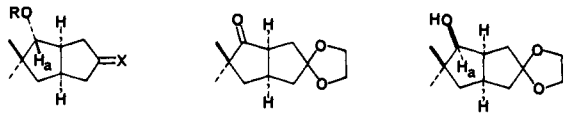

6 R = $SiMe_2But$, X = O
7 R = H, X = O
8 R = H, X = OCH_2CH_2O

derived ethylene ketal **8** (92%) on oxidation (Me_2SO/oxalyl chloride) gave **9** (67%). Reduction of **9** gave mixtures of **8** and **10** in the following ratios depending upon the reducing agent: $LiAlH_4$, 2:1; $NaBH_4$, 6:5; LiA(O-*t*-Bu)H, 2:3; Li/NH_3, 9:1. For **8** H_a, J = 7 Hz, and for **10** H_a, J = 4.5 Hz.

The reduction using Li/NH_3 is known to give the thermodynamically more stable exo-alcohol **8**, by analogy with the results obtained by Danishefsky and Ikegami,[4] in their respective syntheses of coriolin. As further proof of the syn relationship between the oxygen substituent at C-8 and C-5 hydrogen, the total synthesis of *dl*-coriolin **2** provides confirmatory evidence (Scheme II).

Treatment of **4** with $PhCH_2^+NEt_3Cl^-/KF{\cdot}2H_2O$/THF heated at reflux (3 h), followed by *n*-BuLi/MeI/−70 to 20 °C gave **11** (87%, bp 85–90 °C (0.4 mmHg)). Exposure to **11** to $Co_2(CO)_8$/CO/heptane/110 °C/20 h in a sealed tube gave the bicyclo[3.3.0]enone **12** (50%, bp 120 °C (1 mmHg)), along with its C-8 epimer (15%, bp 130 °C (1 mmHg) 3.3:1).[7] Hydrogenation (10% Pd/C) of **12** gave **13** (92%), which was converted by standard conditions into **14** (R = allyl; 79%). Wacker oxidation of **14** (R = allyl) gave **14** (R = CH_2COCH_3; 64%), which on treatment with KO-*t*-Bu/HO-*t*-Bu at 20 °C for 0.5 h gave the tricyclic enone **15** (74%); (these last three steps were carried out in a manner similar to those described by Ikegami[4]).

Deconjugation [KO-*t*-Bu (10 equiv)/DME/20 °C/2 h, workup with AcOH][4] gave **16**, which on treatment with MCPBA (1.0 equiv)/CH_2Cl_2/1 h followed by exposure of the crude epoxide to DBU/CH_2Cl_2 gave **17** (34% from **15**). Deprotection of **17** (pyridine–polyhydrogenfluoride; according to Trost)[4] gave **18** (74%) identical with an authentic sample.

The surprise difference in stereoselectivity between the (trimethylsilyl)acetylene system **5** (26:1) and the terminal methylacetylene case **15** (3.3:1) implies that this group, which is three carbon atoms removed from both new stereocenters and itself eventually attached to a trigonal center, must exert the major influence upon the stereochemical outcome. The origin of this stereoselectivity is not known. At this stage, any speculation would not clarify the situation since the mechanism of the conversion of **4** into **5** and **11** into **12** is not well understood.

In summary, the dicobalt octacarbonyl strategy for the stereoselective synthesis of hydroxylated bicyclo[3.3.0]enones provides a short route to the tricyclic coriolin precursor **18** (12 steps, overall yield 3.2% from the readily available aldehyde **3**). Since **18** has been converted into coriolin itself, this constitutes a synthesis of the natural product and verifies the stereochemistry of the major product in the $Co_2(CO)_8$ cyclization step.

The dicobalt octacarbonyl alkene–alkyne–CO insertion reaction should provide a direct method of making many other natural and unnatural cyclopentanoid products.

Acknowledgment. The National Science Foundation is gratefully thanked for their support of this work (Grant CHE 8110674). They also provided funds (Grant CHE-8105004) for the purchase of a Nicolet 360-Hz NMR spectrometer. Professor Barry M. Trost is thanked for a comparison sample of **18** and relevant spectra.

Supplementary Material Available: NMR, melting point, and ν_{max} data for **4–9**, **11**, **12**, **14**, **15**, **17**, and **18** (3 pages). Ordering information is given on any current masthead page.

(7) All compounds were purified by chromatography over Florisil and subsequent bulb-to-bulb distillation if necessary.

Phospholipids Chiral at Phosphorus. 4. Could Membranes Be Chiral at Phosphorus?[1]

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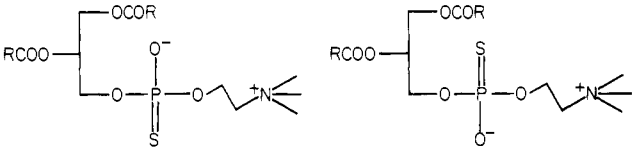
Received September 2, 1982

We present results of model study that suggest that phospholipid membranes could be chiral at phosphorus and the configuration of phosphorus could be important in the structure and properties of membranes.

The prochiral phosphorus center of phospholipids could in principle exist in four possible states in the liquid crystalline phase: (I) achiral, $^{\delta-}O{-}P{-}O^{\delta-}$; (II) chiral, O═P—$O^-$ (with the negative charge partially or fully localized); (III) chiral, ^-O—P═O; (IV) racemic, as a mixture of II and III. This fundamental problem has never been considered in the models for membrane structures and for protein–lipid interactions, although there is increasing evidence for the involvement of the phosphate head group in protein–lipid interactions,[2] and the conformations of head group of phospholipids have been studied recently.[3]

The problem is even more intriguing when considered with the recent report of Arnett and Gold[4] that the chiral C-2 center of dipalmitoyl phosphatidylcholine (DPPC) cannot be recognized by (*R*)-*N*-(α-methylbenzyl)stearamide (NMBS), but L-DPPC is able to recognize the chiral center of NMBS. Although they provided no explanation, a very logical one is that DPPC has another chiral recognition site other than C-2. Could this be the prochiral phosphorus center?

The model compounds used for states II–IV of DPPC are the isomer A (**1**), isomer B (**2**), and mixture (A + B) (**3**), respectively



1, DPPsC (A) **2**, DPPsC (B)

(R = $C_{15}H_{31}$), of 1,2-dipalmitoyl-*sn*-glycero-3-thiophosphorylcholine (DPPsC).[5] It should be noted that in **1** and **2** the absolute configuration at phosphorus is still unknown, and the localization of the negative charge at oxygen has no experimental proof. However, on the basis of the work in the sulfur analogues of nucleotides,[6] **1** and **2** should be good models for II and III.

To compare the properties of **1–3** in the liquid crystalline phase, we chose to measure the quadrupolar splitting $\Delta\nu_Q$ in ^{14}N NMR[7] and the chemical shift anisotropy $\Delta\sigma$ in ^{31}P NMR,[8] both of which are sensitive to the structural and motional properties of the phosphate head group. Figure 1 shows the ^{14}N NMR spectra (single-pulse experiment)[9] of the unsonicated aqueous dispersion

(1) Supported by grants from NSF (PCM 8140443) and from NIH (GM30327). The NMR spectrometers used were funded by NIH GM 27431 and NSF CHE 7910019. Part 3: Bruzik, K.; Jiang, R.-T.; Tsai, M.-D. *Biochemistry*, in press. Abbreviations used: NMR, nuclear magnetic resonance; DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphorylcholine; DPPsC, 1,2-dipalmitoyl-*sn*-glycero-3-thiophosphorylcholine; NMBS, *N*-(α-methylbenzyl)-stearamide.

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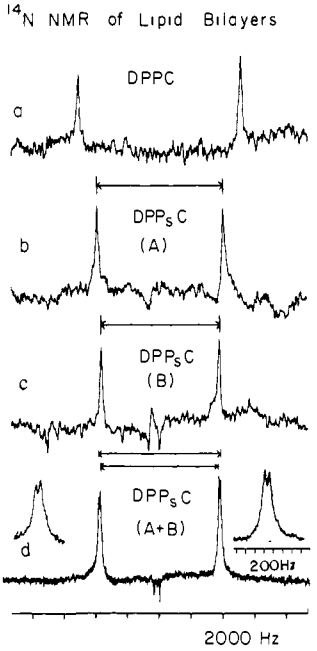

Figure 1. ^{14}N NMR spectra (at 21.7 MHz, Bruker WM-300) showing the quadrupolar splitting of DPPC (a), DPPsC (A) (b), DPPsC (B) (c), and DPPsC (A + B) (d) dispersed in excess water (H_2O/D_2O = 3/1). The weight percents of lipids are 12% (a–c) and 20% (d). Spectral parameters: spectral width, 50 KHz; acquisition time, 41 ms (except d, 82 ms); 45° pulse, broad-band ^{1}H decoupling (2.5 W); probe temperature, 46 °C, ^{2}H locked, spinning; line broadening, 50 Hz (except d, 10 Hz). Chemical shifts are 25.9 ppm for DPPC and 24.0 ppm for DPPsC (downfield from 5.4 M NH_4Cl).

Table I. ^{31}P and ^{14}N NMR Results of Lipid Bilayers of DPPsC[a]

compd	DPPC	DPPsC (A)	DPPsC (B)	DPPsC (A + B)
^{14}N NMR				
$\Delta\nu_Q$, KHz	10.26 ± 0.1	7.9 ± 0.1	7.5 ± 0.1	7.5 ± 0.1 7.7 ± 0.1
^{31}P NMR[b]				
$\sigma_\perp$, ppm	−16.3 ± 0.2	43.8 ± 0.4	44.7 ± 0.4	46.1 ± 0.2
$\sigma_\parallel$, ppm	30.4 ± 1.0	81.0 ± 1.0	79.0 ± 1.0	77.0 ± 1.0
$\Delta\sigma$, ppm	46.7 ± 1.2	37.2 ± 1.4	34.3 ± 1.4	30.9 ± 1.2

[a] The data are obtained from Figures 1 and 2 and at least three other independent sets of experiments (except for DPPC) at 46 °C. In each experiment the sample came from an independent synthesis or chromatography, and the weight percent lipid varies from 10% to 20%. The errors are estimated from the accuracy of the measurements and from the deviation in the four sets of data. The actual sample temperature was between 46 and 50 °C. Separately, we have shown that the $\Delta\nu_Q$ and $\Delta\sigma$ are constant within experimental error in the range of the probe temperature from 45 to 52 °C. [b] In all cases the $\sigma_\perp$ and the $\sigma_\parallel$ are measured at the half-height of the upfield shoulder and the downfield shoulder, respectively. The values of the peak tops are 44.7 ± 0.2 (A), 46.3 ± 0.3 (B), and 47.6 ± 0.3 (A + B).

of DPPC (**1a**), DPPsC (A) (**1b**), DPPsC (B) (**1c**), and DPPsC (A + B) (**1d**). The $\Delta\nu_Q$ measured from Figure 1 are listed in Table I. Figure 2 shows the ^{31}P NMR spectra of the same samples. The magnitudes of $\sigma_\parallel$, $\sigma_\perp$, and $\Delta\sigma$ obtained from Figure 2 are also listed in Table I. The result of the ^{31}P NMR of DPPsC (A + B) is consistent with that of Vasilenko et al.[10]

The data (Figures 1 and 2 and Table I) indicate several important points: (1) The model phospholipids **1–3**, which are chiral

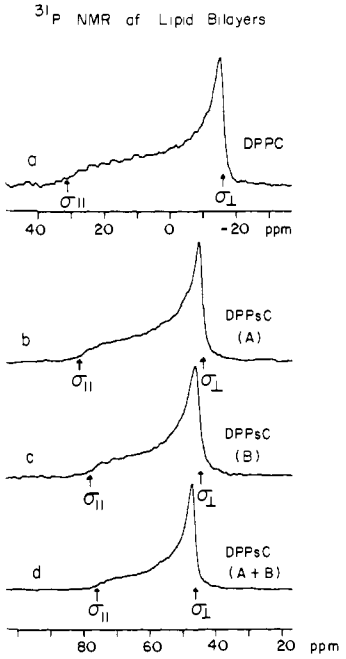

Figure 2. ^{1}H decoupled ^{31}P NMR spectra (at 81 MHz, Bruker WP-200) of DPPC (a), DPPsC (A) (b), DPPsC (B) (c), and DPPsC (A + B) (d) dispersed in excess water (H_2O/D_2O = 3/1). The weight percent of lipids is 12%. Spectral parameters: spectral width, 25 KHz; acquisition time, 0.164 s; pulse width, 15 μs (90° pulse, 20 μs), decoupler power, 3 W (further increase in the decoupler power did not change the line shape), probe temperature 46 °C; ^{2}H locked, spinning, line broadening, 50 Hz. Chemical shifts are referenced to external 1 M H_3PO_4 in D_2O.

at phosphorus, are capable of forming lipid bilayers that give ^{31}P line shapes and ^{14}N quadrupolar splittings characteristic of natural membranes. (2) Both $\Delta\nu_Q$ and $\Delta\sigma$ have reduced to ca. 70 ± 5% for DPPsC relative to DPPC. (3) **1–3** give small yet reproducible differences in the values of $\Delta\nu_Q$, $\sigma_\parallel$, $\sigma_\perp$, and $\Delta\sigma$. In ^{31}P NMR, the $\Delta\sigma$ falls in the order A > B > (A + B). In ^{14}N NMR, the $\Delta\nu_Q$ of isomer A is larger than that of isomer B by 0.4 ± 0.1 KHz, whereas the mixture A + B shows a splitting of 0.2 ± 0.1 KHz. The differences in both $\Delta\sigma$ and $\Delta\nu_Q$ have been shown not to be caused by small variations in sample preparation, weight percent lipid, and sample temperature.

The difference between the properties of DPPsC (A), DPPsC (B), and DPPsC (A + B) in the liquid crystalline phase is significant since in solution isomers A and B show only a small difference (<0.05 ppm) in ^{31}P chemical shifts[5] and show no detectable difference in ^{14}N NMR. In CH_3OD, the mixture DPPsC (A + B) gave a sharp ^{14}N NMR signal (half-width <3 Hz), which could not be resolved into two peaks. In $CDCl_3$, a broader signal (half-width 11 Hz) was observed due to micelle formation, but there was no detectable difference in both chemical shift and line width between DPPsC (A + B) and DPPsC (A).[11]

The mixture DPPsC (A + B) apparently forms a lipid bilayer that has different properties from those of isomer A, isomer B, or their additives. Therefore, the configuration of phosphorus seems important in determining the membrane properties, at least in the phosphate group and choline chain region. Work is in progress in our laboratory to examine other physical properties of **1–3** carefully.[12]

In conclusion, our results suggest that it should be possible for natural membranes to exist in one of the four states I–IV. In other

(9) Due to the limit in sample quantity and in the capability of our spectrometer, we were unable to perform quadrupole echo experiments. The single-pulse experiments gave distorted line shapes, but the $\Delta\nu_Q$ should be accurate and were reproducible within ±0.1 KHz. The samples were prepared by vortexing at 50–60 °C.

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(11) The solution ^{14}N NMR was measured with 100 mg of samples in 4.5 mL of solvents at 45 °C, with broad-band ^{1}H decoupling. Chemical shifts are 24.41 ppm in CH_3OD and 23.41 ppm in $CDCl_3$ (downfield from an external 5.4 M NH_4Cl solution in 15% D_2O).

(12) We have submitted crystal to measure the gel → liquid crystal transition temperature (T_c) by differential scanning calorimeter (Du Pont 1090 thermal analyzer). The T_c observed are 44.7 °C for DPPsC (A), 44.0 are for DPPsC (B), and 44.5 °C for DPPsC (A + B) (0.6 mg in 20 μL of potassium phosphate buffer, pH 7.12). Whether the difference is real or is due to experimental error remains to be further investigated.

words, membranes *could be* chiral at phosphorus, and the configuration at phosphorus could be important in membrane structures. It should not be presumed that the phosphorus is achiral (as in state I) in membranes without experimental proof. In the interaction of phospholipids with membrane proteins or enzymes, it is not impossible that the phosphate group may function as a chiral recognition site.[13]

(13) Although this concept may be difficult to be envisioned in membranes, we have already found that the phosphate group of phospholipids in the form of micelles functions as a chiral recognition site in the catalysis of phospholipase A_2. This enzyme hydrolyzes the C-2 carboxylic ester, which is five bonds away from the phosphorus center. However, it specifically takes the isomer B of DPPsC as a substrate.[5]

Chemically Induced Dynamic Electron Polarization (CIDEP) of Some Sulfur-Containing Cation Radicals: Evidence of the Charge-Transfer Processes between Quinone Cation Radicals and Sulfur Heterocyclic Compounds

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Received December 17, 1982

Although cation radicals have been extensively studied by ESR,[1-3] many of the reactions leading to the formation and observation of these radical cations in solution are complex and often incompletely understood. The recent elegant studies of alkane radical cations at 77 K in $CFCl_3$ or similar solvents[4-8] have utilized beautifully a simple charge-transfer mechanism to produce such interesting radical cations. The concept of charge transfer involving organometals in organic reactions has long been recognized,[9,10] and recently we were able to demonstrate the potential of the combined ESR and CIDEP (chemically induced dynamic electron polarization) technique in providing unequivocal evidence of the nature of the charge-transfer processes in the photochemical reactions between quinones and organotins.[11,12] In this report, we establish a model CIDEP system in charge-transfer studies in solution that involves the use of a unique charge transfer between the well-defined benzoquinone cation radicals and several sulfur-containing heterocycles in trifluoroacetic acid at room temperature. Historically, organosulfur cation radicals have occupied a prominent place both in ESR and organic chemistry literature.[13] The choice of organosulfur radical cations as our initial model CIDEP study will be of much wider general interest.

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Table I. ESR Parameters and CIDEP Observations for Some Organosulfur Cation Radicals in Trifluoroacetic Acid and in the Presence of $BQ^+\cdot$

organosulfur cation radical	g factor ±0.001	a_X, mT	T_1 ± 0.5, μs (temp, °C)
thianthrene	2.0085	0.128 (4 H) 0.89 (^{33}S)	1.5 ± 0.5 (−10)
phenothiazene	2.0051	0.634 (N) 0.729 (H-N) 0.113 (2 H) 0.050 (4 H) 0.249 (2 H)	1.8 (23)
thioxanthen-9-one	2.0072	0.367 (4 H) 0.110 (2 H) 0.092 (2 H)	2.1 (−10)
dibenzothiophene	2.0070	unresolved	1.7 (23)
4,4'-thiodiphenol	2.0068	0.135 (4 H)	1.3 (23)
thianaphthalene	2.0047	unresolved	
$BQ^+\cdot$	2.0038	0.299 (4 H)	4.6 (−10)

Trifluoroacetic acid was used as solvent for these reactions since its acidity and low nucleophilicity[14] contribute to the stabilization of the cation radicals formed in solution. Irradiation of 1,4-benzoquinone in trifluoroacetic acid with a 200-W super-pressure mercury lamp produced a radical species with the following ESR parameters: $g = 2.0038 \pm 0.0001$; $a_H = 0.229$ mT (4 H). This species can be reasonably assigned to the benzoquinone radical cation, $BQ^+\cdot$. At room temperature and in trifluoroacetic acid solvent, $BQ^+\cdot$ radical cations are persistent up to an hour after irradiation. This fact afforded the use of $BQ^+\cdot$ in trifluoroacetic acid as a definitive charge-transfer agent when other electron-donor molecules are added that do not form radical cations by themselves in trifluoroacetic acid. Thus, irradiation of benzoquinone in trifluoroacetic acid followed by the addition of *N,N,N',N'*-tetramethyl-*p*-phenylenediamine (TMPD) from a separated side arm configuration resulted in the immediate formation of the well-known $TMPD^+\cdot$ cation radical. Another example of this model system is diphenylamine, which formed the well-resolved diphenylamine radical cations in the presence of $BQ^+\cdot$. Neither TMPD nor diphenylamine yields radical cations by themself in trifluoroacetic acid.

Several sulfur-containing compounds undergo similar charge-transfer reactions with $BQ^+\cdot$ in trifluoroacetic acid, and the ESR parameters of some of these organosulfur radical cations observed are reported in Table I. Previous CIDEP studies of the quinone system in this laboratory usually dealt with the semiquinone radical or the radical anion, and indeed this is the first time we observed CIDEP from a benzoquinone cation radical. Two organosulfur radical cations, thianthrene and phenothiazine, were chosen for detailed CIDEP characterization. However, the use of the $BQ^+\cdot$ charge-transfer technique permitted observations of CIDEP from other less stable radical cations such as the thianaphthene. Thianthrene and phenothiazine both form radical cations thermally in trifluoroacetic acid, but their concentrations are further enhanced upon addition of benzoquinone. On the other hand, thianaphthene radical cations are produced only when $BQ^+\cdot$ is present.

We have pointed out previously[15] that CIDEP is a powerful tool in mechanistic and kinetic studies of photochemical reactions. In the present model system, the organosulfur radical cations formed thermally cannot exhibit *initial* polarization, which arises only from a photochemical triplet mechanism.[15] On the other hand, secondary thermal reactions involving polarized primary $BQ^{+\cdot *}$ formed photochemically can lead to polarization transfer from $BQ^{+\cdot *}$ to the organosulfur cation radical, provided the secondary reaction takes place before the destruction of polarization of $BQ^{+\cdot *}$ by spin-lattice relaxation:

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