shown in Figure 1. This consists of a triangle of osmium atoms bridged on the longest edge by an acetyl group and a hydrogen atom.[11] The carbene group is terminally bonded to Os(1), to which is also coordinated the oxygen of the bridging acetyl group. The bond distances from C(25), the carbenoid carbon atom, to Os(1) and to the methoxy oxygen and the methyl carbon atoms as well as the angles about C(25) are all typical of those found in Fischer-type carbene complexes[2] (see caption to Figure 1).

Our work clarifies for the first time the rarity of the Fischer carbene groups on metal clusters. This derives from the chemical properties of the η^1-C(O)R group formed in the attack of nucleophile on the cluster. In the medium needed to form such a group, alkylation is very slow; in attempts to exchange solvent, the labilizing influence of the η^1-C(O)R group leads to loss of CO and formation of the bridged μ-O=C(R) complex. It is ironic that synthesis of the Fischer carbene takes place on a hydrido-cluster complex, which gives some idea of the relative tendencies for competing processes such as attack by nucleophile on coordinated CO as opposed to removal of bridging hydrogen as proton.

Acknowledgment. This work has been supported by a grant from the National Science Foundation (No. CHE 79-08406).

Registry No. 4, 65908-54-5; **5**, 82390-92-9; CH_3Li, 917-54-4; $CH_3SO_3CF_3$, 333-27-7.

(10) Orange crystals are monoclinic, space group $P2_1/n$, a = 9.578 (4) Å, b = 13.494 (4) Å, c = 15.187 (6) Å, β = 96.30 (3)°; V = 1951 (1) Å^3, Z = 4, ρ_{calcd} = 3.15 g cm^{-3} (MoKα = 0.71069 Å^3). The structure was solved and refined by using 2728 observed ($I > 3\sigma(I)$) independent reflections measured on a Syntex $P\bar{1}$ automated diffractometer in the range $0° < 2\theta < 50°$. An absorption correction was applied (μ = 195.66 cm^{-1}). Refinement converged at R = 0.050 and R_w = 0.061.

(11) After all non-hydrogen atoms were refined anisotropically, the metal hydride was located and refined.

Dichlorine Monoxide: A Powerful and Selective Chlorinating Reagent†

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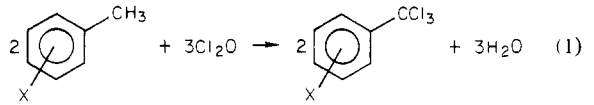
Dichlorine monoxide (Cl_2O) has long been known[1] and has been the subject of some modern mechanistic[2] and physical[3] studies, but it has not been shown to be a useful reagent in synthetic chemistry. We have found that Cl_2O is a powerful and selective reagent for either side-chain or ring chlorination of deactivated aromatic substrates, and it gives excellent yields under mild conditions where conventional reagents fail or require harsh conditions.

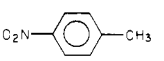
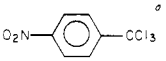
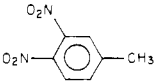
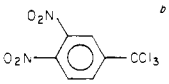
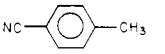
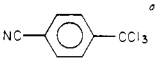
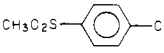
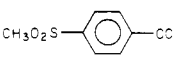
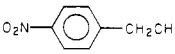
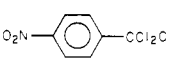
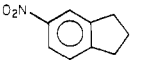
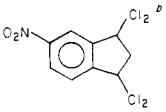
The free-radical, side-chain chlorinations of deactivated alkyl aromatic compounds such as *p*-nitrotoluene normally require high temperatures and give largely benzyl chlorides and hydrochloric acid.[4] Only small amounts of benzal chlorides and little or no benzotrichlorides are produced.[5] More forcing conditions lead to excessive byproducts via the ipso reaction.[6] In marked contrast, chlorinations with Cl_2O at 25 °C can lead exclusively to trichloromethyl derivatives in high yields with water as the only byproduct (eq 1). Representative examples are shown in Table I. Mono- and dichloro products also can be produced in useful yields by adjusting the Cl_2O/arene ratio, but the chief utility of this chemistry is the direct synthesis of relatively inaccesible, negatively substituted trichloromethyl arenes, which are convenient precursors to other functionalized arenes such as the corresponding trifluoromethyl derivatives or carboxylic acids.



(1)

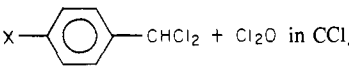
In a typical reaction,[7,8] Cl_2O (42.4 g, 0.49 mol) in CCl_4 (750

Table I. Chlorination of Deactivated Alkyl Aromatic Compounds with Cl_2O in CCl_4

substrate	product	yield, %
		99
		89
		99
		96
		100
		97

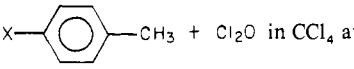
[a] Reaction temperature 25 °C. [b] Reaction temperature 75 °C.

Table II. Pseudo-First-Order Rate Constants for



X	10^4k, s^{-1}
NO_2	1.05
CF_3	1.42
Cl	2.70

Table III. Relative Rate Constants for



X	k_{rel}
Cl	3.44
CO_2CH_3	1.76
CF_3	2.28
NO_2	1.00

(5) We found, for example, the chlorination of *p*-nitrotoluene with excess Cl_2 at 165-170 °C for 9-14 h gave <1% *p*-nitrobenzotrichloride. Free-radical initiators or UV light had little or no affect. Catalysts such as I_2, SbI_3, C_6H_5I, C_6H_5IO, or $SbCl_3$ in some cases reduced the required reaction temperature to 135 °C but did not increase the yield of benzotrichloride. Other chlorinating agents including SO_2Cl_2 or *t*-BuOCl also failed to trichlorinate *p*-nitrotoluene.

(6) Traynham, J. G. *Chem. Rev.* **1979**, *79*, 323.

(7) Marsh, F. D. (to Du Pont) U.S. Patent 4 226 783.

(8) Solutions of Cl_2O in CCl_4 (ca. 1.0 M), prepared by passing a mixture of chlorine and air over yellow mercuirc oxide,[9] were used in this work, but in situ generation has given overall better yields for some large-scale preparations. **Caution**: Neat Cl_2O is toxic, explosive, and a strong oxidizing agent, but solutions in CCl_4 (ca. 1 M) can be handled safely and stored at −15 to 0 °C.

† Contribution No. *3058*.

(1) (a) Balard, A. J. *Ann. Chim. Phys., Ser. 2* **1834**, *57*, 225. (b) Balard, A. J. *Taylor's Sci. Mem.* **1837**, *1*, 269. (c) Gay-Lussac, J. L. *C. R. Acad. Sci.* **1842**, *14*, 927.

(2) Tanner, D. D.; Nychka, N. *J. Am. Chem. Soc.* **1967**, *89*, 121.

(3) See, for example: Renard, J. J.; Bolker, H. I. *Chem. Rev.* **1976**, *76*, 487.

(4) (a) Hoch, P. E. In "Chlorine, Its Manufacture, Properties, and Uses"; Sconce, J. S., Ed.; Reinhold: New York, 1962; pp 834-863. (b) Russell, G. A. In "Free Radicals"; Kochi, J., Ed.; Wiley: New York, 1973; Vol. 1, pp 293-311. (c) Poutsma, M. L. In "Free Radicals"; Kochi, J., Ed.; Wiley: New York, 1973; Vol. 2, pp. 181-185.

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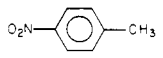
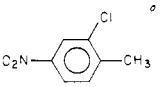
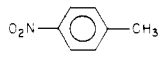
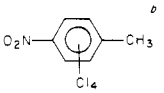
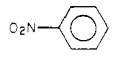
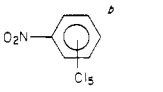
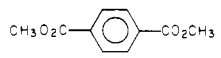
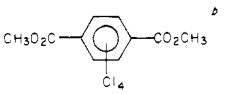
Table IV. Chlorination of Deactivated Aromatic Rings with Cl_2O/Acid at 20–40 °C

substrate	product	acid	yield, %
	 [a]	H_2SO_4	99
	 [b]	CF_3SO_3H	97
	 [b]	H_2SO_4	94
	 [b]	CF_3SO_3H	99

[a] 0.5 equiv of Cl_2O. [b] ≥2.5 equiv of Cl_2O.

mL) was added to *p*-nitrotoluene (33.3 g, 0.243 mol) in CCl_4 (30 mL). After 96 h at room temperature, water and solvent were removed to give *p*-nitrobenzotrichloride (58.8 g, 99% purity, yield 99.8%). At 75 °C the reaction affords an equivalent yield in about 3 h.

The relative rate constants for introducing the first, second, and third chlorines into *p*-nitrotoluene at 30 °C are 1.0, 1.35, and 0.9, respectively. These nearly equivalent rates sharply contrast with the normal decreasing order of benzylic hydrogen reactivities toward electrophilic radicals: $CH_3 > CH_2Cl >> CHCl_2$.[4] Although Cl_2O is exceptionally reactive, the chlorinations of *p*-nitroethylbenzene and 5-nitroindan (Table I) illustrate its remarkable selectivity for the replacement of benzylic hydrogens.

We have probed the mechanistic aspects of the Cl_2O reactions using isotope effects, free-energy relationships, and related kinetic studies. The kinetic deuterium isotope effect determined with 4-nitrobenzyl chloride-α-d_1 is substantial (k_H/k_D = 9.1 at 55 °C in CCl_4). Although the comparative isotope effect for the reaction with Cl_2 in CCl_4 could not be determined at 55 °C because of unreactivity, our value at 165 °C (k_H/k_D = 1.7) compares favorably with literature data for the chlorinations of toluene-d_1 (k_H/k_D = 1.30) and *p*-chlorotoluene-d_1 (k_H/k_D = 1.44) with Cl_2 in CCl_4.[10] The linear free energy relationships found for the chlorination of 4-substituted benzal chlorides and toluenes by Cl_2O (ρ = −0.76 and −0.9, respectively; cf. Tables II and III) reveal a polar effect similar in magnitude to that reported for hydrogen abstraction from toluenes by chlorine radical in CCl_4 at 40 °C (ρ = −0.7).[11]

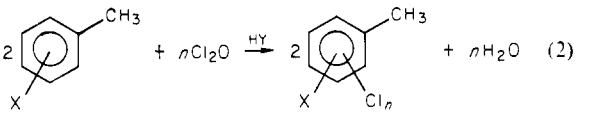
These results are consistent with a free-radical process involving hydrogen abstraction by ClO· radical. The comparative isotope effects indicate more bond breaking and a more symmetrical transition state for hydrogen abstraction by ClO· than by Cl·.[12] The transition state for attack by ClO· therefore has appreciably more benzylic free radical character than that for attack by Cl·. (The apparent anomaly of similar ρ values yet widely different isotope effects for benzylic chlorinations is explained at least in part by the significantly greater electronegativity of Cl· vs. ClO·.[13]) The similar reactivity of the benzylic hydrogens in *p*-nitrotoluene and *p*-nitrobenzyl and -benzal chlorides toward ClO· in fact indicates that radical stability effects can be at least as important as polar effects. This contrasts with attack by Cl·, which is dominated by polar effects.[4]

Table V. Chlorination of Toluene

reagent	chlorotoluene, % ortho	para	meta
Cl_2O/TFA[a]	71	29	ca. 0.1
Cl_2/$HClO_4$/$AgClO_4$[b]	75	23	2.2
Cl_2/HOAc[c]	60	40	0.5

[a] This work. [b] Reference 14. [c] Reference 18.

A new and powerful reagent that gives exclusive ring chlorination of deactivated aromatics in high yields at 0–50 °C is produced if a strong protic acid (pK_a (HY) ≤ $pK_a(CF_3CO_2H)$) is added to the Cl_2O reaction medium (eq 2).



(2)

In comparison with known reagents[14–18] and from the representative chlorinations shown in Table IV, this reagent is among the most reactive and selective known for chlorination of deactivated ring systems. The degree of chlorination is controlled by the quantity of Cl_2O employed, although mono- and perchlorinated products are normally the most easily isolated and purified.[19] The large ρ value of −7.8 obtained for monochlorination of a series of 4-substituted toluenes by Cl_2O in CF_3CO_2H at 25.0 °C and the observed regioselectivity (Table V) are consistent with electrophilic aromatic substitution.

The electrophilic species produced from Cl_2O and strong acids has limited stability at room temperature and has not been characterized. The "substitutive electrophilic dehalogenations" we have observed with alkyl halides (eq 3) are similar to those reported for perfluoroalkylsulfonyl hypohalites.[20] This suggests the possible intermediacy of acid hypohalites in the electrophilic chlorinations (eq 4).[21]

$$Cl_2O + CF_3CO_2H + CH_3I \rightarrow CF_3CO_2CH_3 + ICl + HOCl \quad (3)$$

$$Cl_2O + CF_3CO_2H \rightleftarrows CF_3CO_2Cl + HOCl \quad (4)$$

We are continuing to investigate this possibility as well as the scope, limitations, and further mechanistic aspects of these new reactions.

Registry No. *p*-Nitrotoluene, 99-99-0; 3,4-dinitrotoluene, 610-39-9; *p*-cyanotoluene, 104-85-8; methyl *p*-tolyl sulfone, 3185-99-7; *p*-nitroethylebenzene, 100-12-9; 5-nitroindan, 7436-07-9; nitrobenzene, 98-95-3; dimethyl terephthalate, 120-61-6; dichlorine monoxide, 7791-21-1; *p*-nitrobenzo trichloride, 3284-64-8; 3,4-dinitrobenzo trichloride, 76213-13-3; *p*-cyanobenzo trichloride, 2179-45-5; 1-(trichloromethyl)-4-(methylsulfonyl)benzene, 76213-17-7; 1-(1,1-dichloroethyl)-4-nitrobenzene, 76213-14-4; 1,1,3,3-tetrachloro-5-nitroindan, 76213-19-9; 2-chloro-4-

(9) Cady, G. H. *Inorg. Synth.* **1957**, *5*, 156.
(10) Wiberg, K. B.; Slaugh, L. H. *J. Am. Chem. Soc.* **1958**, *80*, 3033.
(11) Russell, G. A.; Williamson, R. C., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 2357.
(12) The assumption that transition-state symmetry and large isotope effects are related, however, has been challenged. See, for example: Motell, E. L.; Boone, A. W.; Fink, W. H. *Tetrahedron* **1978**, *34*, 1619.
(13) Lee, L. C.; Smith, G. P.; Moseley, J. T.; Cosby, P. C.; Guest, J. A. *J. Chem. Phys.* **1979**, *70*, 3237.
(14) Norman, R. O. C.; Radda, G. K. *J. Chem. Soc.* **1961**, 3610.
(15) Effenberger, F.; Kussmaul, U.; Huthmacher, K. *Ber. Dtsch. Chem. Ges.* **1979**, *112*, 1677.
(16) Derbyshire, D. H.; Waters, W. A. *J. Chem. Soc.* **1951**, 73.
(17) Ballester, M.; Molinet, C.; Castaner, J. *J. Am. Chem. Soc.* **1960**, *82*, 4254.
(18) Brown, H. C.; Stock, L. M. *J. Am. Chem. Soc.* **1957**, *79*, 5175.
(19) In a representative experiment, Cl_2O (6.3 g, 0.073 mol) in CCl_4 (68 mL) was added dropwise to *p*-nitrotoluene (2.5 g, 0.018 mol) in CF_3SO_3H (10.9 g, 0.072 mol) with cooling to maintain the reaction at 35–45 °C. After being stirred for 3 h at room temperature, the mixture was poured onto ice and extracted with CH_2Cl_2. The organic extract was washed with 5% aqueous $NaHCO_3$, dried, and concentrated to give a white solid which was recrystallized from acetone–water to give 4.8 g (97% yield) of pure 2,3,5,6-tetrachloro-4-nitrotoluene.
(20) (a) Katsuhara, Y.; DesMarteau, D. D. *J. Fluorine Chem.* **1980**, *16*, 257. (b) Katsuhara, Y.; DesMarteau, D. D. *J. Am. Chem. Soc.* **1980**, *102*, 2681. (c) Johri, K. K.; DesMarteau, D. D. *J. Org. Chem.* **1981**, *46*, 5081.
(21) Dichlorine monoxide in CCl_4 is known to react with acetic acid to give acetyl hypochlorite and water: Anbar, M.; Dostrovsky, I. *J. Chem. Soc.* **1954**, 1105.

nitrotoluene, 121-86-8; 2,3,5,6-tetrachloro-4-nitrotoluene, 22490-21-7; pentachloronitrobenzene, 82-68-8; dimethyl tetrachlorophthalate, 20098-41-3; *p*-chlorotoluene, 106-43-4; methyl *p*-toluate, 99-75-2; *p*-(trifluoromethyl)toluene, 6140-17-6; α,α-dichloro-*p*-nitrotoluene, 619-78-3; 1-(dichloromethyl)-4-(trifluoromethyl)benzene, 82510-98-3; p,α,α-trichlorotoluene, 13940-94-8; toluene, 108-88-3; *o*-chlorotoluene, 95-49-8.

Phospholipids Chiral at Phosphorus. 2. Preparation, Property, and Application of Chiral Thiophospholipids[1]

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Received May 12, 1982

Recently we have reported the synthesis of chiral [$^{18}O_1$]1,2-dipalmitoyl-*sn*-glycero-3-phosphorylcholine (DPPC) and its application in studying the stereochemistry of transphosphatidylation catalyzed by phospholipase D.[2] By similar procedures, we have synthesized chiral [$^{17}O_1$]DPPC (as separate diastereomers and mixture), which are potentially useful in the chemical and physical study of the conformation and the motion of the phosphate head group of phospholipids in different phases and in protein–lipid interactions.[3-5]

However, [$^{18}O_1$]DPPC is useful only for phospholipases C and D and not for other phospholipases. Also, the ^{17}O NMR study of [$^{17}O_1$]DPPC is difficult in vesicles or lipid bilayers[7] due to large line widths and quadrupolar splittings. As an alternative and complementary approach, we now report synthesis and application of separate diastereomers of 1,2-dipalmitoyl-*sn*-glycero-3-thiophosphorylcholine (DPPsC).

The diastereomeric mixture of thiophospholipids (random configuration at both C-2 and P) has been synthesized recently[8] but has not been resolved into separate diastereomers either chemically or spectroscopically. Following the procedure of Nifant'ev et al.,[8a] we have synthesized DPPsC (**1**) from (*S*)-(−)-1,2-dipalmitin (synthesized from D-mannitol[9]). The structures of synthetic intermediates and the final DPPsC have been characterized by ^1H NMR, ^{13}C NMR, IR, and TLC, which are consistent with literature data.[8] ^{31}P NMR analysis of **1** in $CDCl_3$ (Figure 1A) showed two separate peaks due to two diastereomers (isomer A, lower field; isomer B, higher field). It was found that phospholipase A_2 (bee venom, Sigma, 1500 units/mg) preferentially hydrolyzes isomer B of DPPsC, which provides a convenient way to separate the two diastereomers, as outlined in Scheme I. Hydrolysis of DPPsC(A + B) in a mixture of 0.1 M Tris buffer

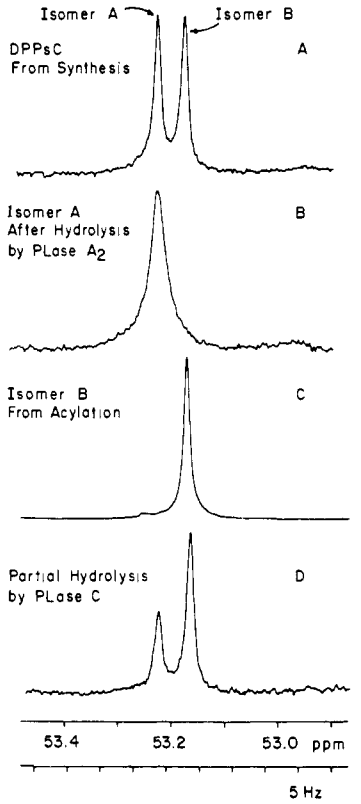
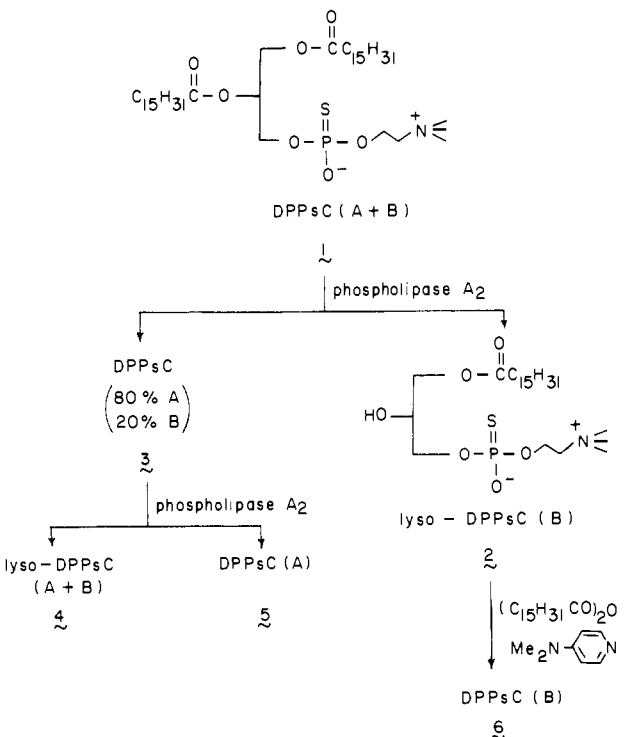


Figure 1. ^{31}P NMR spectra (81.0 MHz) of DPPsC (10 mM in $CDCl_3$): (A) mixture of diastereomers from chemical synthesis; (B) pure isomer A recovered from hydrolysis by phospholipase A_2; (C) pure isomer B (containing 3% isomer A) obtained from acylation of the product of phospholipase A_2 hydrolysis, lyso-DPPsC; (D) DPPsC after partial hydrolysis by phospholipase C. NMR parameters: spectral width 1000 Hz; acquisition time 4.1 s; ^1H decoupling; line broadening 0.1 Hz; pulse width 12 μs (90° pulse at 20 μs); number of scans 500 (A, D), 1000 (B), 2600 (C); temperature 30 °C. Chemical shifts are referenced to external 1 M H_3PO_4, with + indicating a downfield shift.

Scheme I. Separation of Diastereomers of DPPsC



(1) Supported by a grant from NIH (GM30327) and in part by a grant from NSF (PCM 8140443). The NMR spectrometers used were funded by NIH GM 27431 and NSF CHE 7910019. The ^{14}N NMR was obtained with the help of Dr. C. Cottrell. Abbreviations used: NMR, nuclear magnetic resonance; DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphorylcholine; DPPsC, 1,2-dipalmitoyl-*sn*-glycero-3-thiophosphorylcholine; MOPS, 3-[*N*-morpholino]propanesulfonic acid; Tris, 2-amino-2-hydroxymethyl-1,3-propanediol; Pi, inorganic phosphate; IR, infrared spectrum; TLC, thin-layer chromatography.

(2) Bruzik, K.; Tsai, M.-D. *J. Am. Chem. Soc.* **1982**, *104*, 863.

(3) (a) Skarjune, R.; Oldfield, E. *Biochemistry* **1979**, *18*, 5903. (b) Yeagle, P. L. *Acc. Chem. Res.* **1978**, *11*, 321.

(4) The ^{17}O NMR signal of [$^{17}O_1$]DPPC broadens from 440 Hz in CH_3OD (100 mg in 1.5 ml) to 3250 Hz in $CDCl_3$ (at 33 °C) (ref 5) as a result of the micelle formation in chloroform (ref 6). This can best be explained by a 7.4-fold increase in the rotational correlation time τ_r of phosphoryl oxygens, which suggests a restriction in the motion of the phosphate group upon aggregation, which is consistent with the recent finding in the restricted motion of the choline side chain due to aggregation (ref 6a).

(5) Tsai, M.-D.; Bruzik, K. In "Biological Magnetic Resonance" Berliner, L. J., Reuben, J., Eds.; Plenum Press: New York; Vol. 5, in press.

(6) (a) Murari, R.; Baumann, W. J. *J. Am. Chem. Soc.* **1981**, *103*, 1238. (b) Birdsall, N. J. M.; Feeney, J.; Lee, A. G.; Levine, Y. K.; Metcalfe, J. C. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1141.

(7) We have so far not been able to observe any ^{17}O NMR signal of a sonicated or unsonicated dispersion of [$^{17}O_1$]DPPC in water. A possible solution would be to prepare oriented lipid bilayers.

(8) (a) Nifant'ev, E. E.; Predvoditelev, D. A.; Alarkon, Kh. Kh. *Z. Org. Khimii* **1978**, *14*, 63. (b) Vasilenko, I.; De Kruijff, B.; Verkleij, A. J. *Biochim. Biophys. Acta* **1982**, *685*, 144.

(9) (a) Jensen, R. G.; Pitas, R. E. *Adv. Lipid. Res.* **1976**, *14*, 213. (b) Howe, R. J.; Malkin, T. *J. Chem. Soc.* **1951**, 2663.

0002-7863/82/1504-4682$01.25/0