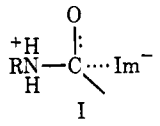
The very large sensitivity of this reaction to the basicity of the attacking amine (Figure 1) means that the transition state is more sensitive to polar substituents on the nitrogen atom than is the equilibrium for the addition of a proton; the reaction behaves *as if* some 1.6 positive charge is generated at the amine nitrogen atom in the transition state. The value of β_{nuc} for the *equilibrium* transfer of an acyl group to an amine or pyridine to give a cationic product is also 1.6,[6,7] so that the transition state for the aminolysis reaction (I) closely resembles the product that is formed without proton transfer. Since proton removal would



I

decrease the amount of positive charge development on the nitrogen atom, this β value means that little or no proton removal from the attacking amine has occurred in the transition state. The pK_a of an N-protonated amide[8] is about -7.6, so that there is no significant proton removal through general base catalysis by water and the proton transfer process does not appear to be at an equilibrium position in the transition state.[9] Apparently the advantage gained from general base catalysis by water is insufficient to offset the unfavorable free energy required for the positioning of a water molecule and the transfer of a proton in the transition state.

The limiting interpretation of the data is that *complete* cleavage of the C–N bond has occurred in the transition state; *i.e.*, that the rate-determining step is the dissociation of the ion pair $RNH_2^+Ac\cdot Im^-$ to solvent-separated ions (eq 1). If the dissociation step,

$$RNH_2 + AcIm \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RNH_2^+Ac\cdot Im^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} RNH_2^+Ac + Im^- \quad (1)$$

$$K_A \Big\uparrow \Big\downarrow \pm H^+ \qquad \pm H^+ \Big\uparrow \Big\downarrow K_I$$

$$RNHAc \qquad ImH$$

k_2, is rate determining in the forward direction, encounter of the ions with the rate constant k_{-2} is rate determining in the reverse direction. Since the overall equilibrium constant K_{ov} may be calculated from the free energies of hydrolysis of acetylimidazole[10] and acetamide,[7,11] a rough estimate of the reverse rate constant k_{-2} according to this interpretation may be obtained from the observed forward rate constant $k_f = k_1k_2/k_{-1}$ and the pK values of the N-protonated amide[7] and imidazole of -7.6 and 14.2, respectively, according to eq 2. The resulting value of $k_{-2} = 3 \times 10^9\ M^{-1}$

$$k_{-2} = \frac{k_1k_2K_A}{k_{-1}K_{ov}K_I} = \frac{k_fK_A}{K_{ov}K_I} \quad (2)$$

sec^{-1} for the reaction of imidazole anion with the protonated amide is in the range expected for a diffusion-controlled reaction. This is consistent with (but of course does not prove) this limiting interpretation of the mechanism. The fact that the observed rate constants for the reactions of acetylpyridinium ions with less basic amines and hydroperoxide ion are close to the diffusion-controlled limit[12] is also in accord with this interpretation.

The reactions of amines with methyl formate[4] are several orders of magnitude slower, with a β value of 0.7, indicating a different mechanism for this reaction in spite of the comparable pK_a values of methanol (15.5)[13] and imidazole. A calculation similar to that for the acetylimidazole reaction gives a value of $1.5 \times 10^{14}\ M^{-1}\ sec^{-1}$, greater than the diffusion-controlled limit, for the reaction of methoxide ion with N-protonated *N*-propylformamide. The limiting mechanism of eq 1 evidently cannot be significant for methyl formate. This is a consequence of the greater stability (smaller K_{ov}) of methyl formate[8] that results from enhanced resonance stabilization compared to acetylimidazole.

(6) A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, **92**, 5432 (1970); W. P. Jencks, B. Schaffhausen, K. Tornheim, and H. White, *ibid.*, **93**, 3917 (1971).
(7) A. R. Fersht and Y. Requena, *ibid.*, **93**, 3499 (1971).
(8) A. R. Fersht, *ibid.*, **93**, 3504 (1971).
(9) W. P. Jencks and K. Salvesen, *ibid.*, **93**, 1419 (1971), and references therein.
(10) J. Gerstein and W. P. Jencks, *ibid.*, **86**, 4655 (1964).
(11) It is assumed that acetyl and formyl compounds have similar free energies of hydrolysis, which has been demonstrated in the case of the thiosemicarbazide derivatives.[7]
(12) A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, **92**, 5442 (1970).
(13) P. Ballinger and F. A. Long, *ibid.*, **82**, 795 (1960).

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Conformations of Saturated Phosphorus Heterocycles. Effect of Europium Dipivaloylmethane and Europium Heptafluorodimethyloctanedione on Conformational Equilibria of 2-Substituted 5-*tert*-Butyl-2-oxo-1,3,2-dioxaphosphorinanes

Sir:

Recent studies have demonstrated the potential utility of europium shift reagents in the determination of molecular geometry.[1] Both coupling constants from spectra simplified by added shift reagent and the accompanying chemical-shift behavior are useful in this regard. We present here results which clearly show, however, that mobile conformational equilibria can be greatly perturbed by added shift reagents and which emphasize that care must be used in interpreting nmr data of this type.[2] In addition, our findings demonstrate further the importance of electronic as well as steric effects in determining conformations in six-membered rings containing heterocyclic atoms.

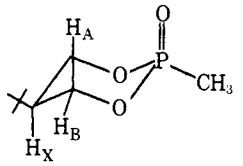
It had been found[3] earlier that the AA'BB'XY pmr spectrum of **1** could be readily simplified by the addition of $Eu(DPM)_3$ to a solution of **1** in $CDCl_3$.

(1) Some recent examples include: (a) B. D. Cuddy, K. Treon, and B. J. Walker, *Tetrahedron Lett.*, 4433 (1971); (b) J. R. Corfield and S. Trippett, *J. Chem. Soc. D.*, 721 (1971); (c) J. F. Caputo and A. R. Martin, *Tetrahedron Lett.*, 4547 (1971); (d) R. Caple and S. C. Kuo, *ibid.*, 4413 (1971); (e) C. C. Hinckley, M. R. Klotz, and F. Patil, *J. Amer. Chem. Soc.*, **93**, 2417 (1971); (f) J. Briggs, F. A. Hart, and G. P. Moss, *J. Chem. Soc. D*, 1506 (1970); (g) R. R. Fraser and Y. Y. Wigfield, *ibid.*, 1471 (1970); (h) P. V. Demarço, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, **92**, 5734 (1970).
(2) It has previously been recognized that results from conformationally mobile systems do not lend themselves to ready interpretation.[1c,g] Our results show these effects clearly in terms of identifiable changes in conformer populations.
(3) K. C. Yee and W. G. Bentrude, *Tetrahedron Lett.*, 2775 (1971).

Table I. Pmr Data for 1, 2,[a] and 3[b]

Compd	Mol of Eu shift reagent/ mol of compd	Coupling constants and chemical shifts[c] J_{AB}[c]	J_{AX}	J_{BX}	J_{AP}	J_{BP}	δ_A[d]	δ_B	δ_X	$\delta_{5\text{-}t\text{-}Bu}$	$\delta_{2\text{-}CH_3}$	% 2a[h]	% 3a[h]
1	0[e]	−11.1	10.5	4.47	4.14	20.2	4.40	4.30	2.05	0.97	1.50		
2	0[e]	−11.38	9.94	4.82	6.80	16.43	4.09 (4.13)[g]	4.41 (4.42)	2.14 (2.07)	0.98 (0.93)	1.54 (1.33)	78	
	0.11	−11.2	8.0[f]	5.0[f]	10.0	13.3						60	
	0.30	−11.3	7.5[f]	4.8[f]	11.3	12.0						52	
	0.60	−11.3	6.5	4.5	13.0	10.2						43	
	0.70	−11.2	6.4	4.5	13.0	9.5						41	
3	0[e]	−11.25	10.79	4.54	5.71	17.69	4.10 (4.00)[g]	4.50 (4.47)	2.30 (2.27)	0.90 (0.90)			84
	0.12	−10.8	9.8	4.9	7.5	16.2							75
	0.25	−10.5	9.8	4.8	8.3	15.0							69
	0.38	−10.8	9.4	4.5	9.0	14.5							65
	0.51	−10.8	9.0	4.7	10.0	13.0							60
	0.64	−10.8	8.0	5.0	11.5	12.5							53
	0.95	−10.8	8.0	5.0	12.5	11.5							47

[a] Addition of Eu(FOD)$_3$ to a 0.20 M solution of **2** in CCl_4 at 60 MHz, ambient temperature. [b] Addition of Eu(DPM)$_3$ to a 0.24 M solution of **3** in $CDCl_3$ at 60 MHz, ambient temperature. [c] Coupling constants in Hz; J_{AB} assumed negative and other J values assumed positive. [d] Chemical shifts in ppm downfield from TMS as internal standard. [e] J and δ values from computer-assisted analysis using LAOCN3; sample in $CDCl_3$ at 60 MHz; ambient temperature. [f] Determined from methylene protons. [g] By extrapolation to zero Eu-shift reagent concentration of plots of chemical shift *vs.* mole ratio [Eu-shift reagent/compound]. [h] And corresponding Eu complex of same conformation. [i] Estimated errors in J values, ±0.5 Hz.



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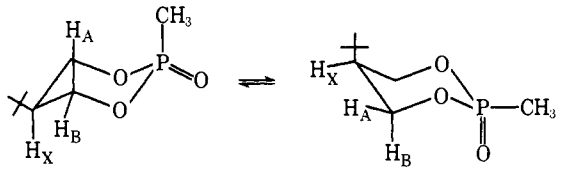
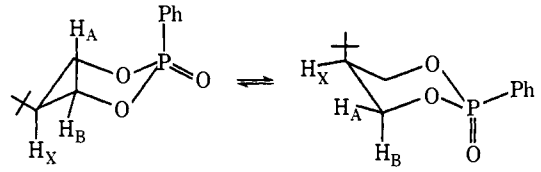


2a 2b

First-order analysis of the resulting spectrum gave coupling constants and extrapolated chemical shifts in close agreement with those obtained[4] by computer-assisted LAOCN3 analysis of the non-first-order 60-MHz spectrum of **1**. The parameters for **1** (Table I) are completely consistent with the chair conformation of **1** shown.

By contrast, on progressive additions of the shift reagent Eu(FOD)$_3$ to a 0.20 M solution of **2** in CCl_4, a monotonic change in all $^3J_{HH}$ and $^3J_{HP}$ values is observed (Table I). The pmr parameters reported in Table I were determined from analysis on a first-order A_2M_2XY basis of both the methylene and methine regions. At the same time, all of the protons in **2** are downfield shifted in a normal manner; *i.e.*, plots of chemical shift *vs.* [Eu(FOD)$_3$]/[**2**] are nicely linear.[5]

The most straightforward interpretation of these trends is that addition of Eu(FOD)$_3$ and formation of Eu(FOD)$_3$–**2** complexes shifts the equilibrium **2a** ⇄ **2b** in the direction of the conformer **2b** in which the 5-*tert*-butyl is axial. The observed shifts and coupling constants are thus time-averaged values resulting from rapid exchange processes involving complexed and uncomplexed **2a** and **2b**. If it is assumed that $^3J_{PH}$(ax) and $^3J_{PH}$(eq) are essentially independent of complexation and of the orientation of the substituents at phosphorus and C-5 (*i.e.*, the same in **2a** and **2b**), then $^3J_{PH}$(ax) and $^3J_{PH}$(eq) can be readily estimated[6] as 2.8 and 20.5 Hz, respectively. Consequently, the percentages of **2a** (free and complexed) and **2b** (free and complexed) at various [Eu(FOD)$_3$] can be readily calculated from the observed $^3J_{AP}$ and $^3J_{BP}$ values. These percentages may also be obtained from observed J_{AX} and J_{BX} if values of $^3J_{HH}$(ax–ax) = 11.5 Hz and $^3J_{HH}$(eq–eq) = 3.2 Hz[8] are used. That similar percentages (±3%) were obtained by the two methods supports the assumption that **2a** and **2b** or their Eu complexes are the conformers involved. These averaged percentages also appear in Table I. A similar effect of added Eu(DPM)$_3$ is seen on the conformational preferences of the phenylphosphonate **3** (see Table I).[9]



3a 3b

The conformational preference of a substituent in cyclic aryl and alkyl phosphonates of this type seems to be determined by the balance between the equatorial preference of the phosphoryl oxygen and the steric

(4) W. G. Bentrude and J. H. Hargis, *Chem. Commun.*, 1113 (1969).

(5) Extrapolation of these plots to zero [Eu(FOD)$_3$] gave chemical shifts consistent with those determined by LAOCN3 methods (see Table I).

(6) See (a) A. R. Katritzky, M. R. Nesbit, J. Michalski, Z. Tulimowski, and A. Zwierzak, *J. Chem. Soc. B*, 140 (1970); (b) R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc. C*, 752 (1970) In these calculatons $^3J_{POCH}$(acy) for diethyl methylphosphonate, 8.7 Hz,[7] was used.

(7) J. L. Burdett and L. L. Burger, *Can. J. Chem.*, **44**, 111 (1966).

(8) $^3J_{HH}$(eq–eq) for *cis*-2-alkyl-5-*tert*-butyl-1,3-dioxanes ranges from 1.1 to 2.0 Hz: E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, **90**, 3444 (1968). For *trans*-2-phenoxy-5-phenyl-2-oxo-1,3,2-dioxaphosphorinane, $^3J_{HH}$(eq–eq) is found to be 4.2 Hz: J. R. Campbell and L. D. Hall, *Chem. Ind.*, 1138 (1971).

(9) The same values of $^3J_{PH}$(ax) and $^3J_{PH}$(eq) used for the calculations involving **2** were applied here along with assumed values for $^3J_{HH}$(ax–ax) and $^3J_{HH}$(eq–eq) of 11.5 and 4.7 Hz, respectively.

requirements of the alkyl or phenyl group.[6a,b,10] The coordination of the europium in these systems occurs at the phosphoryl oxygen.[3,11] Apparently, the nature of the phosphoryl bond is modified thereby, and the balance of steric and electronic interactions is changed such that equatorial phosphoryl preference is reduced. Obviously, 1,3-syn-axial steric interactions do not of themselves control conformation, since coordination should somewhat increase the steric size of the phosphoryl oxygen. Also, a tighter Eu–phosphorus complex might be expected with the P=O of **2a** or **3a** than with that of conformer **2b** or **3b**, again for steric reasons. Thus, various attractive and repulsive vicinal interactions about the P–O single bonds in the ring appear to be of considerable importance in controlling conformation here as well as in the corresponding cyclic trivalent systems.[12]

Acknowledgment. Support of this work by the National Science Foundation (GP 22885) is gratefully acknowledged.

(10) R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc. C*, 2091 (1968); M. Kainosho and T. Shimozawa, *Tetrahedron Lett.*, 865 (1969); J. P. Majoral, R. Kraemer, J. Devillers, and J. Navech, *Bull. Soc. Chim. Fr.*, 3917 (1970); J. P. Majoral and J. Navech, *ibid.*, 95, 1331 (1971); J. P. Majoral, R. Pujol, J. Navech, and F. Mathis, *Tetrahedron Lett.*, 3755 (1971); D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *J. Chem. Soc. B*, 1454 (1971); R. F. M. White, *J. Mol. Struct.*, **6**, 75 (1970). Equatorial phosphoryl preference is also noted in numerous crystal structures in these systems.

(11) T. M. Ward, I. L. Allcox, and G. H. Wahl, Jr., *Tetrahedron Lett.*, 4421 (1971); E. D. Cuddy, K. Treon, and B. J. Walker, *ibid.*, 4433 (1971); J. K. M. Saunders and D. H. Williams, *ibid.*, 2813 (1971); J. R. Corfield and S. Trippett, *Chem. Commun.*, 721 (1971); Y. Kashman and O. Awerbouch, *Tetrahedron*, 27, 5593 (1971).

(12) C. L. Bodkin and P. Simpson, *Chem. Commun.*, 829 (1969); D. W. White, G. K. McEwen, and J. G. Verkade, *Tetrahedron Lett.*, 5369 (1968); D. W. White, R. D. Bertrand, G. K. McEwen, and J. G. Verkade, *J. Amer. Chem. Soc.*, **92**, 7125 (1970); J. H. Hargis and W. G. Bentrude, *ibid.*, **92**, 7136 (1970); W. G. Bentrude and K. C. Yee, *Tetrahedron Lett.*, 3999 (1970); W. G. Bentrude, K. C. Yee, R. D. Bertrand, and D. M. Grant, *J. Amer. Chem. Soc.*, **93**, 797 (1971); C. L. Bodkin and P. Simpson, *J. Chem. Soc. B*, 1136 (1971).

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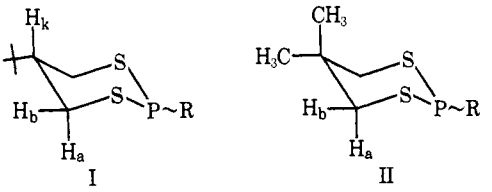
Conformational Analysis of 2-Phospha-1,3-dithiacyclohexanes. Further Evidence for the General Axial Preference of Phosphorus Substituents in Saturated Six-Membered Rings

Sir:

In cyclohexyl systems and in saturated six-membered heterocycles most substituents prefer to adopt equatorial conformations, primarily because of severe 1,3 cross-ring steric interactions encountered when the groups are axial.[1] On the contrary, there is increasing evidence that in 2-phospha-1,3-dioxacyclohexanes[2,3] and in phosphacyclohexanes[4] substituents on phosphorus, including alkyl[3c] and aryl[2,4a] groups, strongly prefer and are unconstrained in axial conformations. This communication reports our preliminary findings on the conformational analysis of 2-R-2-phospha-1,3-dithiacyclohexanes (I and II), which furnish further testimony for the intriguing axial preference of phosphorus substituents in six-membered rings.



a, R = Ph
b, R = OMe
c, R = Me
d, R = Et
e, R = *t*-Bu

The 2-phenyl-5-*tert*-butyl derivative Ia was obtained and was found to be a mixture of cis and trans isomers in an 85/15 (or 15/85) ratio. The isomers in the mixture were differentiated by the *tert*-butyl resonance in the pmr spectrum (δ ($CDCl_3$) major, 0.76; minor, 0.99 ppm). The major isomer (Ia1) was readily separated by fractional crystallization (MeOH), mp 94–95°, δ_{31P} (C_6H_6) −28.9 ppm, but attempts to purify the minor isomer (Ia2) have thus far been fruitless.

That the major isomer was the thermodynamically more stable one was verified by thermal equilibration monitored by pmr. At 200° equilibrium was attained in *ca.* 7 hr and the final ratio was Ia1/Ia2 = 84.5/15.5. The thermal stereomutation process was found to be accelerated by traces of acid.[5] The following equilibrium data were obtained: $K_{175°} = 6.9$, $K_{200°} = 5.6 \pm 0.2$, and $K_{225°} = 4.8$, which give the respective free energies, $\Delta G = -1.67$, -1.59, and -1.55 kcal/mol ($\Delta G_{25°} = = 1.91 \pm 0.2$ kcal/mol).[6] Kinetics were measured under acid-free conditions at these temperatures and it was established that the activation energy ($\Delta G^{\ddagger}_{298}$) for phosphorus inversion in Ia is *ca.* 31 kcal/mol.[7]

Analysis of the proton nmr spectrum of Ia1 in $CDCl_3$ at 220 MHz revealed an approximately first-

(1) Exceptions to this include systems in which (a) the presence of heteroatoms causes a great reduction of axial–axial repulsions: L. Angiolini, R. P. Duke, R. A. Y. Jones, and A. R. Katritzky, *Chem. Commun.*, 1308 (1971), and references therein; (b) strain is encountered by vicinal equatorial group interactions: E. L. Eliel, L. D. Kopp, J. E. Dennis, and S. A. Evans, Jr., *Tetrahedron Lett.*, 3409 (1971); (c) dipole–dipole interactions force polar groups into an axial position: R. U. Lemieux, *Pure Appl. Chem.*, **25** (3), 527 (1971); N. S. Zefirov and N. M. Shekhtman, *Russ. Chem. Rev.*, **40** (4), 315 (1971); E. L. Eliel, *Spec. Lect., XXIIIrd Int. Congr. Pure Appl. Chem.*, **7**, 219 (1971); E. L. Eliel and M. K. Kaloustian, *Chem. Commun.*, 290 (1970); (d) other strain factors are operative: F. Johnson and D. T. Dix, *J. Amer. Chem. Soc.*, **93**, 5931 (1971).

(2) W. G. Bentrude and K. C. Yee, *Tetrahedron Lett.*, 3999 (1970).

(3) (a) M. Haemers, R. Ottinger, J. Reisse, and D. Zimmerman, *ibid.*, 461 (1971); (b) W. G. Bentrude and J. H. Hargis, *J. Amer. Chem. Soc.*, **92**, 7136 (1970); W. G. Bentrude, K. C. Yee, R. D. Bertrand, and D. M. Grant, *ibid.*, **93**, 797 (1971); C. L. Bodkin and P. Simpson, *J. Chem. Soc. B*, 1136 (1971). See also references in ref 1.

(4) (a) A. T. McPhail, J. J. Breen, and L. D. Quin, *J. Amer. Chem. Soc.*, **93**, 2575 (1971); A. T. McPhail, J. J. Breen, J. H. Somers, J. C. H. Steele, Jr., and L. D. Quin, *Chem. Commun.*, 1020 (1971); J. B. Lambert and W. L. Oliver, Jr., *Tetrahedron*, **27**, 4245 (1971).

(5) Equilibrium of pure Ia1 under conditions where acid was punctiliously eliminated was complete in *ca.* 20 hr at 200° and gave the same final isomer ratio.

(6) Although the amount of the minor isomer (Ia2) present was insufficient for pmr analysis, the difference in the *tert*-butyl resonances for Ia1 and Ia2 indicates different environments in the two isomers and suggests that Ia2 is either in a chair conformation with an axial 5-*tert*-butyl or possibly in a twist form. A plot of ln K_{eq} *vs.* $1/T$ and a least-squares fit of the data gave the values, $-\Delta H = 2.4$ kcal/mol; $\Delta S = 1.8$ eu. The relatively small entropy difference points toward a mixture of chair conformations (*i.e.*, entropy of mixing) but we do not regard the limited data to be of sufficient precision to rule out twist forms of higher entropy.

(7) The value for $\Delta G^{\ddagger}$ is in accord with anticipated inversion barrier for this system: A. Rauk, J. D. Androse, W. G. Frick, R. Tang, and K. Mislow, *J. Amer. Chem. Soc.*, **93**, 6507 (1971).