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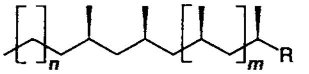
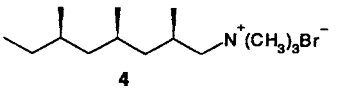
Chiral Methyl-Branched Surfactants and Phospholipids: Synthesis and Properties

Michael Morr,* Jens Fortkamp, and Stefan Rühe

The recent publication of the synthesis and unusual properties of spiro-surfactants by Menger et al.[1] prompted us to report the results of our work on chiral methyl-branched surfactants and phospholipids which are obtained by formal opening of spiro-compounds. For some time we have been engaged in the isolation of chiral methyl-branched fatty acids, for example, (2*R*,4*R*,6*R*)-2,4,6-trimethyloctanoic acid (**1**)[2] from the preen gland of the musk duck *Cairina moschata* as well as (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethyldecanoic acid (**2**) and (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethylundecanoic acid (**3**)[3] from the preen gland of the domestic goose *Anser a.f. domesticus*. In addition to a number of new derivatives of these compounds—such as the mite pheromones lardolure and norlardolure[4, 5] as well as new, chiral ferro- and antiferroelectric liquid crystals with methyl side chains[6]—we were interested in the physical and chemical properties (such as critical micellization concentration (CMC)) of surfactants **4** and **5**, which are derived from **1** and **2**, respectively. We also focused our attention on the diacyl-*sn*-glcero-3-phosphatidylcholines **10**–**15**, which show high enantiomeric purity and a uniform chain length of ten carbon atoms, but varying numbers of methyl-substituted chiral centers. Properties required for their useful applications (e. g. as membrane constituents) were analysed by differential scanning calorimetry (DSC) to determine the main phase-transition temperatures, and with a Langmuir film balance to record π-*A*-isotherms.



m	*n*	R	
1	0	0	COOH
2	1	0	COOH
3	1	1	COOH
lardolure	1	1	OCHO
norlardolure	1	0	OCHO



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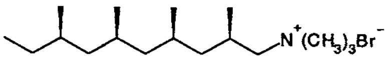

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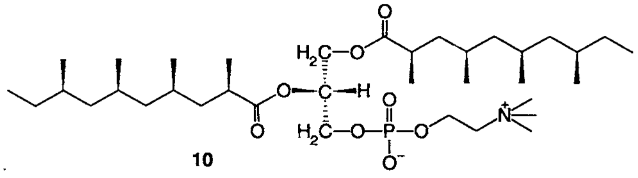

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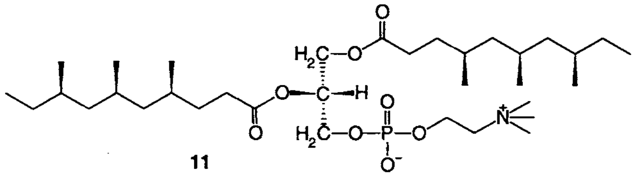

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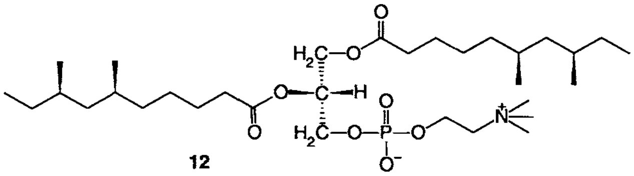

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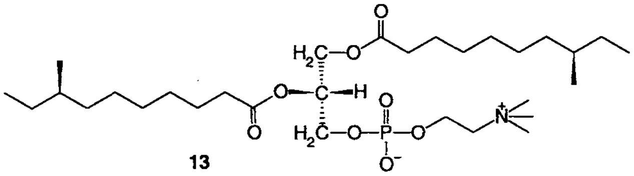

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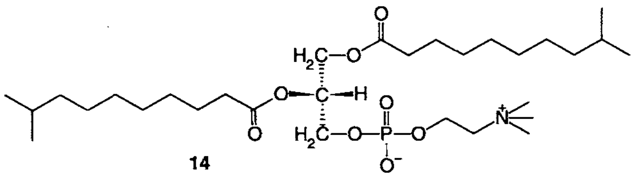

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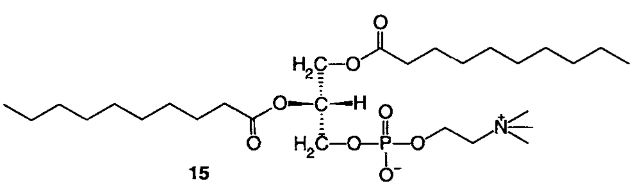

15

The methyl esters **6** of **1** and **2** were allowed to react with lithium aluminum hydride to give alcohols **7** ($n = 0,1$; yield 95%), which were converted by tosylation (via **8**) into the bromides **9** with LiBr in acetone (85%). The reaction of **9** with trimethylamine in ethanol at 80 °C (in a pressure vessel) afforded **4** and **5** in quantitative yield.

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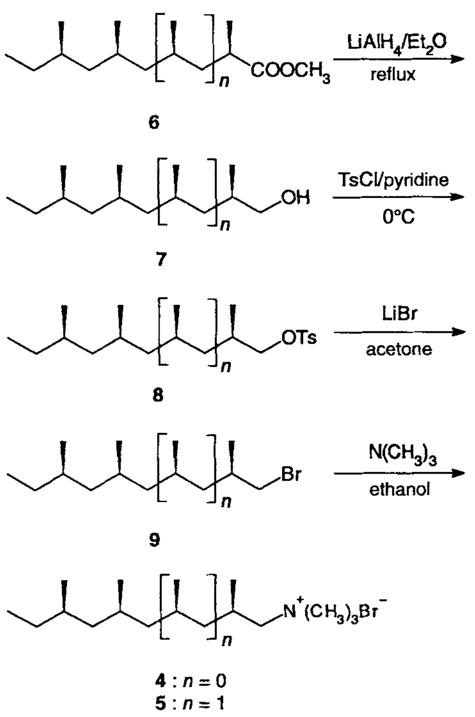
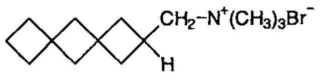
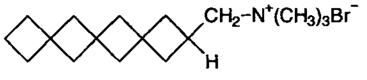


Aqueous solutions of **4** and **5** were analyzed tensiometrically at 25 °C. It is known that with common surfactants the surface tension decreases steadily until the CMC is reached. At higher surfactant concentrations surface tension does not decrease further, as there is a preferred invasion of surfactant molecules into the micelles instead of enrichment at the air–water interface. These characteristic properties were observed for **4**. The CMC is 9.12×10^{-2} M, which is comparable to that of 1.4×10^{-1} M (**A**) for the corresponding spiro-surfactant found by Menger et al.[1] Apparently, the tendency of **4** to form micelles is significantly lower than with common surfactants with the same total number of carbon atoms. Menger et al. also reported that formation of micelles seems to be inhibited by a certain rigidity of the methyl-branched aliphatic chain. They gave an estimated CMC for the spiro-compound of more than 4.4×10^{-3} M (**B**).[1] For the corresponding compound **5** we observed a decrease in the surface tension to about 27 mN m^{-1} and a CMC of 1.5×10^{-2} M. As with the spiro-compound, the plot of the surface tension is anomalous since it is partially convex, and the surface tension changes only slightly at low concentrations.



A



B

Phospholipids **10**–**15** were synthesized according to Hermetter and Paltauf.[7,8] When applied to the synthesis of **10**, the same method caused racemization at the 2-position of the carboxylic acid group; hence, an alternative approach had to be found. Using the method of Wood,[9] **2**, *sn*-glycero-3-phosphocholine (as the CdCl$_2$ complex), and dicyclohexyl carbodiimide (DCC)/4-dimethylamino pyridine (DMAP) in ethanol-free chloroform gave **10** in 66% yield after 10 d at room temperature. Gas-chromatographic analysis of an acidically methylated sample indicated that chirality was conserved to more than 95%. Compound **11** was synthesized by standard chain-elongation procedures (malonic ester method). (6*R*,8*R*)-6,8-Dimethyldecanoic acid, which was used to synthesize **12**, was obtained in a 16-step procedure, and (*R*)-8-methyldecanoic acid, required for **13**, required a 10-step synthesis.[2,10]

The calorimetric analyses of the phospholipid suspensions **10**–**15** were performed on a "high-sensitivity" differential calorimeter (MC-2D, Micro Cal, Inc.), which functions according to the principle of dynamic performance differential calorimetry. No phase transitions were observed for **11**–**13** between −45 and 25 °C; Menger et al. found the same result with the spirophospholipids (Figure 1). This is in agreement with expectations based on comparisons with the results of McElhaney et al.[11] Phospholipid **10** showed a main phase-transition temperature T_m of −31.9 °C. It is clear from the curve that it is a very broad phase transition with a relatively low transition enthalpy ΔH. Although DSC data do not provide information about processes at the molecular level, it is easy to imagine that—based on the three-dimensional structure derived from calculations of molecular dynamics[12] for **2**—the gel phase of such a compound is less ordered than that of the corresponding nonbranched compound. This is indicated by a lower transition enthalpy. The fact that **10**, in contrast to **11**–**13**, shows a phase transition within the temperature range used suggests that the acyl chains in **10** are more easily arranged, even if in a relatively unordered fashion. The chain is more bulky throughout the overall length of the molecule than the head group. This is different to the phosphatidylcholines, which show no phase transition, and is in accordance with the data from the film balance.

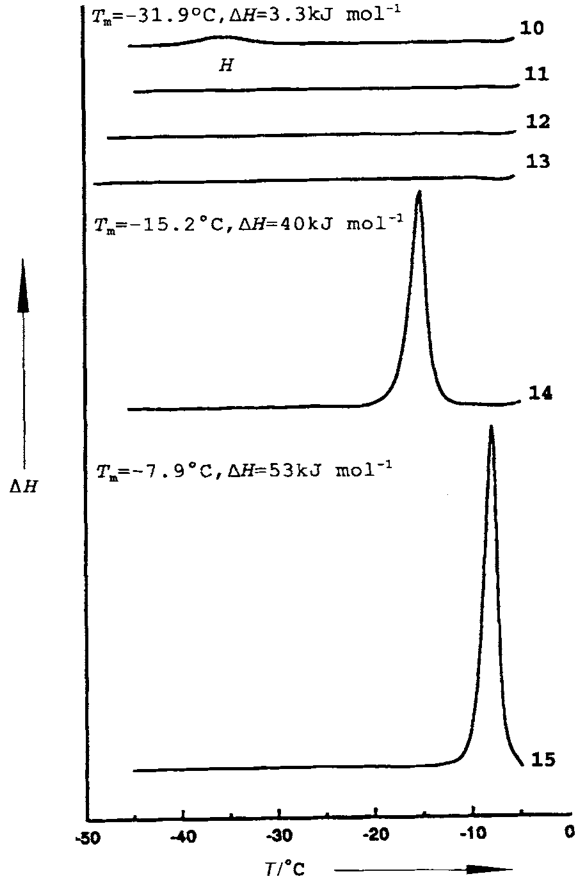


Figure 1. DSC heating thermograms of **10**–**15**, c = 10 mg mL^{-1} in water, heating rate = 20 °C h^{-1}.

The data for **14** ($T_m = -15.2\,°C$, $\Delta H = 40\ kJ\,mol^{-1}$) are consistent with the results of McElhaney et al.[13] for other diacylphosphatidylcholines with longer chain lengths (e.g. $T_m = -18.8\,°C$ and $\Delta H = 32.6\ kJ\,mol^{-1}$ for bis(10-methylundecanoyl)phosphatidylcholine). Comparison of our data with that for the corresponding nonbranched didecanoylphosphatidylcholine (**15**; $T_m = -7.9\,°C$, $\Delta H = 53\ kJ\,mol^{-1}$) shows that, in contrast to compounds with linear chains, a slightly disturbed gel state can be assumed for the diisoacylphosphatidylcholines.

Diacylphosphatidylcholines **10**–**15** were analyzed with a film balance (Lauda FW 2) to ascertain their behavior at the water–air interface. The shapes of the π-A-isotherms at 0 and 20 °C are almost identical and characteristic of those from expanded films (Figure 2). An increase in the surface per molecule of 50 to 76 Å^2 is observed with an increasing number of methyl branches in the acyl chain. This is in accordance with the results for dipalmitoylphosphatidylcholine and the corresponding iso and anteiso compounds,[14] for which the maximum surface tensions differ only slightly (48–51 $mN\,m^{-1}$ for **11**–**14**). Surprisingly, the value for **10** is slightly higher (54 $mN\,m^{-1}$). An explanation for this could be the ratio of the steric requirements of the head group and the acyl chain. For the nonbranched compound the head group has a higher steric requirement than the acyl chains, whereas the methyl side chains in the other compounds disturb an optimized arrangement. For **10** the acyl chains are more bulky than the head group. This is supported by DSC data that show a phase transition within the investigated temperature range for **10**, but not for **11**–**13**. Further confirmation of this hypothesis is the absence of a condensed phase; phase transitions were found only for **10**, **14**, and **15**, and these were clearly below 0 °C. A pharmaceutically interesting application could be the modification of liposome properties with respect to their permeability by specific addition of branched phospholipids.

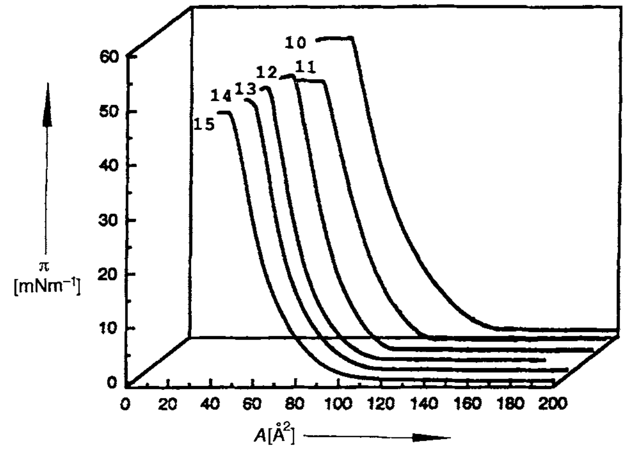


Figure 2. π-A-Isotherms of **10**–**15** on water at 0 °C, compression time = 30 min for 927 cm^2, A = molecule surface per molecule.

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A Supercharged Anion with a Silyl-Substituted Eight-Center, Twelve-Electron π System: Synthesis and Characterization of the Tetralithium Salt of an Octasilyl-Substituted Trimethylenecyclopentene Tetraanion**

Akira Sekiguchi,* Tsukasa Matsuo, and
Chizuko Kabuto

Supercharged anions with extended π-electron systems have attracted considerable interest owing to their unique structures and electronic properties.[1] The existence of a hexaanionic species in the solid state is inferred from the formation of K_6C_{60}, which was characterized by X-ray powder diffraction[2] and ^{13}C NMR spectroscopy.[3] Scott et al. recently reported on the tetralithium salt of the corannulene tetraanion ($C_{20}H_{10}$) and its derivatives.[4] The most recent, and, to our knowledge, only report on the molecular structure of a rubrene tetraanion (crystallized as a tetrasodium salt; rubrene = 5,6,11,12-tetraphenyltetracene, $C_{42}H_{28}$) that has been confirmed by X-ray crystallography was carried out by Bock et al.[5] We report here a tetraanion with a new silyl-substituted eight-center, twelve-electron π system, which was isolated as the tetralithium salt **2**.

As an appropriate precursor of the tetraanion, the octasilyl-substituted trimethylenecyclopentene **1** with an eight-electron π system was prepared as pale yellow crystals by the reaction of hexadecamethyl-3,5,8,10,13,15,18,20-octasilacycloicosa-1,6,11,16-tetrayne with $[(C_5H_4Me)Mn(CO)_3]$ under photochemical conditions. The molecular structure of **1** is shown in Figure 1.[6]

Reduction of **1** with lithium in dry, oxygen-free tetrahydrofuran at room temperature led to the formation of an orange solution of the tetraanion of **1** (Scheme 1). Crystallization from hexane afforded air- and moisture-sensitive pale orange crystals of the tetralithium salt **2**, which contains four molecules of THF.

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