Conformational Analysis of Phosphorus Heterocycles. ^1H and ^{31}P Nuclear Magnetic Resonance Study of *N,N'*-Dimethyl-(2*R*)-2-phospha-1,3-diazacyclohexanes[1a]

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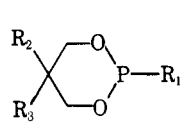
Abstract: An examination of a series of *N,N'*-dimethyl-(2*R*)-2-phospha- and *N,N'*,5,5-tetramethyl-(2*R*)-2-phospha-1,3-diazacyclohexanes (R = Cl, OCH_3, C_2H_5, CH_3, and C_6H_5; compounds **1–10**) by ^1H and ^{31}P nuclear magnetic resonance spectroscopy reveals predominantly single chair conformations, probably with diequatorial *N*-methyl groups. The P–N–C–H coupling constants are quite variant with the phosphorus substituent and suggest that the nitrogen hybridization, and consequently the flattening of the rings, is very dependent upon the electronegativity of the P substituent. The stereochemistry of the phosphorus substituents is discussed.

In contrast to the numerous studies available concerning the conformation of saturated six-membered ring heterocyclic compounds containing oxygen,[2] nitrogen,[2a] or sulfur,[2] relatively little attention has been devoted to the corresponding six-membered ring tervalent phosphorus systems with the exception of (2*R*)-2-phospha-1,3-dioxacyclohexanes (I).[3] Briefly, the investigations of several groups[3] have demonstrated that derivatives of I exist primarily in chair conformations[3] and have suggested that substituents on phosphorus strongly prefer axial orientations.[3a–d] Surprisingly, this latter conclusion appears to include alkyl[3a] and aryl,[3b] in noteworthy contrast to the usual equatorial preference of such groups in other six-membered ring heterocycles[2] and in cyclohexyl systems.[4] This article describes the results of ^{31}P and ^1H nmr spectral analysis of a series of (2*R*)-2-phospha-1,3-diazacyclohexanes (II), a class of



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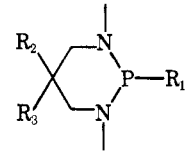


II

compounds which has received virtually no attention with respect to conformational considerations. Particularly important questions to be answered in this area include the geometry and conformation of the ring system; the effects of phosphorus substituents on nmr spectral parameters; the preferred orientations of groups attached to phosphorus; the involvement, if any, of (d–p)π bonding between nitrogen and phosphorus; and the effect of the syn-axial, lone electron pairs of nitrogen on the orientation of alkyl substituents on nitrogen, a topic which has recently attracted considerable attention.[5]

Compounds

A series of *N,N'*-dimethyl-2-phospha-1,3-diazacyclohexanes (Table I, compounds **1–10**) was prepared by standard procedures (see Experimental Section) having chloro, methoxy, methyl, ethyl, or phenyl substituents attached to phosphorus. Both the (2*R*)-2-phospha-1,3-diazacyclohexanes (group A) and the corresponding 5,5-dimethyl compounds (group B) were examined by proton and ^{31}P nmr spectral analysis with the aim that the comparison between group B (in which the *N,N'*-dimethyl groups are forced into equatorial conformations[5a]) and group A (in which the *N*-methyls may be axial or equatorial) would provide information concerning 1,3-diaxial lone-pair repulsions in these systems and hence the stereochemistry of the nitrogen groups.

Nmr Analysis

(a) General Proton Analysis. Proton nmr spectra of compounds **1–10** were recorded at 100 MHz either neat or as benzene or $CDCl_3$ solutions (see Table II). The 5,5-dimethyl compounds **2**, **4**, **6**, **8**, and **10** (group B) displayed similar sets of ring proton multiplets representing AA'KK'X patterns (X = phosphorus, AA'KK' = C_4 and C_6 protons), two well-separated singlets of unequal height and width corresponding to the two methyl groups at position 5, and a doublet further downfield for the methyls on nitrogen. The C_5 unsubstituted derivatives **1**, **3**, **5**, **7**, and **9** (group A)

(1) (a) Taken from part of the Ph.D. Thesis of B. E. M., Drexel University, June 1972; (b) Drexel University; (c) Centre d'Etudes Nucléaires.

(2) For reviews of conformational analysis of heterocyclic compounds containing more than one heteroatom see: (a) E. L. Eliel, *Accounts Chem. Res.*, **3**, 1 (1970), and references therein; (b) C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Top. Stereochem.*, **4**, 39 (1969), and references therein.

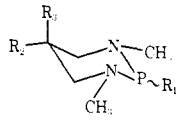
(3) (a) J. H. Hargis and W. G. Bentrude, *Tetrahedron Lett.*, 5356 (1968); (b) W. G. Bentrude and J. H. Hargis, *J. Amer. Chem. Soc.*, **92**, 7136 (1970); (c) W. G. Bentrude, K. C. Yee, R. D. Bertrand, and D. M. Grant, *ibid.*, **93**, 797 (1971); (d) W. G. Bentrude and K. C. Yee, *Tetrahedron Lett.*, 3999 (1970); (e) D. W. White, R. D. Bertrand, G. K. McEwen, and J. G. Verkade, *J. Amer. Chem. Soc.*, **92**, 7125 (1970); and references cited therein.

(4) E. L. Eliel, N. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley-Interscience, New York, N. Y., 1965.

(5) (a) R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *J. Amer. Chem. Soc.*, **90**, 7174 (1968); (b) E. L. Eliel, L. D. Kopp, J. E. Dennis, and S. A. Evans, Jr., *Tetrahedron Lett.*, 3409 (1971); (c) E. L. Eliel, Special Lectures, *XXIIIrd Int. Congr. Pure Appl. Chem.*, 7, 219 (1971); (d) P. J. Halls, R. A. Y. Jones, A. R. Katritzky, M. Snarey, and D. L. Trepanier, *J. Chem. Soc. B*, 1320 (1971); (e) H. Booth and R. M. Lemieux, *Can. J. Chem.*, **49**, 779 (1971); (f) S. Wolfe, A. Rauk, L. Tel, and I. Csizmadia, *J. Chem. Soc. B*, 136 (1971); (g) F. G. Riddell and D. A. R. Williams, *Tetrahedron Lett.*, 2073 (1971); (h) S. Wolfe, *Accounts Chem. Res.*, **5**, 102 (1972).

showed substantially more complex sets of multiplets corresponding to AA'KK'QTX patterns (X = phosphorus, AA'KK' = C_4 and C_6 protons, Q and T = C_5 protons) and a doublet for the *N*-methyl resonance. The existence of anisochronous ring protons in group A and the fact that the spectra were essentially temperature independent over a wide range [*ca.* −80 to 250° (for 0.5 hr)] strongly suggest that all the phosphadiazacyclohexanes in this study exist in predominantly one conformation. The line widths were as expected for this situation. Cross-ring couplings ($J_{AA'}$ and $J_{KK'}$) were small (<0.5 Hz) and consequently not accurately determined. The neat liquid spectrum of the 2-chloro derivatives (**1** and **2**) showed interesting peculiarities which will be treated further in the discussion (*vide infra*).

Table I. (2*R*)-2-Phospha-1,3-diazacyclohexanes[a]



Compd	R_1	R_2	R_3
1	Cl	H	H
2	Cl	CH_3	CH_3
3	OCH_3	H	H
4	OCH_3	CH_3	CH_3
5	CH_3	H	H
6	CH_3	CH_3	CH_3
7	C_2H_5	H	H
8	C_2H_5	CH_3	CH_3
9	C_6H_5	H	H
10	C_6H_5	CH_3	CH_3

[a] $R_2 = R_3 = H$, group A; $R_2 = R_3 = CH_3$, group B.

Complete analyses of the 100-MHz proton spectra of compounds **1–10** were accomplished by ^{31}P spin decoupling to provide simpler, nearly first-order proton patterns from which good approximate values for the chemical shifts and coupling constants could be extracted and refined using an iterative nmr program (LAOCOON3).[6]

The best parameters from total analysis are presented in Table II. The proton identification (A and Q axial, K and T equatorial) is discussed further in the paper. Figure 1 provides a comparison between the experimental and calculated spectra for compound **3**.

(b) 2-Chloro Compounds (1 and 2). The nmr spectrum of a neat sample of **1** displayed a doublet (δ 2.43; J = 18.6 Hz) corresponding to the *N*-methyl protons, a broad quintet (2 protons, δ 1.80; splitting = 5 Hz), and another quintet (4 protons, δ 2.74; splitting = 5 Hz). Dilution with $CDCl_3$ produced a change of this relatively simple spectrum to a more complicated one similar to those observed for the other phosphadiazacyclohexanes. Such modifications in the nmr spectra for neat *vs.* diluted chlorophosphoro compounds have been observed previously[3e,7] with cyclic and noncyclic

(6) J. Castellano, C. Sun, and R. Kostelnik, *J. Chem. Phys.*, 46, 327 (1967); A. A. Bothner-by and S. Castellano, Quantum Chemistry Program Exchange, No. III, Indiana University, Bloomington, Ind.

(7) (a) H. Goldwhite and B. Fontal, *Tetrahedron*, 22, 3275 (1966); (b) P. Haake, J. P. McNeal, and E. J. Goldsmith, *J. Amer. Chem. Soc.*, 90, 715 (1968); (c) J. E. Bissey, H. Goldwhite, and E. J. Goldsmith, *J. Magn. Resonance*, 2, 81 (1970).

Table II. Nmr Spectral Data for (2*R*)-2-Phospha-1,3-diazacyclohexanes (See Figure 1)

No.	Solvent	δ_A[a] [4a]	δ_K [4e]	δ_Q [5a]	δ_T [5e]	δ_{N-CH_3}	J_{AK}[b] [4a,4c]	J_{AQ} [4a,5a]	J_{AT} [4a,5e]	J_{KQ} [4e,5a]	J_{KT} [4e,5e]	J_{QT} [5a,5e]	J_{AX} [4a,P]	J_{KX} [4e,P]	J_{TX} [5e,P]	J_{PNCH_3}
1	$CDCl_3$ (exch)		*ca.* 2.87		*ca.* 1.98	2.63			*ca.* 5					*ca.* 10		18.9
	$CDCl_3$	2.86	2.59	2.01	1.75	2.63	−11.7	12.5	3	4.4	2.9	−13.6	10.3	10.4	1.4	18.6
2	$CDCl_3$ (exch)		2.56		0.99	2.68								*ca.* 10		18.7
	$CDCl_3$	2.71	1.82	0.90	0.67	2.69	*ca.* −11.3						*ca.* 10.2	*ca.* 11		18.6
3	$CDCl_3$	3.12	2.58	2.00	1.60	2.63	−11.4	11.8	3.15	4.35	3.6	−13.2	4.2	8.7	0.9	16.0
4	C_6D_6	2.87	1.98	1.07	0.71		−11.4						4.9	9.1		15.6
	$CDCl_3$			(1.05)	(0.83)	(2.66)										(15.8)
5	Neat	3.16	2.67	2.09	1.24		−12.6	12.8	2.6	4.2	2.7	−13.4	2.6	7.1	0	16.3
6	C_6D_6	2.65	2.05	1.11	0.66		−12.3						3.4	7.8		16
7	C_6D_6	3.14	2.50			2.64	−12.9	13.4	2.7	4.2		−13	2.8	7		15.2
	Acetone-d_6					(2.63)										(15.6)
8	C_6D_6	2.82	2.07	1.08	0.66	2.67	−12.9	13.4					1.6	5.7		14.8
	Acetone-d_6			(1.08)	(0.76)	(2.67)										(14.9)
9	C_6D_6	3.17	2.47	1.96	0.64	2.87	−12.8	12.4	2.8	3		−13	0	5.3	0.5	15.5
10	C_6D_6	2.78	2.05	1.07	0.35	2.97	−13.5						0	5.5		14.2
	Acetone-d_6			(1.13)	(0.50)	(3.01)										(14.0)

[a] The chemical shifts are given in ppm with TMS as internal reference. [b] The coupling constants are given in Hz. J_{QX} invariably had a value of 0.0 Hz.

derivatives and interpreted in terms of a bimolecular chlorine exchange process,[3e,7c] which results in rapid inversion of the configuration at phosphorus, and this interchanges the axial and equatorial conformations of the chlorine.[8] Coupled with ring inversion, this exchanges the environments of the geminate hydrogens and thus results in the relatively simple spectrum obtained. Dilution of the sample slows the exchange process (provided that water is excluded) to the extent that the geminate protons become anisochronous on the nmr time scale, resulting in a more complicated spectrum.

The nmr spectrum of a dilute solution of **2** in benzene was similar to those observed for the other 5,5-dimethyl compounds and could be easily interpreted (see Table II). A concentrated solution or one which was exposed to moisture began to show the chlorine exchange process, the rate of which determined the spectral parameters. The chlorine exchange spectrum (in $CDCl_3$) displayed a doublet (δ 2.68, J = 18.7 Hz) for the *N*-methyl protons, a doublet (4 H, δ 2.56, J = 10 Hz), and a sharp singlet (6 H, δ = 0.99).

(c) Shape of the 1-Phospha-2,6-diazacyclohexane Ring. An examination of the coupling constants for the protons which provide the AA'KK'QT patterns reveals a large coupling between the low-field portions of the C_4, C_6, and C_5 multiplets (AA' and Q; 12.4 Hz < J < 13.4 Hz), indicative of an axial–axial (*ca.* 180°) coupling,[9] and allows the assignment of the axial and equatorial protons on C_4, C_5, and C_6. The smaller couplings observed between KK' and T ($J \cong$ 2.8 Hz; equatorial–equatorial protons), AA' and T (2.6 Hz < J < Hz; $C_{4,6}$ axial–C_5 equatorial protons), and KK' and Q (3 Hz < J < 4.4 Hz; $C_{4,6}$ equatorial–C_5 axial protons)[9,10] are consistent with the assignments. The results seem best accommodated by predominately a single chair conformation for the N_1–C_6–C_5–C_4–N_3 fragment and appear to exclude flexible boat forms in which pseudorotation would tend to average the chemical shifts and coupling constants.[11] In compounds **2**, **4**, **6**, **8**, and **10**, the C_5 methyl resonances are of unequal height and line width with the lower field signal appearing broader. Proton–methyl decoupling demonstrated that this is due to long-range coupling of the axial methyl hydrogens to the low-field C_4 and C_6 protons (AA'). Such coupling usually occurs through the well-documented "W" pathway[12] and has been observed in various rigid six-membered rings systems including 5,5-dimethyl-(2*R*)-2-phospha-1,3-dioxacyclohexanes.[3e]

The proton–proton coupling constants observed are quite similar within the same group (A or B), essentially independent of the substituent on phosphorus, and are in the same range as the values reported for (2*R*)-2-phospha-1,3-dioxacyclohexanes.[3e]

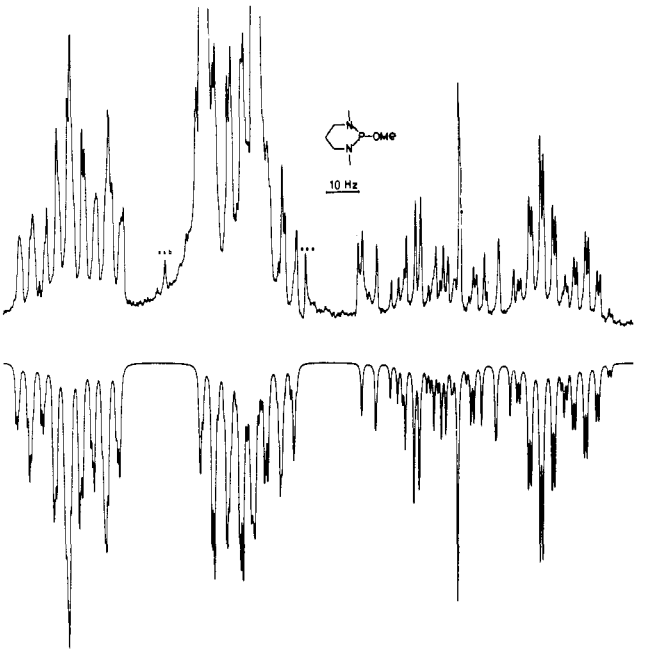


Figure 1. Experimental (upper) and calculated nmr spectrum for 2-methoxy-*N*,*N*'-dimethyl-2-phospha-1,3-diazacyclohexane (**3**).

In all the compounds included in this study, the axial hydrogens located at C_4, C_5, or C_6 (and C_5 methyls) appear at low field relative to their equatorial counterparts (Table II). This relative order is the same as that previously observed for the same positions in 2-phospha-1,3-dioxacyclohexanes,[3e,13] C_5 in 1,3-dioxacyclohexanes,[10c] and C_5 in 1,3-dithiacyclohexanes,[11] and is contrary to the situation observed in cyclohexanes in which axial substituents resonate at higher field.[14] The difference in chemical shifts between the axial and equatorial protons at C_4, C_6 ($\Delta_{AK} = H_A - H_K$) varies between 0.27 (for **1**) and 0.89 (for **2** and **3**), but shows no significant trend.

(d) ^3J(P–N–C–H) Coupling. In previous nmr investigations of 2-phospha-1,3-dioxacyclohexanes, values of $^3J(POCH_A)$ and $^3J(POCH_K)$ were observed to be nearly independent of the substituent on phosphorus[3e] (except for $N(CH_3)_2$ and S–C_6H_5 phosphorus substituents[3e]) and were in the approximate range of 2.1–5.7 Hz for H_{ax} coupling and 10.0–11.3 Hz for H_{eq} coupling. The phosphorus–proton coupling also appears to be relatively insensitive to the stereochemical disposition of the phosphorus lone pair.[3e] Somewhat surprisingly, the data in Table II clearly demonstrate that both $^3J(PNCH_{eq})$ and $^3J(PNCH_{ax})$ in 2-phospha-1,3-diazacyclohexanes are quite dependent upon the phosphorus substituent. The degree of variance is substantial, ranging from 0 Hz in **10** (P–C_6H_5) to 10.3 Hz in **1** (R–Cl) for H_{ax} coupling, and from 5.3 Hz in **9** (P–C_6H_5) to 11.0 Hz in **2** for H_{eq}. The relative couplings for pairs in groups A and B with the same phosphorus substituent are approximately the same, and the values for the similar alkyl groups, methyl and ethyl, are also relatively close (compare **5**, **6**, **7**, and **8**). With the excep-

(8) Recent investigations suggest that trace impurities in the samples are responsible for the exchange process: R. H. Cox, H. G. Newton, and B. S. Campbell, *J. Amer. Chem. Soc.*, **93**, 530 (1971).

(9) N. Bhacca and D. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964.

(10) The smaller H_{eq}–H_{eq} and H_{4eq}–H_{5ax} coupling constants are expected since couplings of protons anti to electronegative atoms (*i.e.*, nitrogen oroxygen) are usually smaller than normal. See (a) H. Booth, *Tetrahedron Lett.*, 411 (1965); (b) M. Anteunis, D. Tavernier, and F. Borremans, *Bull. Soc. Chim. Belg.*, **75**, 396 (1966); (c) E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, **90**, 3444 (1968).

(11) (a) E. L. Eliel and R. O. Hutchins, *J. Amer. Chem. Soc.*, **91**, 2703 (1969), and references therein.

(12) Reference 9, pp 115–118.

(13) An exception to this has been noted by Bentrude and Yee[3b] for *cis*-2-phenyl-2-phospha-5-*tert*-butyl-1,3-dioxacyclohexane in which the axial C_4,C_6 protons are at higher field, presumably due to shielding by the phenyl ring.

(14) L. M. Jackman and S. Sternhell, "Nuclear Magnetic Resonance Spectroscopy in Organic Applications of Chemistry," Pergamon Press, London, 1969, pp 238–240.

tion of the *P*-chloro compounds, **1** and **2**, the $^3J(PNCH_3)$ values, on the other hand, remain relatively close (14.2 Hz in **10** to 15.6 Hz in **4**). Similar variances in ^3J(PNCH) with phosphorus substituents were also observed in the corresponding 2-phospha-1,3-diazacyclopentanes[15] and in several acyclic aminophosphines.[16a] The situation may be related to the hybridization of the nitrogen. Cowley and Schweiger[17] have concluded from ^{15}N–H coupling constants that planar geometries about nitrogen (sp^2 hybridization) are expected for N–P compounds with strongly electronegative substituents on phosphorus; this lowers the energy of the 3d (and/or 4p) orbitals and facilitates (2p–3d)π bonding. In the absence of highly electronegative substituents such as in methyl substituted aminophosphines, tetrahedral geometry is expected. For example, $(CF_3)_2PNH_2$ is predicted to be planar (30.8% nitrogen 2s character in the σ bonds) while $CF_3CH_3PNH_2$ should be nearly tetrahedral about nitrogen (27.9% nitrogen 2s character). Increasing the sp^2 character of nitrogen is reflected in larger ^{15}N–H coupling resulting either by increased bonding or by an increase in the Fermi contact contribution.[18] The interpretation is consistent with an X-ray crystallographic study and with a recent microwave study, which have revealed a planar nitrogen configuration for $(CH_3)_2NPF_2$[19a] and PF_2NH_2,[19b] respectively. It appears reasonable, therefore, that the nitrogen hybridization in the (2*R*)-2-phospha-1,3-diazacyclohexanes may be changing from principally sp^2 to sp^3 as the phosphorus substituent varies from very electronegative Cl or OCH_3 to alkyl and phenyl groups. The effects of nitrogen hybridization on ^3J(PNCH) are not known, but coupling should increase as the degree of (p–d)π bonding (or the per cent of 2s character in the nitrogen orbitals) between nitrogen and phosphorus increases which, in turn, will be increased by strongly electron-withdrawing groups on phosphorus.[17,20] The trend in $^3J(PNCH_{4,6})$ in **1**–**10** is in line with this exception in that H_4 and H_6 couple strongly with phosphorus in compounds **1**, **2**, **3**, and **4**. In addition, the orientation of the phosphorus lone pair has been suggested[16,21] to contribute heavily to ^3J(PNCH). The disposition of the phosphorus lone pair is uncertain in the compounds under study (see later discussion) and thus conclusions regarding the effect of the orientation are unwarranted at this time. It is noteworthy, however, that flattening of the ring in the *P*-chloro compounds **1** and **2** by increased pπ–dπ bonding would move the C_4 and C_6 hydrogens into more similar orientations relative to an equatorial lone pair on phosphorus and account for the nearly identical $J(PNCH_A)$ and $J(PNCH_K)$ values obtained for these compounds. One would expect from this argument that, as the ^3J(PNCH) couplings decrease (as nitrogen sp^3 character increases), the difference between $^3J(PNCH_A)$ and $^3J(PNCH_K)$ should increase, and this trend is observed (Table II). The relatively large and invariable $^3J(P–N–CH_3)$ couplings do suggest that the orientations between the *N*-methyls and the phosphorus lone pair are relatively similar for the entire series and that they lie in close proximity.[16] The *P*-chloro derivatives **1** and **2** show substantially larger $^3J(P–N–CH_3)$ coupling than the remainder of the series (18.6 Hz for **1** and **2** *vs.* 14.2–16.3 Hz for **3**–**10**), which again is consistent with increased π bonding. Certainly further investigations are warranted on this interesting and important question.

(e) Stereochemistry of the *N*-Methyl Groups. Investigations of *N*,*N*′-dimethyl-1,3-diazacyclohexanes[5a,d,g] (*e.g.*, **11**) have revealed that an *N*-alkyl substituent can prefer an axial orientation (as in **11b**). The phenomenon, which is observed in various systems having two lone-pair-bearing heteroatoms located 1,3 to each other, has been termed the "rabbit-ear,"[2a,5a–d] "Edward–Lemeiux,"[5f] or "generalized anomeric"[22a] effect and has been attributed to 1,3-syn-axial lone pair repulsions[5a–c,22b] or polar bond interactions.[5f] In *N*,*N*′-dimethyl-2-phospha-1,3-diazacyclohexanes, therefore, the effect may be operating so that the N_{eq},N'_{ax}-methyl conformation (*i.e.*, **13**) would make at least a significant contribution to the conformational equilibrium resulting from nitrogen inversion. We hoped to probe this question using two approaches: examination of the phosphorus chemical shifts and examination of the *J gem* coupling of the C_4 and C_6 protons. First, by comparing ^{31}P chemical shifts for compounds in group A with the corresponding 5,5-dimethyl derivatives in group B (in which the *N*-methyls are strongly biased diequatorial[5a]), any difference in the conformational equilibrium about nitrogen in group A might have been reflected by change in shielding of phosphorus and hence a change in ^{31}P chemical shifts. The ^{31}P values presented in Table III indicate that 5,5-dimethyl substitution causes a concomitant ^{31}P shift to higher field of about 9–10 ppm. However, the corresponding 5-methyl derivatives **14a** and **14b** (which should have the same nitrogen stereochemistry as the unsubstituted compounds) also showed upfield ^{31}P shifts amounting to about half that induced by introduction of two 5-methyl groups. Furthermore, introduction of 5,5-dimethyls in 2-phospha-1,3-dioxacyclohexanes (*e.g.*, **15** and **16**) has also been observed to produce a substantial upfield ^{31}P shift[3e] (−131 and −123 ppm for **15** and **16**, respectively), although there can be no change in the geometry about oxygen. The phenomena in these latter systems has been attributed[3e] to a decrease

(15) J. P. Albrand, A. Cogne, D. Gagnaire, J. Martin, and J. B. Robert, *Tetrahedron*, in press.

(16) (a) J. Nelson, R. Spratt, and B. Walker, *J. Chem. Soc. D*, 1509 (1970). (b) An exception to this has recently been demonstrated for *cis*- and *trans*-4-*tert*-butyl-2-(*N*,*N*-dimethylamino)-2-phospha-1,3-dioxacyclohexanes in which the orientation of the P substituent greatly affects $^3J_{PH}$; see W. G. Bentrude and H. W. Tan, *J. Amer. Chem. Soc.*, **94**, 8224 (1972). The same situation has been observed for similar 2-phospha-1,3-dithiacyclohexanes (see ref 32).

(17) A. H. Cowley and J. R. Schweiger, *J. Chem. Soc. D*, 1492 (1970).

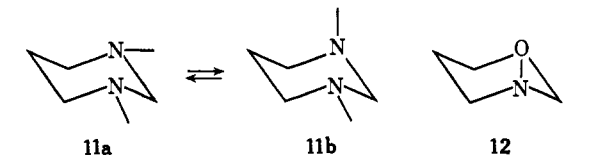
(18) H. A. Bent, *Chem. Rev.*, 61, 275 (1961).

(19) (a) E. D. Morris, Jr., and C. E. Nordman, *Inorg. Chem.*, 8, 1672 (1969); (b) A. H. Brittain, J. E. Smith, P. L. Lee, K. Cohn, and R. H. Schwendeman, *J. Amer. Chem. Soc.*, **93**, 6772 (1971).

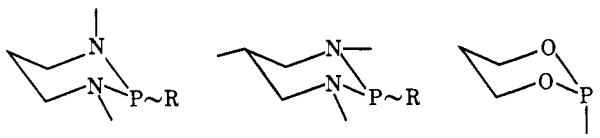
(20) Compounds **10a** and **10b**, in which the *P*-phenyl is para substituted by *electron-withdrawing* CF_3 and *electron-releasing* OCH_3, respectively, showed P–N–C–H couplings indistinguishable from the unsubstituted parent **10**. Evidently, the electronegativity change introduced by these groups is not great enough to significantly affect the couplings. In line with this, the ^{31}P chemical shifts of **10a** and **10b** were only slightly (but experimentally) distinguishable from **10**. However, the trend was as expected with the *p*-CF_3 derivative, **10a**, shielded (by increased electron donation by nitrogen) and the *p*-OMe derivative, **10b**, deshielded with respect to **10**.

(21) (a) A. H. Cowley, M. J. S. Dewar, W. R. Jackson, and W. B. Jennings, *J. Amer. Chem. Soc.*, **92**, 5206 (1970); (b) A. H. Cowley, M. J. S. Dewar, W. R. Jackson, and W. B. Jennings, *ibid.*, **92**, 5206 (1970); (c) H. Paulsen and W. Greve, *Chem. Ber.*, 103, 486 (1970); (d) Y. Yonezawa, I. Morishima, K. Fukuta, and Y. Ohmori, *J. Mol. Spectrosc.*, 31, 341 (1969).

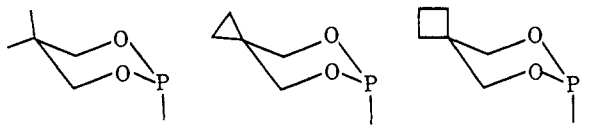
(22) (a) Y. Allingham, R. Cookson, T. Crabb, and S. Vary, *Tetrahedron*, **24**, 4625 (1968); (b) F. P. Chen and R. Jesaitis, *Chem. Commun.*, 1533 (1970).



11a 11b 12

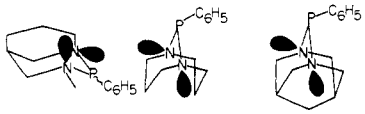


13 14a, R = Et 14b, R = C_6H_5 15



16 16a 16b

in the C–C–C angles induced by the *gem*-methyl groups[23] which, in turn, caused a decrease in the O–P–O angles and resulted in the upfield shift.[24] It appears likely that, if such an effect did exist, it would operate in the nitrogen systems also, especially since the chemical shift differences are so similar.[25] In order to further probe the question of the nitrogen stereochemistry, compounds **17**, **18**, and **19** were examined in which the relative orientations of the nitrogen lone pairs (and the *N*-alkyl groups) could be controlled. In **18** and **19** the rigid geometries require that both pairs be situated in equatorial conformations relative to either six-membered ring while in **17**, one pair is constrained equatorial and the other is probably axial because of severe syn-axial alkyl–methyl steric interactions. The ^{31}P chemical shifts (Table III) suggest that substantial stepwise deshielding occurs in response to changing first one lone pair (as in **17**) and then both (as in **18** and **19**) from axial to equatorial orientations (compare **9** → **17** → **19**). The results seem best explainable in terms



17 18 19

of $p\pi$–$d\pi$ bonding which is dependent upon the angular orientation of the nitrogen pairs and the phosphorus. Such a dependence is possibly due to mixing of phosphorus 3d with 4p[17] or σ orbitals[21b] and creates an angular dependence of N–P[21b] (or N–S)[26] bond strengths.[27]

(23) P. v. R. Schleyer, *J. Amer. Chem. Soc.*, 83, 1368 (1961).

(24) V. Mark and J. R. Van Wazer, *J. Org. Chem.*, 32, 1187 (1967).

(25) However, preliminary results indicate that the overall picture is more complex than it would seem from the suggested explanation. The spiro compounds 16a and 16b, which according to Schleyer[23] should have increased C–C–C ring angles (thus increased O–P–O angles), exhibited ^{31}P chemical shifts of −127.8 and −125.7 ppm, respectively, rather than values equal to or less than −131 ppm as would be expected.

(26) M. Raban and F. B. Jones, Jr., *J. Amer. Chem. Soc.*, 93, 2692 (1971). The torsional barrier in certain N–S or P–N[21b] compounds are at least partly attributable to an angular dependence of $p\pi$–$d\pi$ bonding.

(27) An angular dependence of $p\pi$–$d\pi$ overlap in phosphorus–nitrogen bonding is also suggested by the deshielding experienced by phosphorus in $\phi P[N(C_2H_5)_2]_2$ ($\delta^{31}P$ −98.2 ppm) compared to that in *N,N'*-diethyl-2-phenyl-2-phospha-1,3-diazacyclohexane (14c, $\delta^{31}P$ −86.6 ppm). Apparently, in the former the diethylamino groups could be tilted out of "planarity" (ii) by steric interactions resulting in diminished bonding compared to the rigidly held ring system, 14c (see iii).

iii ii

In the present case, such a dependence is evidently reflected in greater shielding (*i.e.*, enhanced $p\pi$–$d\pi$ bonding) when the nitrogen lone pairs are axial and thus points to primarily diequatorial *N*-methyl (*i.e.*, axial lone pairs) conformations in the rings capable of adopting such geometries (as in **9**, **14b**, and **10**).[27]

The stereochemistry at nitrogen was also approached by a consideration of the geminal coupling constants at positions C_4 and C_6, adjacent to the nitrogens. A change in nitrogen lone-pair orientation produced by introduction of 5,5-dimethyl groups into phospha-diazacyclohexanes (which constrains the *N*-methyls to equatorial sites) should be reflected by an increase in J_{AK}.[28] An examination of the values in Table II, however, shows very little change for any pair and no consistent trend. The results suggest that all the compounds studied possibly have similar and principally equatorial orientations about nitrogen. The same conclusion follows from the relatively small change in Δ_{AK} induced by introduction of dimethyl substitution at position 5 (Table II)[29] (with the exception of the *P*-chloro compounds, for which extensive flattening at nitrogen would remove them from consideration with the other compounds). The tentative conclusion that the *N*-methyls are diequatorial is not unexpected considering the long P–N bonds (*ca.* 1.65–1.77 Å)[19,30] which spread out the N–P–N portion of the ring and hence reduce any dipole interactions. Furthermore, very recent work[5b,d,g] has indicated that the anomeric effect contributes in a lesser measure than was first thought and that steric interference of three equatorial groups in **11a** is partly responsible for predominance of **11b**. Here again the long P–N bond length would diminish the interaction.

(f) Stereochemistry at Phosphorus. Most substituents prefer to adopt equatorial conformations in cyclohexyl and heterocyclic systems primarily because of steric interactions encountered when the groups are axial. Exceptions occur when a highly polar substituent (*e.g.*, halogen, alkoxy) is located on a carbon adjacent to a ring heteroatom. In such cases, the axial orientation is often preferrred because of the previously discussed generalized anomeric effect. In 2-phospha-1,3-dioxa-[3a,31] and 2-phospha-1,3-dithiacyclohexanes[32] there is increasing evidence that substituents on phosphorus including alkyl (except *t*-butyl) and aryl groups strongly prefer axial conformations. The result is per-

(28) R. Cahill, R. C. Cookson, and T. A. Crabb, *Tetrahedron*, 25' 4681 (1969); P. J. Chivers, T. A. Crabb, and R. O. Williams, *ibid.*, 24, 7725 (1968).

(29) For examples and discussions of this effect see: J. B. Lambert, R. G. Keske, R. E. Carhart, and A. P. Jovanovich, *J. Amer. Chem. Soc.*, 89, 3761 (1967); J. B. Lambert and R. G. Kesle, *Tetrahedron Lett.*, 2023 (1969); F. G. Riddell and J. M. Lehn, *J. Chem. Soc. B*, 1224 (1968).

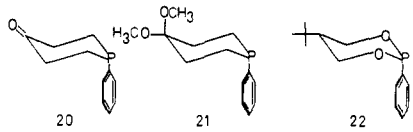
(30) (a) M. D. La Prade and C. E. Norman, *Inorg. Chem.*, 8, 1669 (1969); (b) K. Muir and J. F. Nixon, *Chem. Commun.*, 1405 (1971); E. Hobbs, D. Corbridge, and B. Raistrick, *Acta Crystallogr.*, 6, 621 (1953).

(31) (a) D. W. White, G. K. McEwen, and J. G. Verkade, *Tetrahedron Lett.*, 1905 (1969); (b) M. Hague, C. Caughlan, J. H. Hargis, and W. G. Bentrude, *J. Chem. Soc. A*, 1787 (1970).

(32) R. O. Hutchins and B. E. Maryanoff, *J. Amer. Chem. Soc.*, 94, 3266 (1972).

haps not unusual for polar groups such as halogen or alkoxy groups (since the P is located between two oxygens), but is unprecedented for alkyl or phenyl substituents. The axial preference has been attributed to favorable gauche interactions between adjacent lone pairs on phosphorus and oxygens[5f,3e] and to reduction in syn-axial interactions caused by the longer phosphorus–oxygen bonds.[3c,3e] This latter rationale may be of particular importance since a recent X-ray analysis of 1-phenylphosphocyclohexan-4-one[33] (**20**) and 1-phenyl-1,4-dimethoxyphosphacyclohexane[33b] (**21**) demonstrated axial dispositions of the phenyls even though in these cases no adjacent heteroatoms are present.

Direct evidence concerning the phosphorus stereochemistry in 2-phospha-1,3-diazacyclohexanes is lacking and unfortunately there have been no X-ray studies of the ring system. The similarity of the P–N and P–O bond lengths (*ca.* 1.66[19] and 1.64 Å,[34] respectively) suggests similar relief of axial steric interactions, and gauche attractions[5f] between P and N lone pairs may favor axial conformations for phosphorus substituents (if the N lone pairs are axial, as we have argued earlier). However, Bentrude and Yee[3d] observed that the axial C_4, C_6 protons in *cis*-5-*tert*-butyl-2-phenyl-2-phospha-1,3-dioxacyclohexane (**22**), the more stable isomer, res-



20 21 22

onated at higher field relative to the equatorial protons, a reversal of the usual order in these systems, and this anomaly was attributed to shielding caused by the benzene ring current. The observation was presented as evidence for the preferred axial position of the *P*-phenyl.[3d,35] An examination of δ_A and δ_K for the *P*-phenyl derivatives **9** and **10** reveals that no such reversal has occurred in these compounds and suggests that the phenyls may be equatorial in these cases. To obtain additional evidence on the positioning of phosphorus substituents, an NOE experiment[36] was performed on the *P*-methyl derivative **6**. Presumably, if the methyl was chiefly axial, an intensity enhancement of the $C_{4,6}$ axial protons would result upon saturation of the *P*-methyl signal. However, virtually no increase (<0.5%) was observed upon irradiation although the *N*-methyl signals were enhanced by *ca.* 5%. This appears to favor an equatorial deposition for the *P*-methyl group, but the evidence must be regarded with caution because much of the dipole–dipole relaxation is occurring with other (*i.e.*, *N*-methyl) protons.

Overall, the limited data tentatively suggest principally equatorial orientations for the P substituents, but additional information is required before a definite conclusion can be reached.

(33) (a) A. T. McPhail, J. J. Breen, and L. D. Quin, *J. Amer. Chem. Soc.*, **93**, 2575 (1971); (b) A. T. McPhail, J. J. Breen, J. H. Somers, J. C. H. Steele, Jr., and L. Quin, *Chem. Commun.*, 1020 (1971).

(34) B. Beagley, D. Cruickshand, T. G. Hewitt, and K. H. Jost, *Trans. Faraday Soc.*, **65**, 1219 (1969).

(35) In addition, a similar reversal of the C_4, C_6 axial and equatorial protons has been observed for the more stable isomer of 5-*tert*-butyl-2-phenyl-2-phospha-1,3-dithiacyclohexane which, along with other evidence, suggests that P substituents prefer axial conformations in these systems also.[32]

(36) (a) W. Von Philipsborn, *Angew. Chem., Int. Ed. Engl.*, **10**, 472 (1971); (b) F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, 87, 5250 (1965); see also ref 32.

Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 457 spectrophotometer; liquid samples were recorded neat and solid materials were recorded in potassium bromide pellets. Proton nuclear magnetic resonance spectra were obtained on Varian A-60 and HA-100 spectrometers as 10–20% solutions using tetramethylsilane as an internal reference. Phosphorus decoupling was achieved on a HA-100 spectrometer; the 40-MHz irradiating frequency was provided by an "NMR Specialities" HD 60B spin decoupler. ^{31}P nmr spectra were recorded at 40.5 MHz on a HA-100 spectrometer as 30–50% solutions (except **18** and **19**) using 85% H_3PO_4 as an external reference.

Mass spectra were recorded on a Perkin-Elmer Hitachi RMU-6 high-resolution mass spectrometer, operated at 70 eV. Microanalyses were performed by Midwest Microlab, Indianapolis, Ind.; by Alfred Bernhard Mikroanalytisches Laboratorium, West Germany; or by the Service Central de Microanalyse du Centre National de la Recherche Scientifique, France. *N,N'*,2,2-Tetramethyl-1,3-propanediamine was prepared as previously described.[37]

Methoxyphosphonous dichloride was prepared by the addition of methanol to phosphorus trichloride at 5°. The distilled product (23% yield), bp 92–94° (lit.[38a] 95–96°), had $n^{20}D$ 1.4703 (lit.[38a] 1.47725).

***p*-(Trifluoromethyl)phenylphosphonous Dichloride.** Magnesium turnings (2.8 g, 0.115 g-atom) were covered with dry ether (30 ml) and a solution of *p*-(trifluoromethyl)bromobenzene (25.9 g, 0.115 mol) in dry ether (60 ml) was added in a typical manner. The reddish brown mixture was stirred for 1 hr and then cooled to 0°. To this was added *portionwise* anhydrous $CdCl_2$ (11.6 g, 0.632 mol [10% molar excess]) over a period of 5 min. The mixture was stirred for 2 hr, warmed to room temperature and stirred another 2 hr, and then carefully decanted into a dry addition funnel. The solids were preserved under nitrogen for later use. PCl_3 (19.8 g, in excess) in 50 ml of dry ether was cooled to *ca.* −40°. The cadmium reagent was added with stirring while the temperature was kept between −30 and −20°.[39] After addition, the solids from before were added with the aid of some dry ether, and the mixture was warmed to ambient temperature and stirred overnight. The orange mixture was rapidly filtered through $MgSO_4$ and the concentrated filtrate was distilled at reduced pressure (9 cm Vigreux) to afford 11.8 g (42%) of colorless product (bp 44–47° (0.5 mm), $n^{23.5}D$ 1.5203). Characterization was accomplished through the 2-phospha-1,3-diazacyclohexane (Table III).

***p*-Methoxyphenylphosphonous dichloride,** prepared according to the procedure of Davies and Mann,[40] had bp 143° (13 mm) (lit. 150° (13 mm),[40a] 150° (18 mm)[40b]).

1,1-Bis(hydroxymethyl)cyclopropane was prepared by lithium aluminum hydride reduction of 1,1-dicarbethoxycyclopropane in 82% yield: bp 109–111° (3.5 mm) (lit.[41] 70° (? mm)), $n^{30}D$ 1.4688.

1,1-Bis(hydroxymethyl)cyclobutane was prepared in 86% yield as above: bp 87–90° (1.3 mm) (lit. 132–134° (22 mm)[41]), mp 23–26°, $n^{25}D$ 1.4789 (lit. $n^{22}D$ 1.4778).[41]

2-Phospha-1,3-diazacyclohexanes. General Procedure. The preparation of the title compounds was accomplished by the addition of the appropriate phosphonous dichloride in dry ether (usually *ca.* 1 *M*) to a stirred, ice-cooled solution of the diamine in dry ether (usually *ca.* 1 *M*) containing a ten- to 20-fold molar excess of triethylamine (distilled from KOH), under a dry nitrogen atmosphere. Equimolar amounts of the diamine and phosphonous dichloride were employed. After being warmed to room temperature, the mixture was filtered and the filtrate was concentrated at reduced pressure of a rotary evaporator. The residue was redistilled at reduced pressure (leaving an exceedingly viscous, polymeric residue) and redistilled if necessary. Samples for microanalyses and mass spectra were prepared by evaporative microdistillation of pure material or by preparative glpc (10% OV-1 on Chromosorb W). The 2-methoxy derivatives were also prepared by

(37) F. A. Davis, I. Turchi, B. E. Maryanoff, and R. O. Hutchins, *J. Org. Chem.*, **34**, 1583 (1972).

(38) (a) J. B. Conant, V. H. Wallingford, and S. S. Gandheler, *J. Amer. Chem. Soc.*, **45**, 762 (1923); (b) D. R. Martin and P. J. Pizzolato, *ibid.*, 72, 4584 (1950).

(39) R. B. Fox, *J. Amer. Chem. Soc.*, 72, 4147 (1950).

(40) (a) W. Davies and F. Mann, *J. Chem. Soc.*, 276 (1944); (b) I. Jackson, W. Davies, and W. Jones, *ibid.*, 2298 (1930).

(41) S. Searles, Jr., R. G. Nickerson, and W. K. Witsiepe, *J. Org. Chem.*, **24**, 1839 (1959).

Table III. Data for the (2*R*)-2-Phospha-1,3-diazacyclohexanes

Compd	n_D (temp, °C)	Bp, °C (mm)	$-\delta^{31}P^c$	Calcd C	Calcd H	Found C	Found H
1	1.5246 (27)	45–47 (0.20)	155.5	36.0	7.2	36.06	7.31
2	1.5078 (22) 1.5060 (26.5)	49–50 (0.45)	148.5	43.19	8.28	43.17	8.40
3	1.4755 (27)[a] 1.4693 (27)	66–68 (11)	131.6	44.44	9.32	44.52	9.38
4	1.4653 (26.5)[a]		122.6	50.52	10.07	50.65	10.21
5[b]	1.4927 (22)	64 (13)	88.3	49.30	10.35	49.70	10.36
6			79.9	55.15	10.99	54.48	11.30
7	1.4535 (23)	38–40 (0.90); 81 (21)	97.9	52.48	10.70	52.36	10.39
8	1.4770 (24)	48–50 (0.55)	88.6	57.42	11.24	56.67	11.29
9	1.5669 (26) 1.5682 (22)	119–123 (0.30)	91.9	63.44	8.23	63.14	8.38
10	1.5454 (26) 1.5463 (27)	82–84 (0.02)	81.3	66.08	8.96	66.08	8.77
10a	1.5008 (24)	80–84 (0.015)	80.3	55.26	6.63	55.13	6.45
10b	1.5430 (24)	114–117 (0.03)	82.4	63.14	8.71	62.97	8.48
14a	1.4756 (20.5)	85–86 (14.5)	91.2	55.15	10.99	53.61	10.89
14b	1.5573 (23)	76–80 (0.01)	85.8[d]	64.84 N: 12.60 P: 13.94	8.62	64.56 N: 12.43 P: 13.53	8.55
14c	1.5471 (27.5)	95–97 (0.09)	86.6	66.08	8.96	65.95	8.85
16a	1.4627 (27)	106–108 (37) mp *ca.* 24–26°	127.8	44.45	6.84	44.24	6.82
16b	1.4690 (26.5)	107–108 (26)	125.7	47.73	7.44	47.66	7.53
17		120 (0.01)	94.3[e]	66.65	8.17	66.53	8.26
18		98–101 (0.01)	103.6	65.44	7.78	65.08	8.13
19		Subl.	108.8	67.22	7.38	66.94	7.53

[a] Purified by glpc (6 ft × 1/8 in. 10% OV-1 on Chromosorb W). [b] Characterized as the *P*-dimethylphosphonium iodide, mp >250° dec. *Anal.* Calcd for $C_7H_{18}IN_2P$: C, 29.18; H, 6.30. Found: C, 29.03; H, 6.07. [c] In ppm from 85% phosphoric acid, external standard; ±0.3 ppm. Solvent was C_6H_6. [d] In cyclohexane, 85.8 (no solvent effect). [e] For the major stereoisomer. A minor isomer was also detected with $\delta^{31}P$ 100.3 ppm.

reaction of the very reactive 2-chloro compounds with methanol in the presence of a tertiary amine base at 0°. Pertinent data on the title compound are available in Table III. We had difficulty obtaining elemental analysis for some of the *P*-alkyl compounds because of their extreme sensitivity to oxygen. Complete ir, mass spectroscopy, and nmr data are available.[1]

3-Methyl-3-phospha-2,4-dioxaspiro[5.2]octane (16a) and -[5.3]-nonane (16b). These compounds were prepared by the addition of an ethereal solution of the appropriate diol (10 mmol) and an ethereal solution of methoxyphosphonous dichloride (10 mmol) simultaneously and dropwise to triethylamine (22 mmol) in dry ether at 0°. The work-up was identical with that for the phosphadiazacyclohexanes.

1,5-Diazacyclooctane. The dihydrobromide was prepared essentially as described,[42a] except that addition of 1,3-dibromopropane was carried out over twice the suggested time and refluxing was continued for 2 hr. The crude dihydrobromide (31% yield) afforded, after recrystallization,[42a] 14% of off-white needles, mp 255–256° dec (lit.[42b] 259–260° dec). Treatment of the salt with 25% (w/w) aqueous sodium hydroxide provided the free diamine (*ca.* 60%), bp 87–90° (25 mm), 76–78° (15 mm) (lit.[42a] 70–73° (15 mm)), $n^{24}D$ 1.4849.

***N*-Methyl-3-(aminomethyl)piperidine.** Hydrogenation of freshly distilled *n*-methyl-3-(aminomethyl)pyridine in glacial acetic acid (PtO_2) furnished the saturated diamine, bp 103–105° (29 mm), $n^{28}D$ 1.4759.

9-Phenyl-1,5-diaza-9-phosphabicyclo[3.3.1]nonane (18). A solution of 1,5-diazacyclooctane (3.42 g, 30 mmol) in 100 ml of anhydrous ether and a solution of phenylphosphonous dichloride (5.38 g, 30 mmol) in 100 ml of dry ether were added simultaneously dropwise over a period of 6 hr to a well stirred, ice-cold solution of triethylamine (60.6 g, 0.6 mol) in 600 ml of dry ether. The mixture was filtered and concentrated at reduced pressure. Distillation gave *ca.* 1.5 g of a colorless liquid, bp 98–101° (0.01 mm), which solidified.

The product was extremely sensitive to air and was rapidly converted to the oxide, 9-oxo-9-phenyl-9-phospha-1,5-diazabicyclo-[3.3.1]nonane. *Anal.* Calcd for $C_{12}H_{17}N_2OP$: C_1 61.01; H, 7.25; N, 11.86; P, 13.11. Found: C, 61.18; H, 7.44; N, 11.68; P, 13.06.

3,7-Diazabicyclo[3.3.1]nonane (Bispidine). Bispidine was obtained essentially as described by Stetter[43] except the required intermediate pyridine-3,5-dicarboxylic acid was prepared by a more convenient and efficient procedure.[44] The bispidine was isolated by sublimation as a waxy, hygroscopic, CO_2-sensitive solid in *ca.* 15–22% yield from 3,5-dicarbethoxy-2,6-lutidine.

2-Phenyl-1,3,2-diazaphosphaadamantane (19). To *n*-butyllithium (20 mmol, 20% hexane solution) under dry nitrogen at 0° was added dropwise bispidine (1.26 g, 10 mmol) in 20 ml of dry tetrahydrofuran (THF). The mixture was transferred quickly to an addition funnel (previously purged with dry nitrogen) and diluted with 20 ml of THF. The dilithio salt and phenylphosphonous dichloride (1.97 g, 11 mmol) in dry ether (*ca.* 25 ml) were added slowly dropwise to 150 ml of dry ether with stirring at a rate such that both additions were completed at about the same time. The mixture was stirred for 30 min and filtered through anhydrous $MgSO_4$. The filtate was concentrated *in vacuo* to afford a small quantity of colorless, semiwaxy, volatile solid, which sublimed at reduced pressure as needles. The compound melted rapidly on exposure to air.

2-Phenyl-3-methyl-1,3-diaza-2-phosphabicyclo[3.3.1]nonane (17). A solution of the dilithio salt of *N*-methyl-3-(aminomethyl)piperidine (1.28 g, 10 mmol) in dry THF and a solution of phenylphosphonous dichloride (1.88 g, 11 mmol) in dry ether were added slowly and synchronously dropwise to 150 ml of dry ether. Distillation provided a pale yellow liquid, bp *ca.* 120° (0.01 mm), which was a mixture of diastereomers (ratio *ca.* 3.5:1 from the ^{31}P nmr

(42) (a) E. L. Buhle, A. M. Moore, and F. Y. Wiselogle, *J. Amer. Chem. Soc.*, **65**, 29 (1943); (b) J. H. Billman and L. C. Dorman, *J. Org. Chem.*, 27, 2419 (1962).

(43) H. Stetter and M. Hennig, *Chem. Ber.*, **88**, 789 (1955); *Chem. Abstr.*, **50**, 7815 (1956); H. Stetter and R. Merten, *ibid.*, **90**, 868 (1957); *Chem. Abstr.*, **52**, 7312 (1958).

(44) B. E. Maryanoff and R. O. Hutchins, *Org. Prep. Proced. Int.*, **3**, 131 (1971).

spectrum; see Table III). Purification was accomplished by evaporative distillation or preparative glpc, but the two isomers could not be separated.

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Stereopopulation Control. I. Rate Enhancement in the Lactonizations of *o*-Hydroxyhydrocinnamic Acids[1,2]

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Abstract: The kinetics of lactonization of a series of *o*-hydroxyhydrocinnamic acids have been studied in the pH range 7–8 (30°, 20% dioxane–imidazole buffer) and in the pH range 6–7 without buffer. Concurrent, but not concerted, catalysis by both the acidic and basic forms of the buffer is observed. The introduction of appropriate alkyl substitution on both the aromatic ring and the side chain leads to rate-enhancement factors as high as 5×10^{10}; in comparison with the bimolecular esterification of phenol with acetic acid, the rate enhancement is greater than 10^{15} *M*. In the most favorable case studied, the half-time for formation of 4,4,5,7,8-pentamethylhydrocoumarin (pH 7) is 6 sec, with 90% of the total rate being due to buffer catalysis. The effect is attributed to a unique interlocking of methyl groups, which produces a severe conformational restriction of the side chain and a ground-state geometry highly favorable to formation of the transition state. Analysis of rate data suggests that the conformational effect operates, primarily, to increase the steady-state concentration of tetrahedral intermediate, but also causes the intermediate to be more sensitive to acid than to base catalysis in the rate-determining breakdown step. This phenomenon is presented as a model for the conformational restraint imposed by an enzyme on its substrate, and for the large acceleration effects resulting therefrom.

The rate constants for many enzyme-catalyzed reactions have been estimated to exceed those for their nonenzymatic, bimolecular counterparts by factors of 10^{10} to 10^{18}.[3] In some instances, such comparison is impossible because a close nonenzymatic parallel is undemonstrable, or is immeasurably slow, under reasonable conditions of pH, temperature, and solvent. The "magical" action of an enzyme on its substrate has been attributed,[3,4] principally, to the combined effects of (a) reduction in kinetic order (formation of an enzyme–substrate complex); (b) activation of the substrate by distortion of ground-state geometry or of electron-density distribution; (c) general acid–general base catalysis (possibly concerted) by protein functional groups; (d) favorable polarity of the active-site region; and (e) restriction of conformational freedom of the substrate. Rough estimates of the rate enhancement values of these factors, individually, have been based on the kinetic characteristics of many nonenzymatic model reactions; despite the use of liberal estimates, however, a sizable portion of the total rate enhancement achieved by the enzyme has yet to be justified.

Our immediate concern is with the rate-enhancement factor associated with the severe loss of conformational freedom of a substrate, resulting from its binding to an enzyme. The enzyme has available a variety of devices for binding a substrate tightly, while manipulating its conformation: attractive forces, such as covalent-bond, hydrogen-bond, and metal-chelate; forces which may be attractive or repulsive, such as electrostatic, van der Waals, dipole, and charge-transfer. The enzyme may be considered capable of "freezing" the substrate into a single conformation,[5] presumably that most favorable for achievement of the enzyme's mission. Although the rate-enhancement value of this factor has been estimated at 10^3 to 10^4, such magnitude is based on rather limited model data, and on systems in which the degree of conformational restriction fails to approach that possible in an enzyme–substrate complex.[6] Thus, a more detailed examination of the phenomenon of conformational restriction seems warranted.

Suitable intramolecular model systems require that

(1) A preliminary account of this work has been published: S. Milstien and L. A. Cohen, *Proc. Nat. Acad. Sci. U. S.*, 67, 1143 (1970).

(2) For prior studies related to this investigation, see (a) S. Milstien and L. A. Cohen, *J. Amer. Chem. Soc.*, 91, 4585 (1969); (b) *ibid.*, 92, 4377 (1970).

(3) D. E. Koshland, Jr., and K. E. Neet, *Annu. Rev. Biochem.*, 37, 359 (1968).

(4) (a) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, Chapter 1; (b) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, Chapter 1; (c) M. L. Bender, F. J. Kezdy, and C. R. Gunter, *J. Amer. Chem. Soc.*, 86, 3714 (1964); (d) T. C. Bruice in "The Enzymes," Vol. II, 3rd ed, P. D. Boyer, Ed., Academic Press, New York, N. Y., 1970, Chapter 4.

(5) At least that portion of the substrate in contact with the enzyme's active site.

(6) Theoretical arguments have been advanced for rate-enhancement factors as high as 10^8 due to the "freezing" process: M. I. Page and W. P. Jencks, *Proc. Nat. Acad. Sci. U. S.*, 68, 1678 (1971).