Carboxyl-Assisted Hydrolyses. Synthesis and Hydrolysis of Diphenyl *cis*-2-(3-Carboxy)norbornyl Phosphates

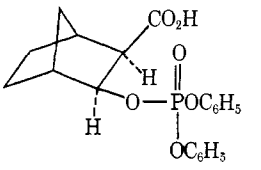
S. Stoney Simons, Jr.*

Contribution from James Bryant Conant Laboratories, Harvard University, Cambridge, Massachusetts 02138. *Received December 5, 1973*

Abstract: The diphenyl phosphate esters of the *cis*-hydroxy acids **1** and **2** have been prepared. These compounds show carboxyl-assisted hydrolysis, with rate enhancements at pH ~5 that may be as great as 10^7-fold.

The hydrolysis of phosphate esters can be greatly accelerated by internal catalysis, and such internal catalysis may provide models for enzymic hydrolysis of phosphates.[1] Although studies of the hydrolysis of monoesters and diesters are specifically of interest for comparison with enzymic reactions, the general physical–organic chemistry of all phosphate esters needs elucidation. In addition to hydrolysis assisted by adjacent hydroxyl groups (as in the alkaline hydrolysis of RNA[2] and models for that process[3]), a number of examples of carboxyl-assisted hydrolyses are known.[1,4] Among the most thorough studies are those of Kirby, *et al.*,[5] on the alkaline hydrolyses of phenyl salicyl phosphate, diphenyl salicyl phosphate, and diphenyl 2,3-dicarboxyphenyl phosphate. In these latter examples, the adjacent carboxyl group increases the rate of hydrolysis as much as 10^7-fold, and the reactions have clearly been shown to proceed by way of nucleophilic attack of the carboxyl group on the adjacent phosphorus atom. Incidentally, pseudorotation[6] is required as a part of the hydrolytic process.

Much recent discussion has centered on the questions of steric control and steric acceleration in cyclization reactions.[7–10] We therefore decided to prepare phosphate esters with carboxyl groups rigidly placed relative to the ester function but where the carboxyl group possessed a configuration relative to the phosphate ester that is different from that of the salicyl phosphates. In particular, we synthesized compounds **1** and **2** and compared their rates of hydrolysis with those of unassisted phosphates and with those of the salicyl phosphates studied by Kirby.



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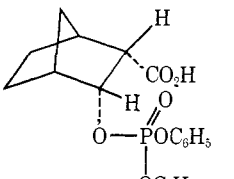

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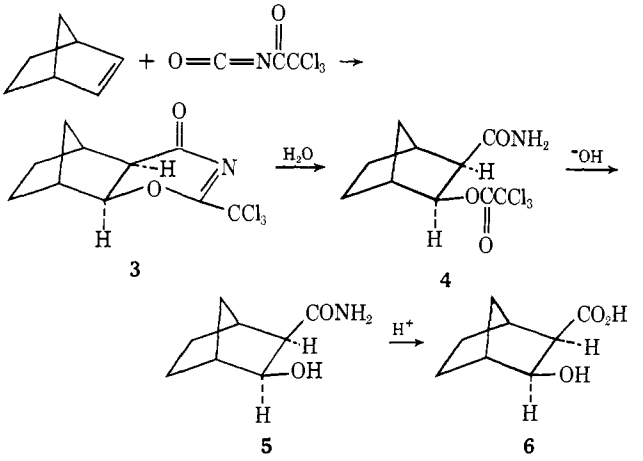
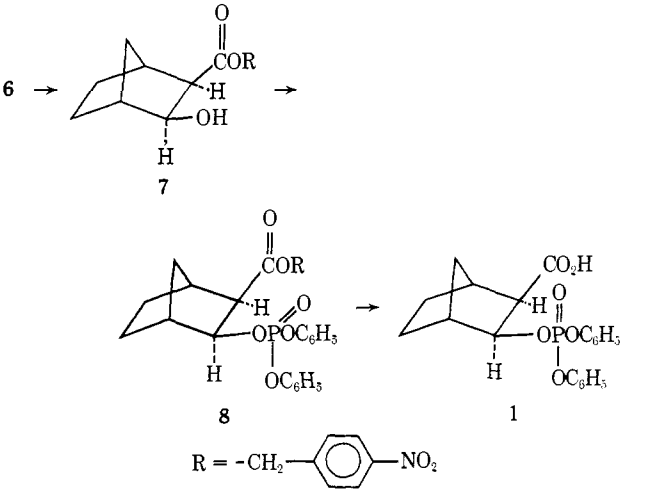
The synthesis of *exo-cis*-3-carboxy-2-norborneol (**6**) was carried out by the method outlined below, where the preparation of **3** and **4** was conducted by the methods introduced by Speziale, *et al.*[11,12]



3 4 5 6

The *p*-nitrobenzyl ester **7** was phosphorylated with diphenyl phosphorochloridate to yield **8**, which was in



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* Address correspondence to this author at the Department of Biochemistry, University of California, San Francisco, San Francisco, Calif. 94143.

(1) T. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. II, W. A. Benjamin, 1966, Chapter 5.

(2) (a) R. Markham and J. D. Smith, *Biochem. J.*, **52**, 552 (1952); (b) D. M. Brown and A. R. Todd, *J. Chem. Soc.*, 52 (1952).

(3) J. Kumamoto, J. R. Cos., Jr., and F. H. Westheimer, *J. Amer. Chem. Soc.*, **78**, 4858 (1956).

(4) S. J. Benkovic and E. J. Lampson, *J. Amer. Chem. Soc.*, **93**, 4009 (1971).

(5) A. J. Kirby and M. Younan, *J. Chem. Soc. B*, 1165 (1970); (b) S. A. Khan, A. J. Kirby, M. Wakselman, D. P. Horning, and J. M. Lawlor, *ibid.*, 1182 (1970); (c) R. H. Bromilow, S. A. Khan, and A. J. Kirby, *ibid.*, 1091 (1971); (d) *J. Chem. Soc., Perkin Trans. 2*, 911 (1972).

(6) (a) E. A. Dennis and F. H. Westheimer, *J. Amer. Chem. Soc.*, **88**, 3431, 3432 (1966); (b) F. H. Westheimer, *Accounts Chem. Res.*, 1, 70 (1968).

(7) R. Borchardt and L. Cohen, *J. Amer. Chem. Soc.*, **94**, 9175 (1972).

(8) D. Storm and D. E. Koshland, Jr., *J. Amer. Chem. Soc.*, **94**, 5805, 5815 (1972); *Proc. Nat. Acad. Sci. U. S.*, **66**, 445 (1970).

(9) (a) T. C. Bruice and A. Turner, *J. Amer. Chem. Soc.*, **92**, 3422 (1970); (b) T. C. Bruice, A. Brown, and D. O. Harris, *Proc. Nat. Acad. Sci. U. S.*, **68**, 658 (1971).

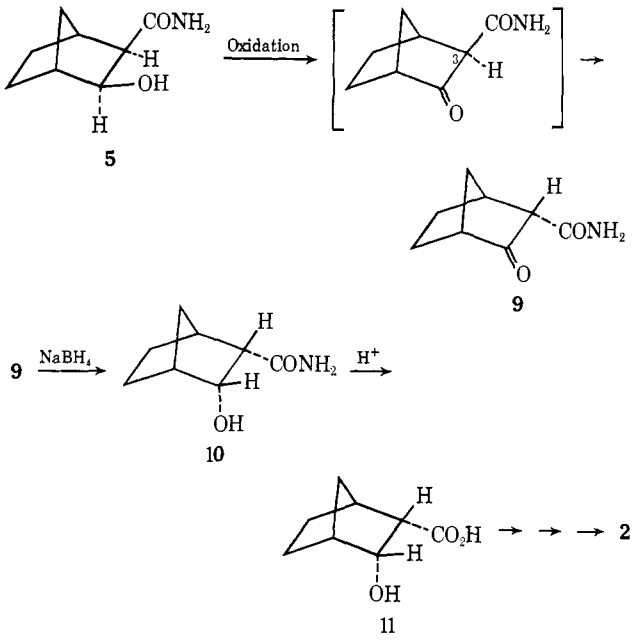
(10) W. P. Jencks and M. Page, *Proc. Nat. Acad. Sci. U. S.*, **68**, 1678 (1971).

(11) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **28**, 1805 (1963).

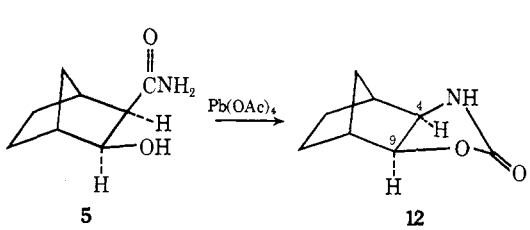
(12) L. R. Smith, A. J. Speziale, and J. E. Fedder, *J. Org. Chem.*, **34**, 633 (1969).

turn cleaved by hydrogenolysis to yield the desired cis-exo phosphate ester **1**.

The corresponding cis-endo series was entered by oxidation of the cis-exo amide **5** to the endo ketone. [Evidence that the oxidation, with several different reagents and under different experimental conditions, is accompanied by stereochemical inversion at the carbon atom holding the carbamyl group (carbon atom 3) is outlined in the following paragraphs.] Borohydride reduction of the keto amide **9** led to the cis-endo amide **10** which was hydrolyzed to the cis-endo acid **11**. This acid was then phosphorylated by the same general scheme as that used for the exo series to obtain the cis-endo phosphate ester **2**.

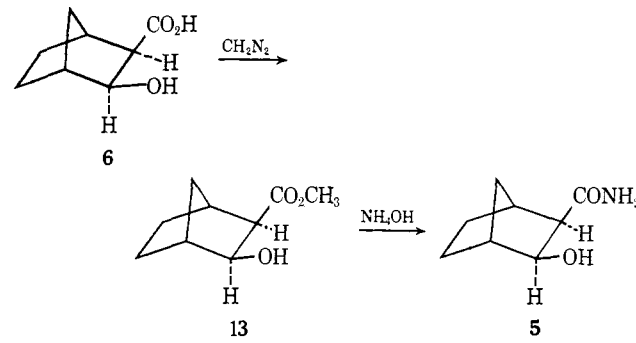


The assignments of stereochemistry to the various products here reported seem reasonsble on the basis of the following arguments. The cis-exo configuration of the oxazinone **3** is appropriate to a Diels–Alder adduct and was confirmed by Speziale, *et al.*,[11,12] by a thorough nmr study. The mild hydrolysis of the oxazinone to the hydroxy amide suggests that this product, too, is cis-exo. The cis configuration of the compound was further confirmed in this investigation when reaction of the hydroxy amide **5** with lead tetraacetate yielded[13] the cis-exo-fused norbornyl[2,3-*d*]-2-oxazolidinone (**12**). This stereochemistry was confirmed by the barely discernible doublet of doublets in the nmr for the C_4 and C_9 methine hydrogens ($J_{4\,\mathrm{endo},\,9\,\mathrm{endo}}$ = 7 Hz, $J_{4,5} = J_{8,9} = 0.5$ Hz).[14,15]



(13) S. S. Simons, Jr., *J. Org. Chem.*, **38**, 414 (1973).
(14) R. R. Frazer and Y. S. Lin, *Can. J. Chem.*, **46**, 801 (1968).
(15) J. I. Musher, *Mol. Phys.*, **6**, 93 (1963).

Acid hydrolysis of the hydroxy amide **5** occurs without alteration of stereochemistry; this was established by reconverting the acid **6**, *via* the methyl ester, to the



starting amide **5**. The reconversion of the hydroxy acid **6** to the amide also proves that no rearrangement of the norbornyl skeleton occurred during the acid-catalyzed hydrolysis of the amide.

The preparation of the endo series depends on epimerization accompanying oxidation. Since the oxidation product is a β-keto amide, the hydrogen atom α to these functions on carbon atom 3 is necessarily highly enolizable. Hydrogen–deuterium exchange experiments in fact demonstrate that this hydrogen atom exchanges rapidly (a few minutes at room temperature) under experimental conditions (aqueous pyridine solution) similar to or milder than those used for the successful oxidation of the hydroxy amide with Collins reagent. The stereochemistry of the keto amide cannot therefore be inferred from that of the starting material; it can, however, be inferred as endo from the following considerations. Brominative oxidation of the *cis-exo*-hydroxy amide with *N*-bromoacetamide[16] affords a bromoketo amide that yields the keto amide **9** on zinc reduction; analogy with similar reactions leads to the prediction of *endo*-keto amide.[17,18] Skeletal rearrangements on oxidation are improbable since oxidations under widely different conditions lead to the same product; these methods include Jones reagent, Collins reagent, heterogeneous chromic acid, and brominative oxidation by *N*-bromoacetamide. Furthermore, the nmr spectrum of the product and its fragmentation in mass spectroscopy give no evidence of skeletal rearrangement.

Confirmatory results were obtained on borohydride reduction of the keto amide. Two hydroxy amides were obtained and, although one was obtained only in minute yield, neither of them was identical with the cis-exo product. The two new hydroxy amides therefore are most probably the 2-*endo*-hydroxy 3-*endo*-amide and the 2-*exo*-hydroxy 3-*endo* amide-products. The major product may be assigned the cis-endo configuration on the basis of analogy with the products of similar reduction with borohydride;[19] the opposite stereochemistry, induced by a neighboring carbamyl group, has so far been observed only in reductions with lith-

(16) W. G. Woods and J. D. Roberts, *J. Org. Chem.*, **22**, 1124 (1957).
(17) (a) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 32 (1958); (b) R. R. Sauers and C. K. Ha, *J. Org. Chem.*, **36**, 1153 (1971).
(18) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 6269 (1956).
(19) H. C. Brown and J. Muzzio, *J. Amer. Chem. Soc.*, **88**, 2811 (1966).

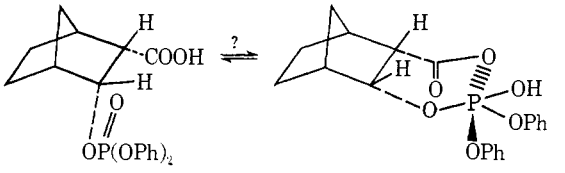
ium aluminum hydride.[20] A more convincing demonstration can be obtained from considerations of the nmr spectrum of the final phosphate ester. In particular, the hydrogen atom on position 2 appears as a complex pattern at δ 5.2, with three coupling constants of 4.5, 6.5, and 10.5 Hz, assigned $J_{2\,exo,\,1}$, $J_{2\,exo,\,P}$, and $J_{2exo,3exo}$, respectively. The identification of the coupling constants was demonstrated by irradiation of the sample at 292 (C_3-H) and 520 Hz (C_2-H) and by comparing the nmr with those of the two immediate precursors (*i.e.*, hydroxy ester and ester phosphate ester). All couplings are consistent[14] with the assigned structure and not with that expected if the proton at position 3 had been endo; under this assumption the coupling constants would probably have been $J_{2exo,1}$ = 4.5 Hz, $J_{2\,exo,\,P}$ = 6.5 Hz, and $J_{2\,exo,\,3\,endo}$ = 2–4 Hz. Furthermore, the nmr chemical shift of the protons at positions 2 and 3 in the compounds assigned the cis-exo and cis-endo configurations (shown in Table I) is consistent

Table I

	Chemical shifts (δ) at C_2-H	C_3-H
Cis-exo phosphate ester **1**	4.82	2.61
Cis-endo phosphate ester **2**	5.2	2.92

with the generalization[21] that, in epimerically substituted bornanes, the signal from exo protons always appears further downfield than that from endo protons.

The stereochemistry of the *cis*-hydroxy acids **6** and **11** and of the corresponding phosphate esters **1** and **2** thus appears reasonably secure. There remained, however, the possibility that the constrained approximation of the acid and phosphate ester groups in **1** and **2** could force the formation of a hitherto unknown hydroxyphosphorane (*e.g.*, **14**). The ^{31}P nmr signal of similar pentacoordinated phosphorus compounds shows a strong, positive shift (16–52 ppm upfield from triphenyl



2 **14**

phosphate),[22] while the ^{31}P nmr signal for butyl diphenyl phosphate appears at −6 ppm.[23] The fact that a ^{31}P Fourier transform nmr of **2** revealed only a single peak 5 ppm downfield from triphenyl phosphate (external standard) confirms the acid phosphate ester structure of **2**.

Experimental Section

Materials. ***exo*-3-Carbamyl-*exo*-2-norbornyl trichloroacetate (4)** was synthesized from trichloroacetyl isocyanate[11] and norbornene by the method of Smith, Speziale, and Fedder.[12] Crude benzoxazinone **3**, the intermediate in this synthesis, was hydrolyzed to **4** by 15 min of refluxing in 75% aqueous acetone. The melting point of the amide ester, 175.0–176.0°, corresponded with that reported,[12] and the material was analytically pure,[24] although the ir showed small anomalous peaks at 1695 and 1600 cm^{-1}, indicative of unreacted oxazinone.

***exo*-3-Carbamyl-*exo*-2-norborneol (5).** A slurry of 10 g of a mixture of crude benzoxazinone **3** and ester **4** (mp 97–104°)[24] in 35 ml of acetone was added drop by drop with stirring at room temperature to 70 ml of 0.35 *N* sodium hydroxide in 30% acetone. The reaction mixture, which turned bright yellow, was kept alkaline by addition of 1 *N* aqueous sodium hydroxide. At the end of the addition, 130 ml of water was added, and the solution adjusted to a pH of about 7.5 with more base; exactly 1 equiv was finally consumed. The solution was stirred for 30 min and flash evaporated to a viscous oil which was dissolved in 100 ml of acetonitrile. After 3 hr the white solid which had precipitated was removed by filtration and extracted with three 100-ml portions of acetonitrile. The combined acetonitrile solutions were rotary evaporated and the crude residue was recrystallized from acetonitrile. The hydroxy amide melted at 132.0–132.8°; the yield, including a second crop, was 92%. An analytical sample, obtained from ethyl acetate, melted at 132.9–133.3°: ir (Nujol) $\nu_{NH,\,OH}$ 3350, 3220 cm^{-1}; ir (Nujol) $\nu_{C=O}$ 1650, 1590 cm^{-1}; mass spectrum (rel intensities) 155 (P$^+$, 1), 127 (P − CO, 100), 88 (63), 85 (90); nmr (100 MHz, DMSO-d_6) δ 7.15 and 6.80 (br s, 2 H), 4.99 (d, *J* = 5 Hz, 1 H), 3.82 (d of d, *J* = 5 and 7 Hz, 1 H), 3.4–0.9 (m, 9–10 H). *Anal.* Calcd for $C_8H_{13}NO_2$ (mol wt 155.19): C, 61.91; H, 8.44; N, 9.03. Found: C, 61.84; H, 8.54; N, 9.11.

***exo*-3-Carboxy-*exo*-2-norborneol (6).** A solution of 1.20 g of *cis-exo*-hydroxy amide **5** in 24 ml of 2 *N* hydrochloric acid was refluxed for 40 min and evaporated *in vacuo* at about 40°. After removal of more water by azeotropic distillation with benzene *in vacuo*, the residue was extracted with three 50-ml portions of benzene; the crude product obtained on evaporation of the benzene and recrystallization from benzene–*n*-hexane yielded 1.02 g of product, mp 92.8–93.5°. A final recrystallization from benzene–*n*-hexane gave the analytical sample: mp 93.3–94.0°; ir (Nujol) ν_{OH} 3350, 2550 cm^{-1}; ir (Nujol) $\nu_{C=O}$ 1700 cm^{-1}; mass spectrum (rel intensities) 156 (P$^+$, 0.07), 138 (P − H_2O, 33), 128 (P − CO, 78), 110 (49), 93 (35), 86 (36), 66 (100). *Anal.* Calcd for $C_8H_{12}O_3$ (mol wt 158.18): C, 61.52; H, 7.75. Found: C, 61.88; H, 7.68.

Hydrolysis with base (potassium or barium hydroxide) was unsuccessful.

Reconversion of *exo*-3-Carboxy-*exo*-2-norborneol (6) to the Corresponding Amide 5. A solution of 200 mg of the *cis-exo*-hydroxy acid in 10 ml of purified THF was titrated to a yellow end point with an ethereal solution of diazomethane.[26] After 30 min at room temperature, the residual yellow color was dispersed with a dilute solution of acetic acid in THF, and the solution was evaporated. The residue was dissolved in methylene chloride, extracted with base, washed, and chromatographed in chloroform on 10 g of Florisil. After chromatography, 190 mg of colorless product (assumed to be crude methyl ester **13**) was obtained: ir (neat) ν_{OH} 3475 cm^{-1}; ir (neat) $\nu_{C=O}$ 1725 cm^{-1}. The crude ester (0.10 g) was stirred for 42 hr at room temperature with 6 ml of concentrated ammonium hydroxide. The ammonia solution was evaporated

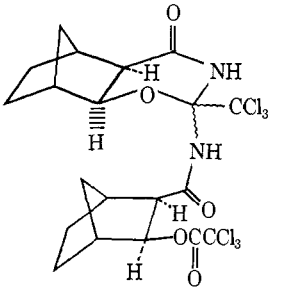
(20) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Shenker, *Tetrahedron*, **18**, 247 (1963).

(21) T. J. Flautt and W. F. Erman, *J. Amer. Chem. Soc.*, **85**, 3213 (1963).

(22) J. C. Tebby in "Organophosphorus Chemistry," Vol. II, The Chemical Society, London, 1971, p 236.

(23) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, Oxford, 1966, pp 1063, 1066.

(24) Mixtures of these two compounds gave, upon heating for 15–30 min at 160–165°, a Michael-type addition product i:[25] mp 207.2–



i

208.0°. *Anal.* Calcd for $C_{20}H_{22}N_2O_6Cl_6$ (mol wt 583.13): C, 41.19; H, 3.80; N, 4.81; Cl, 36.48. Found: C, 41.07; H, 3.87; N, 4.86; Cl, 36.31.

(25) S. S. Simons, Jr., Ph.D. Thesis, Harvard University, 1972.

(26) J. A. Moore and D. E. Reed, *Org. Syn.*, **41**, 16 (1961).

and the residue extracted with benzene; the benzene was removed and replaced with acetonitrile. Filtration gave 40 mg of white solid which, on acidification, was converted to starting hydroxy acid **6**, identified by ir. The acetonitrile solution on evaporation yielded 60 mg of solid that, after recrystallization from ethyl acetate, gave the hydroxy amide **5**, identified by ir; its purity was established by tlc on silica gel with ethyl acetate.

endo-**3-Carbamyl-2-norbornanone (9).** Three different chromic acid oxidation procedures yielded the same product. Oxidation by Jones reagent[27] or by the procedure of Brown and Garg[28] is described in detail elsewhere.[25] In a slight modification[29] of Collins' procedure,[30] 3.00 g of the *cis-exo*-hydroxy amide **6**, in 22 ml of dry pyridine and 125 ml of methylene chloride, was added over 18 min at 8° to a stirred solution of 77 g of dry Celite and 49 g of Collins reagent in 950 ml of dry methylene chloride. After 10 min of stirring at 8° and 2 hr at room temperature, 96 g of powdered sodium bisulfate monohydrate was added, and the mixture was stirred for 100 min. The reaction mixture was filtered through Celite which was in turn washed four times with a total of about 1 l. of methylene chloride. The methylene chloride solutions were then evaporated, and the residue was extracted into ether. The ether was freed from pyridine by repeated vacuum azeotropic distillation with benzene to yield 1.8 g (61%) of a tan solid. Recrystallization from ethyl acetate–*n*-hexane (hot filtration) afforded, in the first crop, 720 mg of a pure product: mp 107.7–108.9°; ir (Nujol) ν_{NH} 3400, 3200 cm^{-1}; ir (Nujol) $\nu_{C=O}$ 1730, 1640 cm^{-1}; mass spectrum (rel intensities) 153 (P$^+$, 36), 97 (37), 86 (100), 81 (37), 67 (37); nmr (100 MHz, $CDCl_3$) δ 7.10 and 6.60 (br s, 2 H), 3.04 (m, 2 H), 2.74 (m, 2 H), 1.70 (m, 5 H). *Anal.* Calcd for $C_8H_{11}NO_2$ (mol wt 153.18): C, 62.72; H, 7.24; N, 9.14. Found: C, 62.79; H, 7.29; N, 9.08.

exo-**3-Bromo-*endo*-3-carbamyl-2-norbornanone.** A solution of 4.20 g of *N*-bromoacetamide (Aldrich) in 33 ml of methanol was prepared at 0° in the dark, and 0.2 ml of water, 1.13 ml of pyridine, and a solution of 0.465 g of the *exo*-hydroxy amide **5** in 6 ml of methanol were added.[31] After 21 hr of refluxing in the dark, the solution was treated with a few crystals of sodium thiosulfate and enough 6 *N* hydrochloric acid to reduce the pH below 2. The acidic solution was evaporated *in vacuo* and extracted with three 25-ml portions of methylene chloride. The organic solvent was again evaporated and the resulting oil chromatographed on 6 g of Florisil in ethyl acetate. This separated the crude product from 0.24 g of recovered starting material. Rechromatography in ethyl acetate on 42 g of Florisil (3.0 × 20 cm column) gave a solution from which 280 mg of crystalline product could be recovered; this is an 80% yield allowing for recovery of starting material. One recrystallization of the product from cyclohexane–benzene (6:1) gave analytically pure **14**: mp 151.0–153.0°; ir (Nujol) ν_{NH_2} 3380, 3160 cm^{-1}; ir (Nujol) $\nu_{C=O}$ 1750 cm^{-1}; ir (Nujol) ν_{amide} 1680 cm^{-1}; mass spectrum (rel intensities) 203 and 205 (P − CO, 21 and 21), 175 and 177 (P − 2CO, 40 and 39), 152 (P − Br, 20), 124 (50), 81 (100). *Anal.* Calcd for $C_8H_{10}NO_2Br$ (mol wt 232.08): C, 41.40; H, 4.34; N, 6.04; Br, 34.43. Found: C, 41.50; H, 4.28; N, 6.17; Br, 34.55.

Reduction of the Bromonorboranone to *endo*-3-Carbamyl-2-norboranone (9). *exo*-3-Bromo-*endo*-3-carbamyl-2-norbornanone (50 mg) was dissolved in 1.2 ml of 3:1 acetic acid–water. Fresh zinc dust (120 mg) was added at room temperature and the mixture stirred vigorously for 30 min. Excess zinc was removed by filtration and thoroughly washed with methylene chloride. Aqueous sodium hydroxide was added to the water–methylene chloride solution to bring the pH to 8. Some of the white precipitate was dissolved with added HCl and the rest was removed by filtration, and the filtrate was extracted with methylene chloride. The combined methylene chloride solutions were dried and evaporated to yield 20 mg of crystallizing solid, with an ir identical with that of the analytically pure keto amide **9**, prepared by chromic acid oxidation.

endo-**3-Carbamyl-*endo*-2-norborneol (10).** A solution of 1.14 g of *endo*-keto amide **9** in 50 ml of isopropyl alcohol was added at 0° to a solution of 350 mg of sodium borohydride in 260 ml of the same solvent.[32] After 68 hr at 0°, the reaction mixture was treated with 38 ml of 1 *N* hydrochloric acid and evaporated *in vacuo*. The residue was treated with two 225-ml portions of methanol and the organic solvent evaporated *in vacuo* to remove boron compounds;[33] the residue consisted of 850 mg of solid that crystallized from water. After repeated recrystallizations from ethyl acetate, the product melted at 167.3–168.0°: ir (Nujol) $\nu_{NH,\ OH}$ 3250 cm^{-1}; ir (Nujol) $\nu_{C=O}$ 1640, 1570 cm^{-1}; mass spectrum (rel intensities) 155 (P$^+$, 1.1), 127 (P − CO, 100). *Anal.* Calcd for $C_8H_{13}NO_2$ (mol wt 155.19): C, 61.91; H, 8.44; N, 9.03. Found: C, 62.10; H, 8.53; N, 9.00.

A minor product, obtained in minute yield from the mother liquors, could be obtained as an oil from water and then recrystallized from acetonitrile, and melted at 116–119°: ir (Nujol) $\nu_{OH,\ NH}$ 3380, 3210 cm^{-1}; ir (Nujol) ν_{amide} 1680, 1625 cm^{-1}; mass spectrum (rel intensities) 155 (P$^+$, 15), 127 (P − CO, 99), 88 (55), 85 (100), 72 (62), 59 (53). Insufficient material was available for analysis.

endo-**3-Carboxy-*endo*-2-norborneol (11).** A solution of 460 mg of *cis-endo*-hydroxy amide **11** was refluxed in 9.2 ml of 2 *N* hydrochloric acid for 1 hr. When the reaction mixture was cooled, 310 mg of solid crystallized; more material, to give an essentially quantitative yield, could be obtained on extraction of the aqueous acid with ethyl acetate. One recrystallization from ethyl acetate–benzene afforded an analytical sample: mp 138.8–139.1°; ir (Nujol) ν_{OH} 3280, 2600 cm^{-1}; ir (Nujol) $\nu_{C=O}$ 1675 cm^{-1}; mass spectrum (rel intensities) 156 (P$^+$, 0.8), 138 (P − H_2O, 31), 128 (P − CO, 84), 110 (46), 93 (36), 86 (34), 66 (100). *Anal.* Calcd for $C_8H_{12}O_3$ (mol wt 156.18): C, 61.52; H, 7.75. Found: C, 61.69; H, 7.69.

Exchange of the Hydrogen Atom at Position 3 of the Keto Amide 9. The nmr spectrum of the keto amide **9** in pyridine showed characteristic peaks for all the relevant protons, including a broad multiplet for 3 proton at δ 2.74. A repetition of the spectrum in the same solvent with 2–3 drops of added D_2O gave essentially the same spectrum except that the signal for the 3 proton was missing, and, of course, a large new peak for HDO was present. The exchange was complete by the time the spectrum was taken, *i.e.*, in about 10 min at room temperature.

endo-**2-Norbornyl Diphenyl Phosphate.** A solution of 350 mg of *endo*-2-norborneol, mp 147.0–148.0°,[34] in 4.2 ml of dry pyridine was stirred under argon at −12° (ice–acetone) with 965 mg of diphenyl phosphorochloridate and then allowed to stand for 1 hr at room temperature.[35] The reaction mixture was poured into 65 ml of ice water, and enough hydrochloric acid was added to lower the pH about 1. The solution was extracted with 100 ml of of methylene chloride and the organic solvent washed with acid, water, and bicarbonate, then dried, and evaporated. The oily product, obtained in quantitative yield, crystallized from the oil after several weeks in a deep freeze; subsequent samples crystallized more promptly after seeding. Two recrystallizations from petroleum ether yielded 800 mg of analytically pure needles: mp 58.0–58.9°; ir (Nujol) 3070, 1590, 1450, 1275, 1185, 1035, 772, and 685 cm^{-1}; mass spectrum (rel intensities) 344 (P$^+$, 35), 250 100); (P + 1)/P = 20.7% (calcd 20.5%). *Anal.* Calcd for $C_{19}H_{21}O_4P$ (mol wt 344.34): C, 66.27; H, 6.15; P, 9.00. Found: C, 66.20 and 66.37; H, 6.13; P, 8.94.

exo-**2-Norbornyl diphenyl phosphate** was synthesized in similar fashion to the endo epimer from *exo*-2-norborneol kindly supplied by J. Lerman (Harvard University). The product, obtained in 78% yield after two recrystallizations from pentane, melted at 51.6–52.0°: ir (Nujol) 3080, 1590, 1450, 1270, 1190, 1015, 775, 754, and 685 cm^{-1}; mass spectrum (rel intensities) 344 (P$^+$, 31), 250 (100); (P + 1)/P = 20.2% (calcd 20.5%). *Anal.* Calcd for $C_{19}H_{21}O_4P$ (mol wt 344.34): C, 66.27; H, 6.15; P, 9.00. Found: C, 66.15; H, 6.30; P, 8.80.

Diphenyl *exo*-2-(*exo*-3-Carboxy)norbornyl Phosphate (1). *cis-exo*-Hydroxy acid **6** (121 mg) was neutralized with 10% sodium hydroxide in 0.6 ml of water and refluxed for 1 hr with 195 mg of *p*-nitrobenzyl bromide in 1.2 ml of alcohol. The ester **7** was extracted into methylene chloride, dried ($MgSO_4$), and evaporated *in vacuo*

(27) J. Meinwald, J. Crandall, and W. E. Hymans, *Org. Syn.*, **45**, 77 (1965).

(28) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

(29) Hisashi Yamamoto, Harvard University, private communication.

(30) J. R. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(31) This procedure parallels that of R. E. Jones and F. W. Kocher, *J. Amer. Chem. Soc.*, **76**, 3682 (1954).

(32) This reduction is modeled on that of H. Krieger and K. Manninen, *Suom. Kemistilehti, B*, **38**, 175 (1965).

(33) H. C. Brown, P. Heim, and N. M. Yoon, *J. Amer. Chem. Soc.*, **92**, 1637 (1970).

(34) Prepared from norbornanone and diborane by the method of H. C. Brown, P. Heim, and N. M. Yoon, *J. Amer. Chem. Soc.*, **92**, 1637 (1970).

(35) The phosphorylation is modeled after that of C. Zioudrou and G. L. Schmir, *J. Amer. Chem. Soc.*, **85**, 3528 (1963).

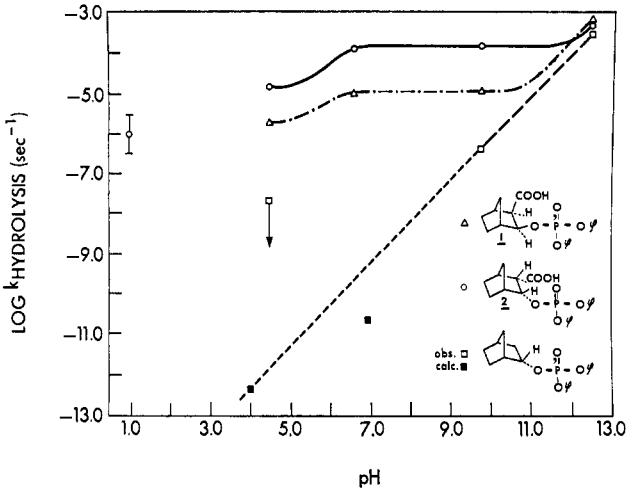


Figure 1. pH–rate profiles for phosphate esters.

to yield 290 mg of crude ester. A mixture of this crude ester in 1.6 ml of pyridine was stirred for 1 hour in the cold and then for 20 hr at room temperature with 370 mg of diphenyl phosphorochloridate. The reaction mixture was then poured into ice water and hydrochloric acid and extracted with methylene chloride as above. The resulting oil was almost pure by tlc on silica gel with ether and showed the parent ion **8** (although only at 0.09% of the base peak) in its mass spectrum. The oil was not purified but directly debenzylated as follows. About 290 mg of liquid phosphate ester in 10 ml of dry ethyl acetate was hydrogenated at room temperature and atmospheric pressure over 50 mg of 10% palladium on charcoal (Matheson).[36,37] About 98% of the theorectical amount of hydrogen was absorbed over 60 min and no more in the next 90 min. The catalyst was removed by filtration through Celite, and the filtrate was concentrated *in vacuo*, dissolved in methylene chloride, washed with water and acid, and dried over magnesium sulfate. When the solution was concentrated *in vacuo*, 190 mg of an oil was obtained that soon crystallized. Two recrystallizations from benzene–hexane (1:2) yielded 95 mg of pure white needles of **1**: mp 90.8–91.5°; ir (Nujol) ν_{OH} 3080, 2700 cm^{-1}; ir (Nujol) $\nu_{C=O}$ 1735; ir (Nujol), 1590, 1480, and 1242 cm^{-1}; mass spectrum (rel intensities) 388 (P^+, 2), 295 (50), 251 (17), 121 (100), 93 (45); nmr (60 MHz, $CDCl_3$) δ 11.25 (s, 1 H), 7.17 (s, 10 H), 4.82 (overlapping d with $J = J' = 6.5$ Hz, 1 H), 2.7–0.9 (m, 9 H). *Anal.* Calcd for $C_{20}H_{21}PO_4$: mol wt 388.1076. Found: 388.1064. Carbon, hydrogen, and phosphorus analyses, although approximately correct, did not fall within the usual limits of error, presumably because of analytical problems that frequently arise with phosphates. The compound appeared spectroscopically pure and melted sharply.

Diphenyl *endo*-2-(*endo*-3-Carboxy)norbornyl Phosphate (2). The same procedure used to prepare the cis-exo ester was employed here. After the hydrogenation, the liquid ester proved difficult to crystallize, but after it had stood for several days in the refrigerator, a seed crystal appeared, and crystallization then proceeded normally. Two recrystallizations from benzene–hexane (1:1) afforded 170 mg (a 55% yield from the hydroxy acid **11**) of white needles: mp 107.0–107.8°; ir (Nujol) ν_{OH} 3070, 2700 cm^{-1}; ir (Nujol) $\nu_{C=O}$ 1703; ir (Nujol) 1595, 1480, and 1283 cm^{-1}; mass spectrum (rel intensities) 388 (P^+, 1), 295 (45), 251 (21), 121 (80), 93 (100), 77 (31). *Anal.* Calcd for $C_{20}H_{21}O_6P$: mol wt 388.1076. Found: 388.1062. Carbon, hydrogen, and phosphorus analyses, although approximately correct, did not fall within the usual limits of error, presumably because of analytical problems that frequently arise with phosphates. The compound appeared spectroscopically pure and melted sharply.

Kinetic Measurements. The rates of reaction were measured by observing the change in uv spectrum accompanying the production of phenol from the triester. Stock solutions of the various esters at about 4×10^{-2} *M* in dimethoxyethane were prepared, and 18–30 μl of this solution was added to 3 ml of the various buffers in stoppered uv cells. The cells were heated at 49.8 ± 0.4° in thermostated cell compartment of the Cary 15 spectrophotometer, or, for very slow reactions, the cells were kept in the thermostat and removed at intervals for spectrophotometric observation.

All buffers were prepared in 30:70 dimethoxyethane–water by volume. Peroxide-free DME was obtained by passing reagent grade solvent over neutral alumina and then distilling it from lithium aluminum hydride. Aqueous buffers were mixed with purified DME with sufficient potassium chloride to bring the ionic strength to 1.00. The pH's of the buffers in 30% DME were measured against an aqueous half-cell, and the meter was reset so that 0.001 *M* HCl in 1 *M* potassium chloride gave a reading of 3.00; the assumption is inherent in the pH measurements here reported that the water–aqueous DME junction potential in the presence of 1 *M* salt remains constant for the different buffers. These were 0.001 *M* hydrochloric acid for pH 3.00, 0.29 *M* acetic acid and 0.10 *M* sodium acetate for pH 4.51, 0.051 *M* $H_2PO_4^-$ and 0.51 *M* HPO_4^{2-} for pH 6.64, 0.052 *M* HCO_3^- and 0.043 *M* CO_3^{2-} for pH 9.84, and 0.1 *N* NaOH or 0.1 *N* KOH for pH 12.60.

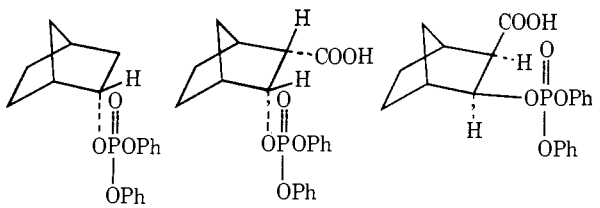
Instruments. Nmr spectra were obtained with a Varian T-60, HA 100, or XL-100 spectrometer, ir spectra with a Perkin-Elmer infrared spectrophotometer Model 137, and mass spectra, including exact masses, with an AEI MS-9 mass spectrometer.

A Cary 15 recording spectrophotometer was used for ultraviolet spectra and a Radiometer type TTTlc pH meter for pH measurements. Elementary analyses were performed by Galbraith Laboratories, Knoxville, Tenn., by Scandanavian Microanalytical Laboratories, Denmark, and by Spang Microanalytical Laboratories, Ann Arbor, Mich.

Results

The pseudo-first-order rate constants observed for the hydrolyses of the phosphate esters at various pH's are shown in Table II and Figure 1.

Table II. Pseudo-First-Order Rate Constants (sec^{-1}) at 49.8°



12.60	27.8×10^{-5}	47.6×10^{-5}	60.6×10^{-5}
9.84	4.7×10^{-7} [a]	14.3×10^{-5}	1.27×10^{-5} [b]
7	Calcd 3×10^{-11}		
6.64		12.0×10^{-5}	1.02×10^{-5} [a]
4.51	$<2.5 \times 10^{-8}$ [a]	1.59×10^{-5}	0.214×10^{-5} [a]
4	Calcd 7×10^{-13}		
0.97		$\sim 10^{-6}$ [a]	

[a] Determined by initial rates only. [b] Rate constant for competing solvolysis is 2.06×10^{-5} sec^{-1}.

In alkaline solutions, where appreciable concentrations of phenoxide ion are found, the release of phenoxide ion could be monitored at 290.0 nm without any complications arising from other species. Further, phenol shows a shoulder on its absorption spectrum at 277.4 nm; at this wavelength the triesters exhibit virtually no absorption, and the extinction coefficient of diphenyl phosphate is only 4% of that of phenol. Rates in the acid region could therefore be followed at 277.4 nm. Monitoring the release of phenoxide or phenol is appropriate since the hydrolytic process will always result in P–OPh cleavage. Completing P–OR (R = 2-norbornyl) cleavage is very unfavorable as it has been shown that the rate of phosphate triester hydrolysis is directly proportional to the K_a of the conjugate acid of the leaving group.[38]

(36) A. E. Barkdoll and W. F. Ross, *J. Amer. Chem. Soc.*, **66**, 951 (1944).

(37) H. O. House, "Modern Synthetic Organic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 2.

(38) S. A. Khan and A. J. Kirby, *J. Chem. Soc. B*, 1172 (1970).

However, a major complication in the rates here determined arises because of the solvolysis of the phosphate esters. Solvolysis to form diphenyl phosphate anion and a norbornyl cation was the major, if not the only, process that occurred with *exo*-norbornyl diphenyl phosphate, as evidenced by the absence of phenoxide or phenol in the hydrolysis products. Further, the rate constant for this solvolysis, about 1.3×10^{-4} sec^{-1} at 49.8°, is about $^1/_{23}$ of that (3×10^{-3} sec^{-1}) at 50° for that of *exo*-2-norbornyl brosylate in acetic acid as solvent.[39] The greater polarity of the aqueous solvent[40] is presumably responsible for diminishing the enormous rate difference anticipated for leaving groups as disparate as diphenyl phosphate and *p*-bromosulfonate.

For the acid phosphate esters **1** and **2**, however, solvolysis was no longer a major problem. A comparison of the pseudo-first-order and initial rate plots for the hydrolysis of the cis-endo acid ester **2**, at pH values of 9.84, 6.64, and 4.51, showed that very little, if any, solvolysis was occurring. Competing solvolysis during the hydrolysis of the cis-exo compound **1** was observed but was sufficiently slow as not to interfere with the calculations of the pseudo-first-order rates of hydrolysis.

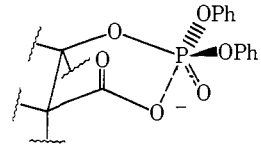
A comparison of the pH–rate profiles for the ester acids with that of the simple norbornyl phosphate (Figure 1) shows that the carboxyl groups do indeed assist the hydrolysis substantially. How substantial the assistance may be is, however, unavailable to experiment, since the P–O cleavage of even the *endo*-norbornyl diphenyl phosphate is completely obscured, at pH 6.64 and lower, by C–O cleavage, and the necessary rate cannot be determined. One cannot therefore say with certainty whether the rate of the P–O cleavage for this compound would decrease linearly with decrease in the hydroxide ion concentration or whether, near neutrality, the process would show a competing water reaction. In any event, the catalysis by carboxyl groups in **1** and **2** amounts to many powers of ten and may easily amount to 1×10^7-fold at pH 4.5, as shown by the following calculations.

Kirby has been able to obtain linear-free-energy relationships between the rate of hydrolysis and the pK_a of the conjugate acid of the leaving group for a series of phosphate triesters at pH values of ~4 and ~7 (39°, ionic strength = 1.0 in water).[38] Using the extrapolated portions of these linear free energy plots and taking the pK_a of phenol in water at 50° to be 9.66,[41] we can obtain an estimate for the pseudo-first-order rate constants for hydrolysis of *endo*-norbornyl diphenyl phosphate at pH 4 and 7 (see Table II). The value estimated for pH 7 appears low by a factor of 10, though, since a decrease in hydroxide concentration of 10^3 from pH 9.84 would not be expected to produce a rate of reduction of 10^4.

The still relatively high rate of hydrolysis of **2** at pH 0.97 indicates that the undissociated acid group is also capable of causing a large rate enhancement. Kirby, *et al.*, have found the hydrolysis of dialkyl salicyl phosphates at low pH to be subject to catalysis by the carboxyl group (rate increases of ~10^7) but were unable to determine the exact mechanism.[5c] Efficient intramolecular carboxylic acid catalysis of phosphate triester hydrolysis thus appears to be a general phenomenon. Unfortunately, the extent of such catalysis in the present study is unavailable to experiment due to solvolysis of the reference compounds.

The absolute rates of hydrolysis of the phosphates **1** and **2** and the extent of catalysis by the neighboring carboxyl group may be about the same as those observed by Kirby, *et al.*,[5] with salicyl diphenyl phosphate. Due to the similarity between the norbornyl and the salicyl diphenyl phosphates, we favor as an explanation of our data the intramolecular nucleophilic catalysis scheme proposed by Kirby, *et al.*, to account for the salicyl phosphate results.[5c] Although both systems are rigid and well disposed for the formation of six-membered rings in the essential intermediates, it is somewhat surprising that the two systems nevertheless show such similar internal catalysis. Perhaps in both systems the starting materials are so constrained that they cannot give up much more translational or rotational entropy on forming the transition state, and so both approach the upper limits for effective intramolecular catalysis.[10]

In concluding, we feel that the differences in the absolute rates of hydrolysis of the cis-exo and the cis-endo acid phosphate esters **1** and **2** in the pH range of 4.5–10 require some explanation. In this range, the cis-endo ester **2** always hydrolyzed a factor of 10 faster than the cis-exo compound **1**. Space-filling models of the two esters[42] revealed very few differences except between the *exo*- and *endo*-carboxyl groups. The exo group possesses free rotation and is quite exposed. In contrast, the *endo*-carboxyl group is hindered in its rotation and is comparatively buried in the rest of the molecule. The transition state leading to the postulated cyclic acyl phosphate intermediate seems to be restrained to a boat-like conformation (**15**) for both esters. Any substantial rate differences would thus appear to derive from the ionized carboxyl groups. This hypothesis is supported by the observation that the above rate difference in hydrolysis of **1** and **2** disappears at high pH (*i.e.*, pH 12.60) where carboxyl group catalysis no longer seems important.



15

Page and Jencks[10] have calculated that the loss of entropy upon freezing the rotation about a methylene–carboxyl group bond corresponds to a rate increase of a factor of 10 at 25°. In view of the fact that the rate differences in the hydrolysis of **1** and **2** are observed at 50°, only partial freezing of rotation of the carboxyl group in **2** would be required to produce a tenfold

(39) S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Cone, D. Trifan, and H. Marshall, *J. Amer. Chem. Soc.*, 74, 1127 (1952).
(40) A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, 78, 2770 (1956).
(41) E. J. King, "Acid-Base Equilibria," Macmillan, New York, N. Y., 1965, p 172.
(42) To make the bicyclo[2.2.1]heptane ring, rubber space-filling, sp^3 carbon atoms were pared with a razor. Approximately equal amounts were removed from each atom except for the bridge methylene. This carbon was shaved somewhat more drastically to reflect the smaller C_1–C_7–C_4 bond angle in the real system.

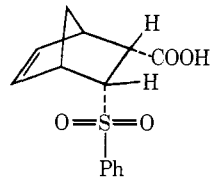
rate increase. The space-filling models indicate that just such a partial freezing could be occurring.

Alternatively, and perhaps additionally, the rate differences might be due to unequal solvation by water of the carboxylate group in **1** and **2**. Again from the models, the *exo*-carboxylate group is predicted to be extensively solvated when compared to the endo group, which is buried in a hydrophobic environment. Solvation of the *exo*-carboxylate anion would decrease the effective negative charge and nucleophilicity of the group. Solvation would also increase the free energy of activation of nucleophilic catalysis since the work required to strip the carboxylate group of the interfering, hydrogen-bound solvent molecules would be expected to be greater than the resulting increase in entropy.[43] Consequently, a $\Delta\Delta F^{\ddagger} = \Delta F^{\ddagger}_{endo} - \Delta F^{\ddagger}_{exo} = -1.4$ kcal, for a rate increase of a factor of 10, does not seem at all unreasonable. Such an explanation is particularly attractive in terms of a model system for an enzyme. Catalysis due to the perturbations induced by a hydrophobic active site in an enzyme seems to play a very large part in enzymic reactions,[43] and it would be interesting if the cis-endo acid phosphate ester **2** exhibited such additional catalysis here, relative to the ester **1**.

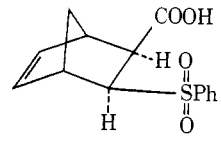
These same factors may also be the cause of the ~16-fold decrease in the rate of hydrolysis of compound **2** in going from pH 4.51 to 0.97. This rate decrease cannot be ascribed to the effect of carboxyl group ionization but could be due to solvation effects. If catalysis is due to nucleophilic catalysis (this is the mechanism favored by Kirby, *et al.*[5c]) with the generation of a charge species in the transition state, which is less stabilized in the more difficultly solvated endo compound **2**, then the rate of hydrolysis of **2** would be expected to decline further with decreasing pH. In fact, this hypothesis predicts that the destabilization might increase to the point that the endo compound would hydrolyze even slower than the exo compound **1**. The rate of hydrolysis of **1** at pH 0.97 was not determined but the fact that the hydrolysis rate of **2** at pH 0.97 is a factor of 2 less than that of **1** at pH 4.51 is in line with the predicted behavior.

(43) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, pp 92–96, 393–436.

Further support for the "unequal solvation" hypothesis comes from the fact that the reasonably similar cis-endo acid **16** does indeed have a higher pK_a than the corresponding exo acid **17** (in 50% v/v EtOH–H_2O at 25°).[44] This effect was attributed to a decrease in the dielectric



16, $pK_a = 6.23$



17, $pK_a = 6.03$

constant in the medium around the carboxylate group of **16**, which was caused by steric hindrance to solvation.

An attempt was made to obtain the pK_a's of the acid phosphate esters **1** and **2** in 30% DME–water at 50° by measuring the pH of half-neutralized samples. Unfortunately, even at concentrations of 4.6×10^{-3} *M*, not all of the acids **1** and **2** dissolved. pK_a values of ~6 for the acids **1** and **2** seem reasonable due to the similarities with the acids **16** and **17** and due to the observed decrease in the rate of hydrolysis of **1** and **2** in going from pH 6.64 to 4.51 (Figure 1). Since the exact pK_a's of the acids **1** and **2** are unknown, the shape of the pH–rate profile in this region is necessarily vague, but the exact shape of this curve is not essential to the main thrust of this article.

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(44) H. Hogeveen and F. Montanari, *J. Chem. Soc.*, 4864 (1963).