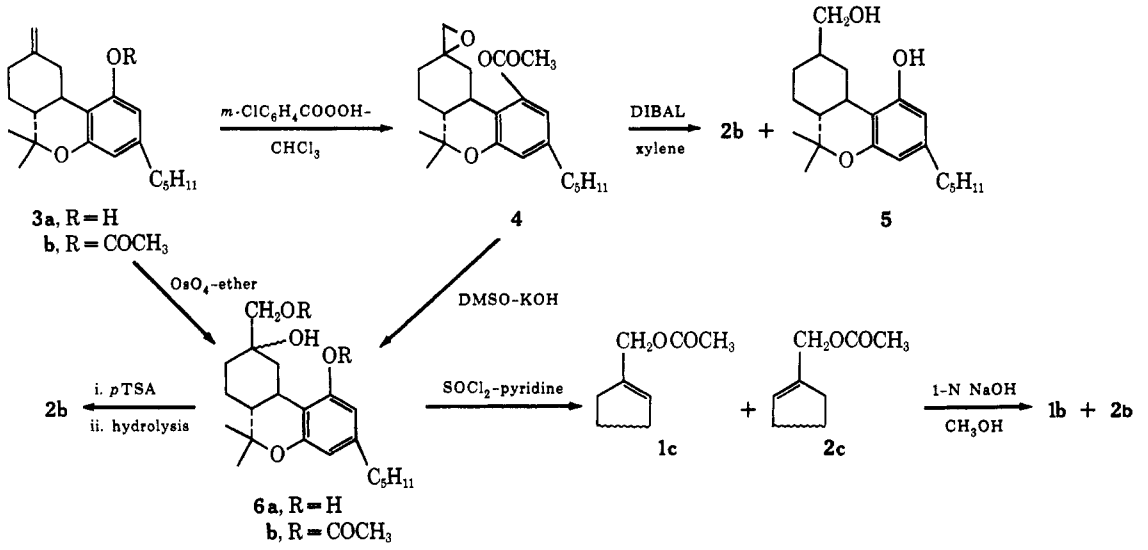
Scheme I



showed slight differences in the acetate region of the nmr and when it was treated with thionyl chloride in pyridine the resulting mixture contained **1c** and **2c** in a ratio of 1:6.[15,18]

Separation of the diacetates **1c** and **2c** was achieved using high-pressure liquid chromatography (lc) on a Waters Associates ALC-202 chromatograph equipped with a Model 6000 solvent delivery system. Various solvent systems were investigated on an 8 ft × 1/8 in. column of Corasil II. With 99.5% 1,2-dichloroethane–0.5% acetonitrile the capacity factor (k') was 2.08 for the Δ^1-diacetate **1c** and 2.52 for $\Delta^{1(6)}$ isomer **2c** giving a separation factor (α) of 1.21. Under these conditions, near base line resolution was obtained at low loading. Preparative separation was carried out with the same solvent system on an 8 ft × 3/8 in. column of Porasil C (k'_{1c} = 1.64, k'_{2c} = 2.00, α = 1.22). In a typical separation 240 mg of crude diacetate mixture containing approximately 18% of **1c** by glc analysis was placed on the column, impurity peaks were collected, and the peaks due to diacetates **1c** and **2c** were recycled into the column. After 2 recycles (2.5 hr) the Δ^1-diacetate **1c** (30 mg) was collected. This material is greater than 95% pure by glc analysis. Similar results have been obtained with sample sizes up to 800 mg.

The metabolites **1b** and **2b** can also be separated[16] by lc. On an 8 ft × 1/8 in. column of Corasil II eluting with heptane–dichloromethane–acetonitrile (90:17.5:7.5), the elution parameters were k'_{1b} = 4.9, k'_{2b} = 5.4, α = 1.10. Preparative separation has been carried out with this solvent system on an 8 ft × 3/8 in. column of Corasil II. This separation is more difficult than that of the diacetates **1c** and **2c** requiring eight recycles (6.5 hr) to obtain satisfactory separation of a 240-mg sample of crude **1b** and **2b**.

Additionally, two convenient syntheses of 7-OH-$\Delta^{1(6)}$-THC (**2b**) are provided by intermediates in Scheme I. Diacetate alcohol **6b** was dehydrated with *p*-toluenesulfonic acid,[9] followed by hydrolysis, to give **2b** in 75% overall yield from **3a** (*via* epoxide **4**). This route appears to be the method of choice for the preparation of **2b** as a comparison of this procedure with the osmium tetroxide route (overall yield 25%)[9] shows that the former gives cleaner products and is much simpler. Treatment of **4** with diisobutylaluminum hydride (DIBAL)[19] in xylene at 120° gave metabolite **2b** in 65% yield (based on glc analysis) together with 22% of 7-hydroxyhexahydrocannabinol (**5**) as identified by its mass spectral data *m/e* (70 eV) 332(M·+), 289, 276, 231, 193. Another product was found in this reaction mixture which showed the same retention time on glc as the metabolite **1b**. However, this material was shown by high-pressure lc and nmr not to be **1b**. It has been tentatively identified as the epimer of **5** at C_1. This finding illustrates the value of high-pressure lc as an analytical tool.

Acknowledgment. This work was carried out with the support of Contract No. HSM-42-72-230, National Institute of Mental Health, NIH, and HEW. We wish to thank Mr. J. Waters of Waters Associates for helpful suggestions in carrying out the lc separation work and Dr. G. Dudek of Harvard University for recording the Fourier transform nmr spectra.

(18) We attribute this change to differences in the stereochemistry of the hydroxyl group at C-1. The possibility that one isomer eliminates stereoselectively to give **1c** is at present under investigation.

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Phosphorylation of Amides. Evidence for Participation in Catalysis

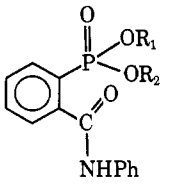
Sir:

Amide groups are known to serve as intramolecular nucleophilic catalysts for reactions at neighboring acyl carbon atoms.[1] However, no similar case of par-

(1) C. K. Sauers, C. L. Gould, and E. S. Ioannou, *J. Amer. Chem. Soc.*, **94**, 8156 (1972), and references therein.

ticipation of an amide at a phosphoryl center is known.[2] We now report the first observation of participation of an amide at a phosphoryl center and the implications of this type of reaction.

The anilide of 2-carboxydiethylphenylphosphonic acid (**1**) was prepared by photolysis of 2-iodobenzani-



1, $R_1 = R_2 = Et$

2, $R_1 = H$; $R_2 = Et$

3, $R_1 = R_2 = H$

lide[3] in triethyl phosphite, following Griffin's procedure[4] (mp 145°; ir (KBr) 1670 (C=O) and 1240 cm^{-1} (P=O); nmr ($CDCl_3$) δ 1.3 (t, 6, J = 8 Hz, CH_3), 4.2 (quin, 4, J = 8 Hz, CH_2), 7–8 (m, 9, ar). *Anal.* Calcd for $C_{17}H_{20}NO_4P$: C, 61.26; H, 6.04; N, 4.28; P, 9.29. Found: C, 61.35; H, 6.00; N 4.20; P, 9.17). The para isomer of **1** was prepared by treatment of the triethyl ester of *p*-carboxyphenylphosphonic acid[5] with the magnesium iodide salt of the aniline anion[6,7] (mp 107°; mass spectrum parent peak calcd for $C_{17}H_{20}NO_4P$, 333.1129; found, 333.1111).

Compound **1** contains an amide group that is situated in the molecule relative to the alkyl groups of the phosphonate at a distance which makes amide participation at carbon[8] unlikely.[9] This prediction is borne out by our observation that in alkaline solution the rate of saponification of the ester is approximately equal to that of diethyl phenylphosphonate.[10] Under these conditions, anchimeric assistance of hydrolysis through attack at carbon by the amide functionality occurs in phosphate compounds of suitable geometry.[11] In acidic solution, however, the rate of hydrolysis of **1** is much greater than that of both its para isomer and diethyl phenylphosphonate. Under conditions where **1** has a half-time of 1 hr for loss of both ester groups, diethyl phenylphosphonate and the para isomer of **1** show no nmr detectable (<5%) hydrolysis in 1 month. Rates of reaction at various acid concentrations were followed by nmr observation of ethanol produced compared to ethyl ester remaining. Analysis of the quantitatively isolated product **3** reveals that no cleavage of the amide linkage occurs during the hydrolysis of the ester. A uniform first-order rate plot over three half-times was obtained for *total* ethanol production at all acidities. The slope of the line in Figure 1, relating observed pseudo-first order rate constants to acid concentration, indicates a first-order dependence of k_{obsd} on acid concentration in dilute acid; k_{obsd} shows an upward deviation from the first-order line at higher acidity, consistent with the dependence of k_{obsd} on an acidity function.[12,13]

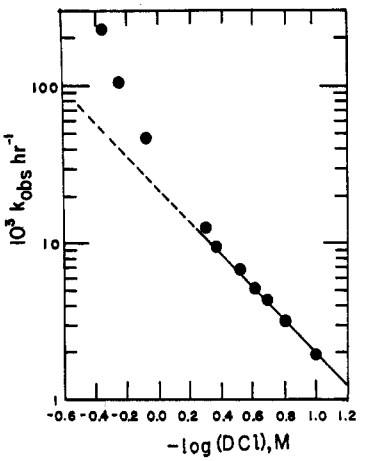


Figure 1. Hydrolysis of **1** in 50:50 acetone-d_6–D_2O with DCl at 30.0°. The line in the figure has a slope corresponding to a first-order dependence of k_{obsd} on acid concentration, yielding a second-order rate constant of 2.3×10^{-2} hr^{-1} M^{-1}. The para isomer of **1** under the same conditions hydrolyzes with a second-order rate constant of less than 3.2×10^{-6} hr^{-1} M^{-1}.

The sodium salt of the monoester **2** was prepared by reaction of **1** with sodium hydroxide in refluxing aqueous acetone. The rate constant for hydrolysis of **2** in 0.5 *M* DCl (acetone-d_6–D_2O) is 150 times greater than that of **1** at comparable acidity, indicating that the loss of the second molecule of ethanol is fast with respect to the loss of the first.[15] Therefore, the earlier step is rate determining, accounting for the uniform overall rate of hydrolysis of **1**. The kinetic requirements of the system are fulfilled by a mechanism involving intramolecular nucleophilic catalysis by the amide at phosphorus in an acid-catalyzed reaction. This is consistent with the large relative magnitude of the rate of the intramolecular reaction[16] of **1**, the extremely low basicity of aromatic amides[17] (making general base catalysis unlikely), and the superiority of amides as nucleophiles.[9] It has been noted that in acidic and neutral solutions the oxygen (rather than nitrogen) atom of the amide serves as the nucleophilic center.[9,18] A reaction sequence in accord with these

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(13) Solubility limitations necessitated observing the hydrolysis reactions in acetone–water mixtures for which no acidity function has been defined over the range of acid concentration. Yet, plots of the data in Figure 1 *vs.* H_0 for aqueous HCl[14] do yield a straight line (slope = 1.2). The proper acidity function for acetone-d_6–D_2O–DCl is being determined in order for the assignment to be tested rigorously.
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(15) The reason for the enhanced rate may be catalysis of the cyclization by the acidic group of the monoacid. This is under investigation.
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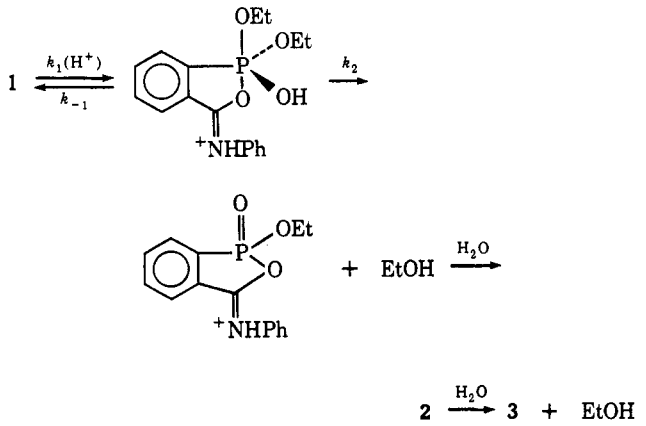
considerations is presented in Scheme I. A pentacovalent hydrolysis intermediate is indicated and has

Scheme I



been configured in a manner consistent with known energetics.[19] Pseudorotation of pentacoordinate intermediates is prohibited by steric and electronic requirements of the phosphonate ring system.[20,21] The involvement of such intermediates is not obligatory since products of the reaction must arise from "in line displacements"[22] as shown in Scheme I in which distinction between intermediate and transition state is not readily discernible. Cyclic tetracoordinate intermediates can react with water only to give ring-opened products in any case (and not alcohol). The rate expression corresponding to Scheme I and consistent with the data in Figure 1, where k_2 is the rate constant of the rate-determining step, is

$$\frac{d[2EtOH]}{dt} = \frac{k_1 k_2 [1][H^+]}{k_{-1} + k_2}$$
$$k_{obsd} = \frac{k_1 k_2 [H^+]}{k_{-1} + k_2} \quad (1)$$

Our data indicate that amide phosphorylation can occur in properly constituted systems (in a manner similar to that proposed for peptide participation in acyl transfer reactions[23]). A phosphorylated peptide linkage could be an intermediate in enzymatic phosphate transfer and hydrolysis reactions. Phosphorylation of a peptide bond could lead to a change of conformation of the protein, since the geometry of that peptide should be quite different from that of a normal peptide bond. In the reverse reaction, conformational change of a protein could lead *via* addition of phosphate to peptide linkages to products associated with oxidative phosphorylation.[24] We are continuing our studies on the phosphorylation of amides and related compounds in order to obtain data that will assist in the detection of such intermediates.

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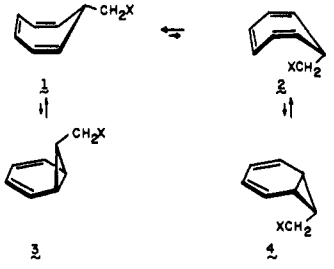
On the Absence of Significant Remote π-Bond Effects during Solvolysis of Epimeric Annelated 7-Cycloheptatrienylmethyl 3,5-Dinitrobenzoates[1]

Sir:

Sargent and his coworkers have drawn attention to the interesting fact that the solvolysis of 7-cycloheptatrienylmethyl 3,5-dinitrobenzoate proceeds by prior isomerization to the norcaradienylcarbinyl valence tautomer.[2] However, because the configuration of the ionizing molecule could not be determined, the following important factor was not considered in the earlier work. Cycloheptatriene is recognized to exist as a rapidly equilibrating pair of boat conformations ($E_{act} \simeq 6$ kcal/mol)[3] which comprises a nondegenerate process for many substituted derivatives (*e.g.*, **1** $\rightleftarrows$ **2**). Since each of these conformers in turn exists in equilibrium with the corresponding bicyclic form, ionization could conceivably occur from thermodynamically more stable isomer **3** (by virtue of fewer nonbonded interactions), from that isomer (**4**) in which the incipient



electron-deficient center is nearer the π system (particularly if enhanced stabilization resulted from this interaction), or from both forms at roughly competitive rates should any special effects be absent or fortuitously cancelling.

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(3) For a recent review of this subject, see G. Maier, *Angew. Chem., Int. Ed. Engl.*, **6**, 402 (1967).