*m*:0)2/16:1(*m*:0)2, *m* = 6, 8, 10, 14	−18–14	Table 10
	18:1(4:0)2/18:1(4:0)2	42.4	Table 10
	O-16:0/*n*:1((*n*-2):0)2, *n* = 14, 16	40–52	Table 10
	n:1ch *n*/*n*:1ch *n*, *n* = 9–18	−11–60	Table 11
	n:1cp *m*/*n*:1cp *m*, *n* = 17, 19; *m* = 9, 11	−20–16	Table 11
	16:1sh2/16:1sh2	26	Table 11
	15:0/15:0-METH	17.9	Table 5
	NH-14:0/NH-14:0	18.0	Table 5
	C-17:0/C-18:0	27.0	Table 5
	chick brain	−12.5	Table 13
	chick liver	−23.0	Table 13
	chick lung	21.0	Table 13
	egg (whole)	1.8	Table 13
	egg yolk	−5.8	Table 13
	rod outer segment	19.6	Table 13
	soybean, hydrogenated	52	Table 13
Rippled gel–lamellar liquid crystal [P_β–L_α]	*n*:0/*n*:0, *n* = 13–23	13–78	Table 1
	2-*n*:0/3-*n*:0, *n* = 14, 16	24–41	Table 3
	rac-*n*:0/*n*:0, *n* = 14, 16	24–41	Table 3
	1-14:0/3-14:0	19.0	Table 3
	O-*n*:0/O-*n*:0, *n* = 14, 16, 18	27–56	Table 4
	16:0/O-16:0	44.5	Table 4
	O-16:0/16:0	41.0	Table 4
	n:0/3–18:0, *n* = 14, 16[a]	30–46	Table 9
	18:0/NH-18:0	53.0	Table 5
Interdigitated lamellar gel–lamellar liquid crystal [L_β^{ud}–L_α]	1–16:0/3–16:0	36.1	Table 3
Partially interdigitated gel–lamellar liquid crystal	*n*:0/*m*:0, *n*, *m* = 9–26 ($n \neq m$), $0.07 < \Delta C/CL < 0.4$ (see text)	−55–90	Table 7
Mixed interdigitated gel–lamellar liquid crystal [mxd int gel–L_α]	*n*:0/*m*:0, *n*, *m* = 9–26 ($n \neq m$), $0.43 < \Delta C/CL < 0.63$ (see text)	−55–90	Table 7
	O-20:0/O-12:0	34.8	Table 9
	O-12:0/O-20:0	25.2	Table 9
Lamellar gel–lamellar gel[b]	*n*:1me(*n*-1)/*n*:1me(*n*-1), *n* = 14, 16–21	7–48	Table 10
	n:1me(*n*-2)/*n*:1me(*n*-2), *n* = 15–20	−5–24	Table 10
	16:1(*m*:0)2/16:1(*m*:0)2, *m* = 3–14	−7–24	Table 10
	16:1(14:0)2/O-16:0	−2.0	Table 10
	n:1me *m*/*n*:1me *m*, *n* = 14, 16, 18; *m* = 2–6	−6–42	Table 10
	16:1et2/16:1et2	25.4	Table 10
	16:1et2/3–16:1et2	28.9	Table 10
	n:1ch *n*/*n*:1ch *n*, *n* = 9–18	−16–60	Table 11
Lamellar gel–rippled gel [L_β–P_β]	*n*:0/*n*:0, *n* = 13–23	0–70	Table 1
	2-*n*:0/3-*n*:0, *n* = 14, 16	15–36	Table 3
	rac-*n*:0/*n*:0, *n* = 14, 16	13–32	Table 3
	18:0/NH-18:0	52.0	Table 5

Table 24 (continued)

Phase transition type[a]	Phosphatidylcholine species	Transition temperature [°C]	Reference source
Lamellar subgel–lamellar gel [L_c–L_β]	*n*:0/*n*:0, *n* = 15–22	18–32	Table 1
Lamellar subgel–lamellar liquid crystal [L_c–L_α]	*n*:0/*n*:0, *n* = 10–13	−6–14	Table 1
	n:1me(*n*-1)/*n*:1me(*n*-1), *n* = 11–13, 15	−19–23	Table 10
	n:2me(*n*-1,*n*-1)/*n*:2me(*n*-1,*n*-1), *n* = 12–20	−36–40	Table 10
	2-16:0/3-16:0-CPENT	46.0	Table 5
Lamellar subgel–rippled gel [L_c–L_β]	*n*:0/*n*:0, *n* = 13, 14	11–12	Table 1
	1–14:0/3–14:0	15.0	Table 3
	n:0/3–18:0, *n* = 14, 16	16–26	Table 9
Lamellar subgel–interdigitated lamellar gel [L_c–L_β^{int}]	1–16:0/3–16:0	24.8	Table 3
	O-16:0/O-16:0	4.9	Table 4
Interdigitated lamellar gel–rippled gel [L_β^{int}–P_β]	O-16:0/O-16:0	32.5	Table 4
	O-16:0/16:0	35.0	Table 4
Lamellar gel–micellar	O-16:0/2:0	0.0	Table 9
Interdigitated multilamellar gel–bilayer vesicle gel	O-18:0/2:0	10.4	Table 9
Bilayer vesicle gel–micellar	O-18:0/2:0	19.1	Table 9
Traces of non-lamellar mesomorphs			
Cubic ($Q_{\|\|}$)	16:1me2/16:1me2, 16:1et2/16:1et2	> 80	Table 10
	14:1(4:0)2/14:1(4:0)2	> 80	Table 10
	16:1(3:0)2/16:1(3:0)2	> 30	Table 10
	16:1(4:0)2/16:1(4:0)2	> 85	Table 10
	16:1(5:0)2/16:1(5:0)2	30 < 45	Table 10
	16:1(3:1me2)2/16:1(3:1me2)2	> 85	Table 10
	16:1(4:1me2)2/16:1(4:1me2)2	> 25	Table 10
	16:1(4:1me3)2/16:1(4:1me3)2	> 40	Table 10
	16:1(4:2me3)2/16:1(4:2me3)2	15	Table 10
	16:1(4:1et2)2/16:1(4:1et2)2	20 < 30	Table 10
	12:1benz2/12:1benz2	> 80	Table 11
	14:1benz2/14:1benz2	> 60	Table 11
Hexagonal ($H_{\|\|}$)	16:1(5:0)2/16:1(5:0)2	> 60	Table 10
	16:1(4:1me3)2/16:1(4:1me3)2	> 80	Table 10
	16:1(4:2me3)2/16:1(4:2me3)2	> 20	Table 10
	16:1(4:1et2)2/16:1(4:1et2)2	> 40	Table 10
	14:1ch-me2/14:1ch-me2	0–85	Table 11
	16:1ch-me2/16:1ch-me2	> 6	Table 11
	18:1ch-me2/16:1ch-me2	> 24	Table 11

[a] In the summary table, we do not indicate whether or not the hydrocarbon chains are tilted. Thus, the 'beta' notation suggests that both possibilities exist and the reference sources cited should be consulted for more details.
[b] Transformations between different lamellar gel phase modifications are included. For specific details, the reference sources cited should be consulted.

rized in Table 23. These data show that increasing pressure raises the pretransition ($L_{\beta'}$–$P_{\beta'}$) and the main transition ($P_{\beta'}$–L_α) temperatures. Interestingly, the sensitivity of the temperature of the chain melting transition to pressure, dT_m/dP, has been found to remain constant at ca. 21°C/kbar (1 bar = 1 atm = 105 Pa) for a variety of saturated and unsaturated phosphatidylcholines [121]. Pressure/temperature

phase diagrams of 14:0/14:0 PC and 16:0/16:0 PC in excess water are shown in Fig. 16. In the high pressure and low temperature region of the phase diagrams, a subgel (Gel III) phase with monoclinic chain packing is observed [542]. This same phase was discovered in 14:0/14:0 PC at −60°C and at atmospheric pressure [582,583]. In this same lipid, a Gel III–$L_{\beta'}$–$P_{\beta'}$ triple point is observed at 3.5 kbar and 41°C (Fig. 16A). In 16:0/16:0 PC, the Gel III phase forms upon equilibration at 1.8 kbar at ambient temperature (~30°C) (Fig. 16B). At pressures above 0.93 kbar, an additional intermediate gel phase with interdigitated hydrocarbon chains intervenes between the $L_{\beta'}$ and $P_{\beta'}$ phases in 16:0/16:0 PC that is not seen in the shorter chain homolog. It transforms directly into the L_{α} phase upon heating at pressures above 2.87 kbar. Two triple points are observed in the pressure/temperature phase diagram of fully hydrated 16:0/16:0 PC: $L_{\beta'}$–L_{β}^{int}–$P_{\beta'}$ at 0.93 kbar and 42.5°C, and L_{β}^{int}–$P_{\beta'}$–L_{α} at 2.86 kbar and 98.3°C [542].

8. Concluding remarks

The purpose of this review has been to summarize existing thermotropic data in the literature on phosphatidylcholines. In so doing, we have highlighted what is known about PC polymorphism and mesomorphism and how this is modulated by molecular structure, by temperature, pressure, and by overall sample composition. A summary of the polymorphs and mesomorphs and the transitions they undergo in hydrated PCs is presented in Table 24. The purpose of bringing together data in this form is to facilitate the selection of species of PCs that exist in a particular phase or exhibit a particular type of phase transition in a defined temperature range.

One additional purpose of this review has been to highlight gaps in our knowledge base of PC phase behavior in the hope that future research efforts will make good these deficits. A huge database exists for PCs with identical saturated acyl chains. Increasingly, the more biologically relevant asymmetric saturated and unsaturated PCs are being worked on. Considerable additional effort is required in this area to fill out the enormous matrix for asymmetric lipids. In partnership with these experimental studies is the development of mathematical relationship based on existing data that can be used to predict mesophase behavior of new lipid species. Considerable success has been achieved in this area [33,39,42,45,73,556, 558,624,625].

The role of polar lipids in general, and the phosphatidylcholines in particular, in biological membranes has, until recently, been viewed primarily as structural. Of late, increasing attention is being paid to the phosphatidylcholines, and related molecules produced in the course of metabolism, as agents of signal transduction [23–26]. These results are beginning to change the traditional view of phosphatidylcholine's role as strictly structural to a more active role in the life of the cell. Accordingly, it is appreciated more and more that the phase behavior of various naturally occurring phosphatidylcholines, of well defined composition, must be examined systematically so that their contribution to the behavior of the intact biological or reconstituted membrane can be deciphered and used to advantage.

Despite the current limits on our understanding of phosphatidylcholine phase behavior, a sizable body of useful quantitative data exists for this lipid species. The collective and immediate objective must be to fill in the obvious gaps and to set about establishing the underlying principles of phosphatidylcholine polymorphic and mesophase behavior as dictated by chemical structure and the properties of the dispersing medium. Given the size of the existing database, the latter goal cannot be too far from being realized to the advantage of all. While this article has focused on the phase properties of phosphatidylcholine species in isolation, an understanding of same is a prerequisite to establishing the rules of miscibility in more complex lipid/lipid and lipid/aqueous medium mixed systems. Our ultimate goal is to model and to understand lipid phase behavior in complex, multicomponent natural membranes and biologically-relevant lipid aggregates.

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Appendix A. Lipid nomenclature

The nomenclature scheme used in this article and in the LIPIDAT database is as follows. To begin with the lipid molecule is considered to be composed of three identifiable parts: (i) the apolar, hydrocarbon chain region, (ii) the polar head group region, and (iii) the backbone region to which the first two parts are attached. The default structure is based on the natural glycerol phosphate isomer, L-α-glycerol phosphate (or D-glycerol-1-phosphate) with two, unbranched saturated hydrocarbon chains esterified to the C1 and C2 positions on a glycerol backbone with the head group covalently attached through a phosphodiester group at the C3 position of glycerol (Fig. 4A).

For pure synthetic lipid preparations, all acyl and alkyl chain residues are fully specified, using a systematic nomenclature as follows. The two chain lengths, in units of number of carbon atoms in the main chain (and with the first carbon of the chain defined to be the one bonded through an oxygen atom to the glycerol backbone) are given, each to the left of a colon (:). The two chain descriptors are separated from each other by a slash (/). Modifications to each chain are indicated to the right of the colon and are listed according to number, kind, and location. First, to the right of the colon appears the number of modifications on that chain. A zero (0) indicates that the chain is in the default configuration, with no modifications. Following the number of modifications, the modifications themselves are listed alphabetically. Following each modification is a number indicating the carbon atom position on the chain where the modification is located.

Modifications to lipid hydrocarbon chains are manifold. The database nomenclature system employs a strategy to reflect this diversity by describing changes from the default on an atom-by-atom basis along the chain. Modifications to the default ester chain attachment to the C1 and C2 positions on the glycerol backbone are also considered as modifications to the lipid hydrocarbon chains. Thus, modifications include, but are not limited to, position and type of chain attachment to the glycerol, unsaturation at one or more sites along the chain, and the presence of functional groups or heteroatoms. For example, O-16:0 denotes a hexadecyl chain in ether linkage to the glycerol (note the prefix is an 'oh', not a zero). Another example of a chain modification is the moiety 1,3-dipalmitoyl-*sn-glycero*-2- which is designated as 16:0/3-16:0. For signifying double bonds, the following format is used. The letters 'c' and 't' denote, respectively, the *cis* and *trans* configuration of the double bond, followed by a number or set of numbers, identifying double bond position. Thus, the linolenoyl chain which is an 18 C acyl moiety with *cis* double bonds at C9, C12 and C15, is described simply by 18:3c9,12,15. Likewise, an elaidoyl chain, which is an 18 C moiety with a *trans* double bond at the C9 position, is designated 18:1t9. An isobranched chain, such as 16:1me15, corresponds to a 17 C acyl moiety with a methyl branch at carbon number 15. These and other chain modifications that appear in the phosphocholine subset of LIPIDAT are presented on Fig. 4D.

There are occasionally lipids that appear in the literature that have modified glycerol backbones. The modified glycerol is then represented in abbreviated form, all in capital letters, and is appended to the hydrocarbon chain description by a hyphen. For example, glycerol backbones with methyl groups substituted at the C1, C2, or C3 positions are designated, respectively, $-CH(CH_3)-CH-CH_2$, $-CH_2-C(CH_3)-CH_2$, or $-CH_2-CH-CH(CH_3)$. These and other backbone modifications that appear in the phosphocholine subset of LIPIDAT are illustrated in Fig. 4C.

In the default condition the head group is assumed to be bonded to the C3 position of glycerol (L-enantiomer) by a phosphodiester linkage PC is used to denote the phosphocholine moiety. Modifications to the head group are described in a manner similar to that used for chain modifications. Thus, the head group moiety $-PO_4-CH_2-CH_2-CH_2-N(CH_3)_3$ is designated $P(CH_2)C$, indicating that an extra methylene (CH_2) unit is present between the phosphate and trimethylammonium group in comparison to the default PC structure which is $-PO_4-CH_2-CH_2-N(CH_3)_3$. When more than one extra methylene group is present, the descriptor $P(CH_2)_nC$, is used where *n*

denotes the number of additional methylene units. The head group moiety with a sulfur atom replacing one of the non-bridging oxygen atoms, $-PSO_3-CH_2-CH_2-N(CH_3)_3$ (thiophosphocholine), is designated PC:1(O × S); the sulfocholine moiety, in which the nitrogen atom is replaced by a sulfur atom, $-PO_4-CH_2-CH_2-S(CH_3)_2$, is designated PC:1(N × S), and the phosphonocholine head group, with PO_3 linked to the C3 of glycerol via a C–P bond, $-PO_3-CH_2-CH_2-N(CH_3)_3$, is designated as PC:1(-O). These and other head group modifications that appear in the phosphocholine subset of LIPIDAT are presented on Fig. 4B.

Appendix B. Abbreviation list

3-	chain attached to the C3 position of the glycerol backbone
Biochim. Biophys. Acta	Biochimica et Biophysica Acta
benz	benzyl
c	double bond of the *cis* type
ch	cyclohexyl
cp	cyclopropyl
-CPENT	cyclopentane backbone
d	lamellar repeat period
DL-	dextro-, levo-rotary racemic mixture
DSC	differential scanning calorimetry
et	ethyl
Gel III	subgel phase with monoclinic chain packing
Gu	guanidine
IR	infrared spectroscopy
JCIS	Journal of Colloid and Interface Science
$H_{\|\|}$	inverted hexagonal liquid crystalline phase
L_α	lamellar liquid crystalline phase
L_β	lamellar gel phase
$L_{\beta'}$	lamellar gel phase (tilted chains)
L_β^{int}	lamellar gel phase with interdigitated chains
L_c	lamellar crystalline (subgel) phase
LUV	large unilamellar vesicles (diameter > 100 nm, according to the informally agreed upon nomenclature [607,608])
MCLC	Molecular Crystals and Liquid Crystals
me	methyl
-METH	methylidene backbone
MLV	multilamellar vesicles
mxd int gel	mixed interdigitated lamellar gel phase
n	hydrocarbon chain length in units of number of carbon atoms
O-	chain-backbone linkage of the ether type
OAc	acetate
P	pressure
PC	phosphocholine
PC:1(O × S)	thiophosphocholine
PC:1(N × S)	sulphocholine
PC:1(-O)	phosphonocholine
PE	phosphatidylethanolamine
PEG	polyethylene glycol
prop	propyl
Q	cubic liquid crystalline phase
SGII	metastable subgel phase, sub-subgel phase
sh	thiol
SUV	small unilamellar vesicles (diameter below 100 nm, according to the informally agreed upon nomenclature [607,608])
t	double bond of the *trans* type
T	transition temperature
T_m	temperature of the main (gel–liquid crystal, chain melting) transition
TRXRD	time-resolved X-ray diffraction
y	triple bond
ΔH	transition enthalpy change

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