(**2**–**6**) from the corresponding bromoaldehydes in the yields (after isolation by column chromatography) indicated.

As compared with the current processes for the preparation of the large ring lactones, this route provides a convenient and versatile method for the introduction of *α-methyl-β-hydroxy lactones* as they appear in many naturally occurring macrolides[17] starting with simple 1,ω-diols.[18]

References and Notes

(1) For a general discussion, see H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, New York, N.Y., 1972, pp 629–682. For recent synthetic methods for regiospecific aldol synthesis, see (a) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95,** 3310 (1973); (b) T. Mukaiyama, K. Banno, and K. Narasaka, *ibid.*, **96,** 7503 (1974); (c) G. Stork, G. A. Kraus, and G. A. Garcia, *J. Org. Chem.*, **39,** 3459 (1974); (d) T. Mukaiyama, T. Sato, S. Suzuki, T. Inoue, and H. Nakamura, *Chem. Lett.*, 95 (1976); (e) T. Mukaiyama, and T. Inoue, *ibid.*, 559 (1976); (f) R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, **99,** 1265 (1977), and references cited therein.

(2) N. F. Lanskova, A. I. Ilnyasova, A. U. Baisheva, Ya. A. Sangalov, and K. S. Minsker, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **23,** 648 (1974); *Bull. Akad. Sci. USSR (Chem.)*, **23,** 612 (1974). See also ref 1a.

(3) This procedure has its origins in the classical Reformatsky reaction (see R. L. Shriner, *Org. React.*, **1,** 1 (1942); M. W. Rathke, *ibid.*, **22,** 423 (1975)) and, at the present time, we have no reason to believe the zinc enolate would not be involved in the above reaction. However, the milder reaction conditions and the higher selectivities (see, for example, footnote *c* of Table I) of this reaction would support the existence of the intermediary aluminum enolate in our process. For a related reaction of α-halo ketone to form silyl enol ether, see G. G. Joshi and L. M. Pande, *Synthesis*, 450 (1975); S. Hashimoto, A. Itoh, Y. Kitagawa, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, in press.

(4) In the absence of carbonyl compounds, the dimeric condensation product of the α-halo ketone was isolated as the major product: $RC(=O)CH_2Br \rightarrow RC(=O)CH_2C(OH)(CH_2Br)R$. See also T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Am. Chem. Soc.*, **89,** 5727 (1967).

(5) Although commercial zinc dust could be used without any activation, the addition of cuprous bromide is recommended for the reproducible results.

(6) 1.1 mL of a 1 M hexane solution was used. All operations involving organoaluminum reagents were conducted in an atmosphere of dry argon or nitrogen.

(7) The simplicity and the key details of the new aldol synthesis are illustrated by the following procedure for the preparation of **1**. Diethylaluminum chloride (1.1 mmol, 1.1 mL of a 1 M solution) was added to a slurry of zinc dust (98 mg, 1.5 mmol) and a catalytic amount of cuprous bromide (7 mg, 0.05 mmol) in dry THF (3 mL) with stirring under argon at 20 °C. The resulting mixture was cooled to −20 °C and a solution of 2-bromo-2-methylcyclohexanone (191 mg, 1 mmol) and benzaldehyde (117 mg, 1.1 mmol) in dry THF (5 mL) was added slowly over 40 min at −20 °C. After 15 min at −20 °C the reaction mixture was quenched by the addition of pyridine (0.3 mL) and then poured into 2 N hydrochloric acid and the product was extracted with ether three times. The ether extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford erythro and threo mixtures of 2-(1′-hydroxybenzyl)-2-methylcyclohexanone (**1**) in quantitative yield after preparative layer chromatography on silica gel (1:1 ether/hexane). The ratio of the erythro and threo isomer was determined by the relative intensities of the benzylic proton absorptions (NMR ($CDCl_3$) δ 4.92 (erythro) and 5.00 (threo)) to be nearly 4:3.

(8) The extraordinary mild reaction conditions and high efficiencies of this new process are in sharp contrast to the classical Reformatsky reaction.

(9) (a) Internal esterification: E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96,** 5614 (1974), and references cited therein; S. Masamune, S. Kamata, and W. Schilling, *ibid.*, **97,** 3515 (1975). (b) Formation of C–C bonds in a cyclization reaction: B. M. Trost and T. R. Verhoeven, *ibid.*, **99,** 3867 (1977); E. J. Corey and H. A. Kirst, *ibid.*, **94,** 667 (1972); R. N. Hurd and D. H. Shah, *J. Org. Chem.*, **38,** 390 (1973). For a recent review, see K. C. Nicolaou, *Tetrahedron*, **33,** 683 (1977).

(10) B. Abramovitch, J. C. Shivers, B. E. Hudson, and C. R. Hauser, *J. Am. Chem. Soc.*, **65,** 986 (1943).

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

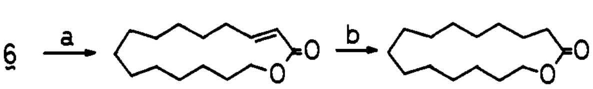
(12) All new compounds reported in this communication have been characterized spectrometrically and analytically.

(13) Zn–Ag couple was used for this reaction: J. M. Denis, C. Girard, and J. M. Conia, *Synthesis*, 549 (1972).

(14) 1.5 mL of a 1 M hexane solution.

(15) Although **3** and **5** were found to be mixtures of erythro and threo isomers (~1:1 by TLC assay (1:2 hexane–ether, two developments) after trimethylsilylation; attempted separation of these isomers by GLC or column chromatography was unsuccessful), the better selectivities would be expected in the naturally occurring macrolide synthesis by this methodology since such compounds were known to be conformationally rather rigid molecules.[9] A study on the synthesis of macrolides along this possibility is under way.

(16) **6** (colorless liquid): IR (liquid film) 3425, 1726 cm^{-1}; NMR ($CDCl_3$) δ 2.50 (d, 2 H); mass *m/e* (%) 41 (100), 238 (4, $M^+ - 18$); TLC (silica gel, 1:1 ether-hexane) R_f 0.27. The structure of **6** was further confirmed by its conversion into exaltolide (identical by spectroscopic (NMR, IR, and mass spectra) and chromatographic (GLC and TLC) comparison with an authentic sample).[9b]



a: CH_3SO_2Cl, Et_3N, CH_2Cl_2, r.t. 11 h. b: H_2, Pd/C, EtOH–EtOAc.

(17) The α-methyl-β-hydroxy unit is a common functionality in a variety of macrolide antibiotics including erythromycin and methymycin; see, for a general review, K. Nakanishi, T. Goto, S. Itoh, S. Natori, and S. Nozoe, "Natural Products Chemistry", Vol. 2, Kodansha Ltd., Tokyo, 1975.

(18) This work was supported financially by the Grant-in-aid administered by the Ministry of Education, Japanese Government (247077).

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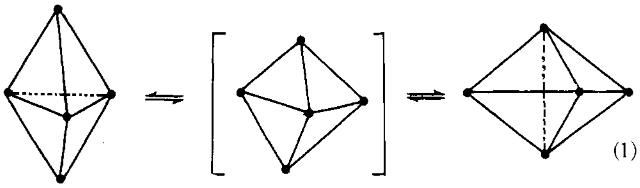
Gas Phase Hydrolysis of Phosphorus Esters

Sir:

There has been considerable interest for some time in the hydrolysis of phosphorus esters.[1] This is due in part to the importance of phosphate esters in biological systems as well as similarities and differences compared with carboxylates. The remarkable differences in hydrolysis rates of cyclic phosphorus esters have provided important insights into the effects of strain and energetics on trigonal-bipyramidal intermediates in these reactions.[1–5] In this communication we report gas phase hydrolysis studies which show that the effects observed in solution persist in the gas phase and thus are mechanistically intrinsic and not an artifact of solvation.

In solution, alkaline hydrolysis of five-membered cyclic phosphate esters without ring opening is considerably faster than cleavage in acyclic analogues.[3] However, exocyclic hydrolysis of five-membered cyclic phosphonate and phosphinate esters shows virtually no acceleration relative to acyclic analogues.[3,4] While rapid hydrolysis with ring opening can be readily explained by the release of ring strain in the transition state, exocyclic cleavage requires that the pentacoordinate intermediate must undergo positional isomerization (pseudorotation) (eq 1) to place the leaving group in the apical position necessary for cleavage.[5] Such intervening intermediates have been shown to be energetically favorable for the cyclic phosphate esters but not for the cyclic phosphonate and phosphinate esters.

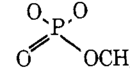


(1)

Using the trapped ion, pulsed ICR technique,[6] we have measured the rates of reaction of trimethyl phosphate (**1**), methyl ethylenephosphate (**2**), methyl propylphostonate (**3**), ethyl tetramethylenephosphinate (**4**), and ethyl propylphos-

$(CH_3O)_3PO$

1



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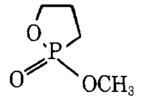

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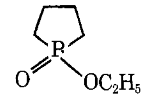

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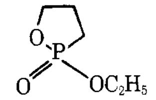

5

tonate (**5**) with OH^- as the nucleophile.[7,8] The rates of CH_3O^- appearance are comparable for **1** ($k = 3.2 \pm 0.3 \times 10^{-10}$ cm^3 molecule^{-1} s^{-1}) and **2** ($k = 1.8 \pm 0.1 \times 10^{-10}$ cm^3 molecule^{-1} s^{-1}), while for **3**, **4**, and **5**, alkoxide appearance was too slow for us to measure[9] ($k < 10^{-12}$ cm^3 molecule^{-1} s^{-1}).

Under the conditions of our experiments, only products of exocyclic cleavage of the esters are observable. Ring opening would lead to a vibrationally excited ion-molecule adduct which would probably not live long enough to be collisionally stabilized at these low pressures (10^{-6} Torr). It is significant that both the cyclic and acyclic rates are low (by about an order of magnitude) compared with collision rates. This suggests the existence of a barrier somewhere along the potential surface.[10]

Alkaline hydrolysis of cyclic phosphinate esters is slow in solution, and, similarly, the rate of reaction of OH^- with **4** is too slow for us to measure in the gas phase. Here the pentacoordinate intermediate required for exocyclic cleavage is energetically unfavorable because it places an alkyl group in an apical position. Reaction of **3** in solution leads to fast ring opening but slow exocyclic cleavage. In agreement with solution work, the rate of reaction of **3** to give exocyclic product is also slow in the gas phase. In this case, although the initial pentacoordinate intermediate should be formed easily, pseudorotation to the intermediate in which CH_3O is in an apical position is energetically unfavorable because it simultaneously places an alkyl group in an apical position.[11,12] Alkaline hydrolysis of **2** in solution gives very fast ring opening and moderately fast exocyclic cleavage. In agreement with these results, **2** is the only one of the cyclic esters investigated whose exocyclic cleavage is fast enough for us to measure. Here, both the initial pentacoordinate intermediate and that formed after pseudorotation have oxygen atoms in apical positions, thus making the necessary intermediates (and transition states) readily accessible.

Interestingly, alkaline solution hydrolysis of **1** is much slower than exocyclic cleavage of **2**, whereas in the gas phase the rates are comparable. In both gas phase and solution, relief of strain in **2** should accelerate reaction. In solution ring opening is much faster than pseudorotation, indicating a measurable barrier to pseudorotation. In the gas phase, the intermediates are energetically activated,[10] and return to reactants (loss of OH^-) with its large *A* factor is faster than pseudorotation. Apparently the pseudorotation barrier superimposed upon the strain relief acceleration results in a rate comparable with that in the acyclic system.

In conclusion, we believe that the general picture proposed to explain solution hydrolysis rates in phosphorus esters[5] is applicable to the gas phase as well. The remarkable agreement suggests that differential behavior of the potential surface after nucleophilic addition has occurred is not dramatically affected by solvation.

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References and Notes

(1) E. Blumenthal and J. B. M. Herbert, *Trans. Faraday Soc.*, **41**, 611 (1945); F. H. Westheimer, *Chem. Soc.* (*London*), *Spec. Pub.*, **No. 8**, 1 (1957); A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus", Elsevier, Amsterdam, 1967, p 276.

(2) J. Kumamoto, J. R. Cox, Jr., and F. H. Westheimer, *J. Am. Chem. Soc.*, **78**, 4858 (1956); F. Covitz and F. H. Westheimer, *ibid.*, **85**, 1773 (1963); A. Eberhard and F. H. Westheimer, *ibid.*, **87**, 253 (1965).

(3) E. A. Dennis and F. H. Westheimer, *J. Am. Chem. Soc.*, **88**, 3431 (1966).

(4) E. A. Dennis and F. H. Westheimer, *J. Am. Chem. Soc.*, **88**, 3432 (1966); K. Bergesen, *Acta Chem. Scand.*, **20**, 2508 (1966).

(5) F. H. Westheimer, *Acc. Chem. Res.*, **1**, 70 (1968).

(6) R. T. McIver, Jr., and R. C. Dunbar, *Int. J. Mass Spectrom. Ion. Phys.*, **7**, 471 (1971); R. T. McIver, Jr., *Rev. Sci. Instrum.*, **41**, 555 (1970).

(7) Commercial $(CH_3O)_3PO$ (Aldrich) was purified by distillation. Compounds **2** and **5** were kindly provided by Professor Westheimer. **3** and **4** were prepared according to A. Eberhard. Ph.D. Thesis, Harvard University, 1965. OH^- was formed from H_2O at 5.2 eV (electron energy minus trapping voltage). After complete formation of OH^-, its decay and the growth of the corresponding alkoxide ions were monitored as a function of time. Neutral pressures were measured on an ionization gauge calibrated against an MKS Baratron capacitance manometer for each neutral sample.

(8) Rate constants are uncorrected for ion loss. Errors are standard deviations for 10 experiments. The absolute accuracy is not better than a factor of 2.

(9) This is the lower limit for reactions which we are normally able to observe. In the reaction with **5**, $C_2H_5O^-$ and $C_2H_3O^-$ were sometimes observed, but we could not obtain any consistent data on the rates. These ions may arise from reactions of neutrals produced from pyrolysis on the filament.

(10) For examples of other classes of ion-molecule reactions where barriers have been found and a general description of these phenomena, see W. E. Farneth and J. I. Brauman, *J. Am. Chem. Soc.*, **98**, 7891 (1976); W. N. Olmstead and J. I. Brauman, *J. Am. Chem. Soc.*, **99**, 4219 (1977).

(11) This barrier is estimated to be roughly 12 kcal/mol for a cyclic oxyphosphorene where pseudorotation would place an alkyl group in a apical position; S. J. Benkovic in "Comprehensive Chemical Kinetics", Vol. 10, C. H. Bamford and C. F. H. Tipper, Ed., Elsevier, New York, N.Y., 1972, p 1.

(12) Endocyclic cleavage followed by reclosure could result in an appropriate intermediate for loss of CH_3O, but this apparently does not occur.

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Sulfur 2p Photoelectron Spectrum of Blue Copper Proteins. Comment on Papers by Solomon et al. and Peeling et al.

Sir:

The sulfur 2p region in x-ray photoelectron spectra of plastocyanin and some other blue copper proteins has a strong component at 5-eV higher binding energy (HBE) than the main line.[1-3] The apoplastocyanin does not show a similar HBE line and Solomon et al. therefore suggested that one of the sulfurs (the cysteine sulfur) was bonded to a copper(II) ion.[1] Peeling et al. pointed out that a 5-eV shift is too large to be caused by coordination to a transition metal ion[2] and suggested that the HBE line was due to oxidized sulfur present in the preparations, a conclusion also reached by Rupp and Weser.[4] Peeling et al. also argued that the integrated sulfur 2p intensity had a correct magnitude compared to the nitrogen 1s line only if the S 2p HBE line was omitted in the integration. In a reply, Solomon et al. rejected, however, the possibility of sulfates or other impurities.[3]

Since it is quite unreasonable to expect a 5-eV chemical shift, I would like to suggest as another possible source for the HBE line a charge-transfer satellite which appears because of the bonding to a transition metal ion. The conclusions made by Solomon et al.[1,3] would then be correct although based on a less probable interpretation of the spectrum.

Let us write the valence hole orbital as

$$\varphi = \sin \eta \, u_{\mathrm{Cu}} + \cos \eta \, u_{\mathrm{S}} \qquad (1)$$

where u_{Cu} and u_{S} are Cu 3d and S 3p orbitals and $\sin \eta$ and $\cos \eta$ coefficients. We disregard for simplicity the overlap between u_{Cu} and u_{S}. $\eta = 90°$ corresponds to the completely ionic