Conformational Analysis by Lanthanide Shift Reagents. Application of a Topological Approach to the Study of the Conformational Equilibria of 2-Substituted 5-*tert*-Butyl-2-oxo-1,3,2-dioxaphosphorinanes

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Abstract: A simplified topological approach to the computer simulation of lanthanide induced shifts (LIS) has been applied to the title compounds. Results consistent with the conclusion that the lanthanide complexes with the phosphoryl oxygen and occupies only certain sterically preferred positions are reported. For the cis isomers of the compounds studied, good agreement between calculated and observed LIS values were found. The lanthanide influences the equilibrium between conformational isomers of the cis compounds. The LIS calculations were found to predict the conformational equilibrium for complexed cis conformers with results in reasonable agreement with those based on the response of J_{HH} and J_{HP} to lanthanide addition. For the trans isomers, however, the LIS calculations suggest a conformational equilibrium which is in disagreement with conclusions based on coupling constants. The LIS result in those cases is shown to be of lower significance because of the relatively shallow response of the calculated agreement factors for the trans isomers to changes in conformational equilibrium constants. The effect of added lanthanide on conformational equilibrium may be the result of the greater basicity of an axial phosphoryl oxygen compared to its equatorial counterpart and/or the effect of coordination on the balance of vicinal interactions along the P—O bonds of the ring. Steric repulsions appear not to be important.

Recently we reported[2] a simple topological approach to the computer simulation of lanthanide-induced shifts (LIS). In contrast to the typical random search method, only chemically and physically accessible positions were considered for the lanthanide. With certain substrates bearing the carbonyl group, it was found to be satisfactory to assume that the lanthanide is complexed with the carbonyl oxygen and occupies only specific sterically preferred positions. Results in good agreement with those determined by the more complicated random search method[3] were obtained. Moreover, the results have thrown some light on the factors that may influence the change in equilibria of conformationally mobile systems on complexation with lanthanide shifts reagents[2] (LSR).

Our finding that the conformational equilibria of 2-substituted 5-*tert*-butyl-2-oxo-1,3,2-dioxaphosphorinanes can be influenced by addition of LSR[4] prompted us to further investigate this system, the purpose being to: (a) extend the topological approach to the phosphoryl group; (b) measure the ability of the simple topological approach to predict correctly conformer populations where equilibria are present; (c) further elucidate the factors that lead the lanthanide to alter the conformational equilibria of some of these derivatives.

A general understanding of the above points is of considerable importance. Thus, LIS data can be profitably and *directly* used in solving conformational problems in those cases in which it can be demonstrated that the interaction of LSR with a given substrate leaves unperturbed the conformational equilibrium. In cases in which the LSR *is* able to influence such equilibria, LIS data should give important conformational information once the nature of the perturbations induced by complexing agents are well understood. Applications of the latter approach to biological systems (in which phosphate phosphoryl abounds) appear especially attractive.

Our results are consistent with the assumption that the lanthanide complexes with the phosphoryl oxygen atom lone pairs in the sterically least hindered position. It appears that the perturbation of the conformational equilibria of such systems by LSR originates not from steric interactions but in electronic considerations related to phosphoryl oxygen basicity or, as we suggested earlier,[4a] in the balance of attractive and repulsive vicinal interactions about the P—O single bonds in the ring. This conclusion is in direct contrast to that drawn in the carbonyl compound study.[2]

Results and Discussion

The Topological Approach. It is well known from x-ray data[3e,5-7] that the site of complexation of the lanthanide is quite generally the electron lone pairs of the donor atom. Therefore, in our topological approach,[2] the simplifying assumption is made that the lanthanide occupies only chemically accessible sites (lone pairs); and further, that only physically significant positions (rotamers of probable minimum energies) need be considered. The contributions of various rotational forms are then averaged. Work along somewhat similar lines, also employing rotamer averaging, has been reported recently for LSR–sulfoxide interactions by Wing, Uebel, and Andersen.[6] Their work, however, did not include applications to systems in which more than one conformational isomer of substrate may undergo complexation.

With the phosphoryl group, complexation doubtless takes place on the phosphoryl oxygen, since shift effects are not noted with P=S compounds.[4] On steric grounds, three different sites of complexation of the lanthanide ion at the phosphoryl oxygen atom appear reasonable. These are depicted in Figure 1 as A, B, and C. In our calculations these three rotamers were assumed to be separated by 120 °C rotational angles (minimization of steric interactions). The Ln-O-P angle (ϕ) was taken to be 140°;[8] and the distance Ln-O was assumed to be 3.0 Å, the most widely accepted value.[3a-d,h,i,6,9,10] The small effect of changes in Ln-O distance on LIS has been demonstrated for carbonyl systems[9] and norborneol.[3c]

LIS Calculations. The first objective of our computational procedure was to determine the molar fractions of the three rotamers A, B, and C (Figure 1). Thus, a computer program was devised in which the LIS (molar-induced shifts) for each hydrogen could be calculated according to the following for-

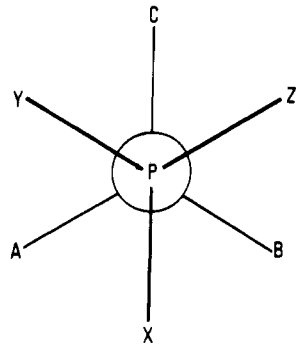


Figure 1. Schematic representation of the three possible sites of complexation of the lanthanide (A, B, C) with a phosphoryl group attached to three different ligands (X, Y, Z). The molecule is viewed along the P-O axis.

mula:

$$\Delta\nu_{i,obsd} = K(W_A G_A + W_B G_B + W_C G_C) \quad (1)$$

W_A, W_B, and W_C are the molar fractions and G_A, G_B, and G_C the geometrical factors corresponding to the forms with the lanthanide in positions A, B, and C, respectively. K is the pseudocontact constant of the McConnell and Robertson equation[11]

$$\Delta\nu_{i,obsd} = K(3\cos^2\chi - 1)r^{-3} \quad (2)$$

The term $(3\cos^2\chi - 1)r^{-3}$ of eq 2 represents the geometrical factor (G) which can be calculated for each proton once the O-Ld-H internuclear angle (χ) and the corresponding Ld-H distance (r) are known (see above). For the molecules here investigated, the 2-substituted 5-*tert*-butyl-2-oxo-1,3,2-dioxaphosphorinanes, Y and Z are ring oxygens. For H-3 and H-4, positions A and B of Figure 1 are enantiomeric, and therefore eq 1 becomes:

$$\Delta\nu_{i,obsd} = K(2W_A G_A + W_C G_C) \quad (3)$$

For eq 2 and 3, there are only two independent variables (K and $W_A = W_B$, or W_C), and $\Delta\nu_{i,obsd}$ is measured for four protons.

The usual procedure at this point is to carry out a least-squares minimization[2a,9] of the difference between observed and calculated LIS values using eq 1 and 3. The G terms calculated by eq 2 are known parameters, and the K, W_A, and W_C terms are varied to obtain the lowest calculated agreement factor (AF).[12] In this instance we were able to discard the term W_C. This was done on the basis of calculations for **3–7** using the Ln complex of only a single conformer, either **a** or **b** of Scheme I. (See Tables I and II for structures.) In every case, inclusion of rotamer C resulted in an increased AF. Variable W_C was thus also assumed to be zero in the calculations which follow in which the contributions of both forms **a** and **b** are considered and allows an important simplification of that procedure in terms of a reduced number of unknowns. (It is obvious that W_A and W_B, thus, become known parameters, 0.50, for these symmetrical molecules.) Site C is clearly a sterically demanding one for Ln attached to axial phosphoryl oxygen (**2a**). However, why rotamer C is unimportant with equatorial phosphoryl oxygen is not clear if only steric and not electronic factors are considered.

Scheme I

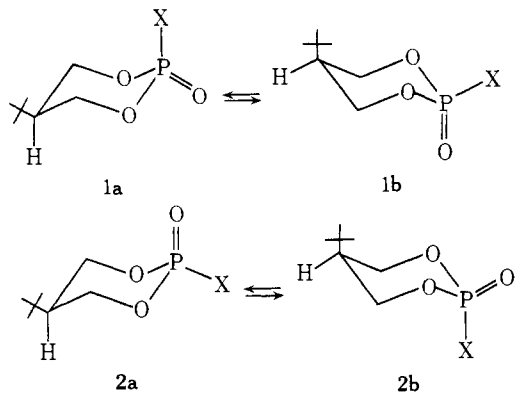
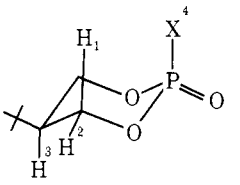


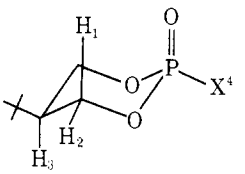
Table I. Chemical Shifts, Measured and Simulated LIS, and Preferred Conformation for Some 5-*tert*-Butyl-2-oxo-1,3,2-dioxaphosphorinanes of General Formula:



Compd	X	H-1[a]	H-2[a]	H-3[a]	H-4[a]	K	W_a[b]	AF
3	CH_3	4.13	4.50	2.17	1.63	936	54	0.005
		4.06	6.01	5.24	8.04			
		4.06	6.01	5.19	8.07			
4	Ph	4.12	4.60	2.37	7.88[c]	643	55	0.049
		3.12	4.23	3.36	5.45			
		2.88	4.22	3.68	5.38			

[a] Figures in the first row indicate chemical shifts (δ) of undoped spectra; figures in the second row indicate observed molar-induced shifts; figures in the third row indicate calculated molar-induced shifts, Molar induced shift = $\Delta\delta$ at [lanthanide]/[substrate] = 1.0. [b] Mole fraction of conformer with the P=O bond equatorial; see formula above and text. [c] Phenyl ring ortho protons.

Table II. Chemical Shifts, Measured and Simulated LIS, and Preferred Conformation for Some 5-*tert*-Butyl-2-oxo-1,3,2-dioxaphosphorinanes of General Formula:



Compd	X	H-1[a]	H-2[a]	H-3[a]	H-4[a]	K	W_a[b]	AF
5	CH_3	4.40	4.30	2.08	1.58	774	76	0.040
		6.72	3.05	4.36	6.68			
		6.86	3.23	3.99	6.67			
6	Ph	4.57	4.27	2.17	7.87[c]	825	71	0.059
		7.21	3.40	3.58	6.92			
		7.03	3.48	4.17	6.69			
7	*t*-Bu	4.43	4.20	1.97	1.20	691	64	0.046
		5.39	2.83	3.64	4.15			
		5.48	2.97	3.36				

[a] Figures in the first row indicate chemical shifts (δ) of undoped spectra; figures in the second row indicate observed molar-induced shifts; figures in the third row indicate calculated molar-induced shifts. [b] Mole fraction of conformer with the P–O bond axial; see formula above and text. [c] Phenyl ring ortho protons.

It must be emphasized at this point, that for derivatives **3–7** of Tables I and II, the LIS simulation process is complicated by the possibility that these compounds can populate both conformers **1a** and **1b** or **2a** and **2b**, which rapidly interconvert on the NMR time scale at ambient temperatures as shown above. If on the addition of LSR, both **a** and **b** conformers become complexed, then both complexes will contribute to the averaged observed LIS. Therefore, in order to apply correctly the LIS simulation process, the population ratio between the two complexed conformers also must be determined.

It should also be noted that the LIS simulation process can give information only on the *complexed substrates* irrespective of the situation present before the addition of LSR. Thus, three

different situations can arise when LSR is added to two substances which are in equilibrium[13] with each other.

(i) The LSR complexes with *only one* substrate conformer. In this case the results of the LIS simulation process will reveal the presence of only one conformer irrespective of the population ratio of the uncomplexed substrates.

(ii) *The LSR complexes* with *both* substrates with *exactly the same equilibrium constant.* This is often the most ideal case, because the LIS simulation process then gives the population ratio not only of the complexed substrates but also of the uncomplexed species.

(iii) The LSR is able to complex with *both* substrates but with *different equilibrium constants.* In this situation, the LIS simulation process will give a population ratio which reflects the ratio of the two complexed substrates but cannot be taken as indicative of the effective population ratio present in the uncomplexed species. This is in fact the case with **3** and **4** of the present study.

The finding that in these compounds the lanthanide ion complex populates only rotameric forms A and B was taken as the starting hypothesis in order to calculate (by use of eq 4) the conformer populations and K values for the derivatives represented in Tables I and II.[3a,9]

$$\begin{aligned}\Delta\nu_{i,obsd} &= K[W_a(W_A{}^aG_A{}^a + W_B{}^aG_B{}^a) \\ &\quad + W_b(W_A{}^bG_A{}^b + W_B{}^bG_B{}^b)] \\ &= 0.5K[W_a(G_A{}^a + G_B{}^a) + W_b(G_A{}^b + G_B{}^b)] \quad (4)\end{aligned}$$

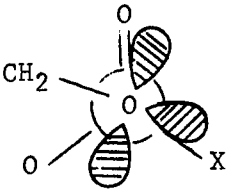
W_a and W_b are the weight or mole fractions of conformers **a** and **b.** $G_A{}^a$, $G_B{}^a$ and $G_A{}^b$, $G_B{}^b$ are the geometrical factors of conformers **a** and **b,** respectively, *with the lanthanide positioned in sites A and B of Figure 1.* As noted earlier, positions A and B are equivalent for protons 3 and 4 in which cases eq 4 simplifies to 5.

$$\Delta\nu_{i,obsd} = K[W_aG_A{}^a + W_bG_A{}^b] \quad (5)$$

The usual least-squares minimization procedure[2a,9] was applied using calculated G values and varying K and W_a (W_b) to get the best agreement between the four calculated and observed molar-induced chemical shifts. The conformer mole fractions, pseudocontact constants (scale factors), and agreement factors (AF) between the observed and calculated LIS for the compounds investigated are listed in Tables I and II. Good agreement between calculated and observed LIS for all the molecules studied is found. However, a full evaluation of the success of this approach requires that the conclusions regarding conformer populations (**1a** ⇌ **1b** and **2a** ⇌ **2b**) be compared with those derived independently from proton NMR studies.

Our earlier report[4a] (based on proton NMR coupling constants) concluded that before complexation phosphonates **3** and **4** populated conformer **1a** to the extent of about 78 and 84%, respectively. Following addition of Eu(fod)$_3$, the respective percentages dropped to 41 and 47. These are probably close to the asymptotic values which are obtained on total complexation. By comparison, the LIS simulation process, which deals only with the equilibrium between complexes, gives a value of 54% **1a** for compound **3** and 55% **1a** for **4.** We believe this to be a reasonable level of agreement, since the ^{1}H NMR method involves possible errors in assumed coupling constants for **1a** and **1b** and in the assumption that only chair-form conformers need be considered. The LIS method involves, amongst more obvious uncertainties, possible errors in assumed structural parameters. *Clearly, both methods show that addition of lanthanide and complex formation results in a shift in the conformational equilibrium towards* ***1b.*** Since complexation of the phosphoryl oxygen should have the effect of making that substituent somewhat larger and therefore shift the equilibrium towards **1a** not **1b,** *repulsive, 1,3-steric interactions are not dominant.* However, if the axial phosphoryl oxygen were for some reason more basic than its equatorial counterpart (considering only electronic contributions to basicity), then the greater stability of **1b** is to be expected. In fact, an early indication of the greater basicity of the axial phosphoryl oxygen can be found in studies of the phenol-induced shifts of ir frequencies for the P–O bond.[14]

We very recently proposed[15] that the unusual axial preferences displayed by substituents on phosphorus in the trivalent 2-X-5-*tert*-butyl-1,3,2-dioxaphosphorinane series can be explained in terms of a back-donation of ring oxygen p-orbital density into the σ antibonding level of the neighboring P–X bond. A similar p-orbital donation into the P=O bonding system could raise the basicity of the phosphoryl oxygen appreciably, and this effect should be greater when the phosphoryl group is axial (**8**) than when it is equatorial (**9**).



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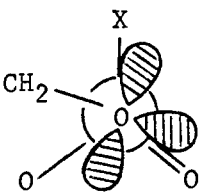

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(Donation from the lower energy sp^2 orbital will be less effective.) The above appears to be a most plausible present rationale for the greater axial phosphoryl basicity. By contrast with the *N*-alkyl-4-phenylpiperidines, equatorial complex formation with cobalt(II) acetylacetonate is favored.[16] Of course the potential for adjacent lone-pair interaction is absent in the piperidines.

The competition between a substituent X and phosphoryl oxygen for the axial or equatorial positions in 2-oxo-2-Z-1,3,2-dioxaphosphorinanes is determined by a balance of steric and electronic effects.[17] As X becomes larger, the equilibrium shifts toward forms with X equatorial. (Solvent polarity also affects the equilibrium in an important manner.)[18] Another possible explanation for the effect of complexation on **1a** ⇌ **1b,** therefore, is that complexation modifies the electronic nature of the P=O bond in such a way as to upset the balance of attractive and repulsive dipolar interactions about the P–O single bonds (vicinal interactions) of the ring. A combination of basicity and vicinal effects likely contribute to the relative stabilities of complexed **1a** and **1b.**

Differences in complexing ability between equilibrating species have been noted before.[2,16,19] However, in the work with secondary amides, which we reported earlier,[2] the alteration of conformational equilibrium by lanthanide arose from steric interactions.

For the trans compounds, **5–7,** the LIS simulation process (Table II) reveals a conformational bias toward **2a.** As shown in Table III, addition of Eu(dpm)$_3$ had almost no effect on the coupling constants J_{HH} and J_{HP} for **5–7** in direct contrast to what we reported previously[4a] for **3** and **4.** This result we take to mean that the equilibrium **2a** ⇌ **2b** is not significantly changed by complexation, because it is already biased nearly 100% in favor of **2a** (axial phosphoryl oxygen). The small changes noted with **6** on complexation bring its couplings to values almost identical with those of **5,** as though both had reached the fully biased (anancomeric) limit. (Small intrinsic effects on J values not associated with a change in conformer distribution may accompany complexation as well, and different solvents were sometimes used.) With **7** the presence of the extremely bulky *t*-Bu group at phosphorus should at least increase the proportion of **2a** compared with **4** and **6,** if not preclude the presence of **2b** altogether. Table III attests to the conclusion that **5–7** are all very much alike conformationally and populate **2a** nearly totally. *Thus, the values of W_a of Table*

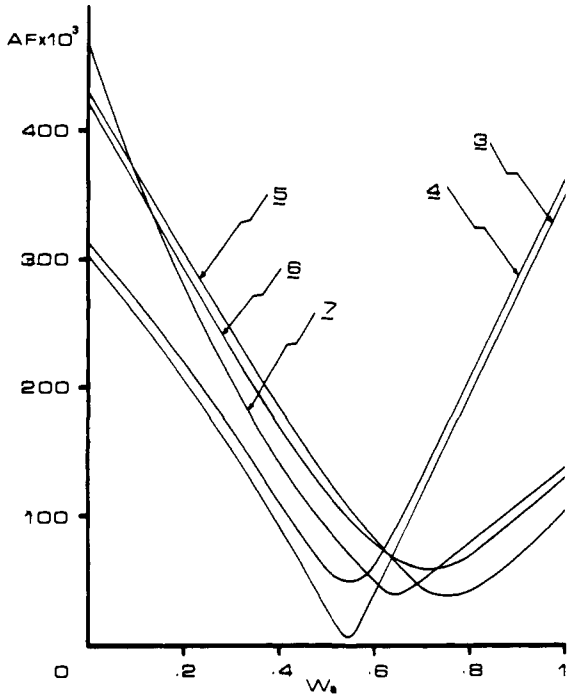
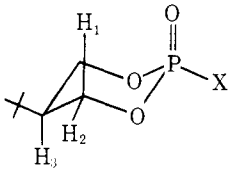


Figure 2. Plots of calculated *AF* for compounds **3–7** as a function of the molar fraction of conformer **a** (W_a).

Table III. Effect of Eu(dpm)$_3$ on Coupling Constants for 5–7



Compd	Solvent	L/S[d]	J_{12}	J_{13}	J_{23}	J_{1P}	J_{2P}
5[a]	$CDCl_3$	0.00	−11.1	10.5	4.5	4.1	20.2
	CCl_4[a]	0.50	−11.0	11.0	4.0	3.0	20.0
6[b]	$CDCl_3$	0.00	−10.5	10.5	4.5	4.5	18.0
	CCl_4	0.98	−11.0	11.0	4.0	2.0	20.0
7[c]	$CDCl_3$	0.00	−10.0	11.5	4.5	1.2	18.5
	$CDCl_3$	0.82	−10.7	11.0	4.3	2.0	18.8

[a] Eu(dpm)$_3$ added to 0.34 M solution of 5. [b] Eu(dpm)$_3$ added to 0.24 M solution of 6. [c] Eu(dpm)$_3$ added to 0.25 M solution of 7. [d] Mole ratio lanthanide/substrate.

II lead to erroneous conclusions regarding the equilibrium ***2a*** *⇌* ***2b*** *following complexation of* ***5–7.***

Because the significance of the W_a values for **5–7** was questioned, we calculated *AF* for all compounds (**3–7**) as a function of W_a to obtain the plots shown in Figure 2. For all derivatives, a minimum *AF* is found in the region of W_a 0.5–0.8, but only for **3** and **4** are sharp minima noted. *Therefore, less significance can be attached to the AF minima and W_a values for* ***5–7.*** This can be put on more quantitative terms by use of the *R*-factor ratio approach[12] (or in our terminology, the *AF*-factor ratio). For these systems, two variable parameters are fitted (*K* and W_a) with four observations, leaving two degrees of freedom. For **3** and **4,** the one-dimensional hypothesis that the true conformational picture of these complexes in solution can be represented as well by either **1a** or **1b** alone can be rejected[12a] for **4b** at the 2% confidence level and for **3a, 4a,** and **3b** at the 1% level or less. On the other hand, if we consider that ^{1}H NMR results perhaps cannot rule out a 10% contribution of **2b** for **5–7,** then the minima at 0.64–0.76 W_a for equilibrium may be compared with the hypothesis that their conformations in solution is equally well represented by a model in which the ratio **2a/2b** is 90/10. The latter hypothesis can only be rejected at the 8–25% confidence level. (The low end of the range is really very optimistic since only three chemical shift differences were minimized for **7.**) Such a rejection is much less significant than those stated above for **3** and **4.** Thus, one has a reasonably large (8–25%) chance of being wrong in rejecting the conformational model demanded by the ^{1}H NMR results in which **2a** is the primary conformer populated. In either qualitative or quantitative terms, we feel much more confident of our findings with **3** and **4** than with **5–7.** In those cases where shallow *AF* minima are found, it clearly is important to compare LIS results with independent findings, those from NMR measurements for example.

We conclude that the topological method of LIS simulation has validity in the 2-X-2-oxo-1,3,2-dioxaphosphorinane series even where conformational equilibria must be considered. However, it is clear that caution must be used, and the significance of AF minima carefully weighed. Presumably this caveat applies to other systems to which this method might be applied.

Experimental Section

Synthesis and characterization of compounds **3** and **5** were described elsewhere.[20] The phenylphosphonates **4** and **6** were synthesized from the 2-*tert*-butyl-1,3-propanediol and $PhP(O)Cl_2$ in the presence of Et_3N in routine fashion and separated by column chromatography on Florisil. Isomer **4** had mp 106–107 °C, while that of **6** was 89.0–89.5°. Microanalysis was by Schwarzkopf Microanalytical Laboratories, Woodside, N.J.

Anal. Calcd for $C_{13}H_{19}PO_3$: C, 61.41; H, 7.53; P, 12.18. Found: C, 61.34; H, 7.56; P, 11.98.

Anal. Calcd for $C_{13}H_{19}PO_3$: C, 61.41; H, 7.53; P, 12.18. Found: C, 61.23; H, 7.43; P, 12.23.

The *tert*-butylphosphonates were prepared and separated into isomers in similar fashion. However, because of the relative inertness of the *t*-$BuP(O)Cl_2$, the diol was first converted with sodium hydride to the dialkoxide before addition of *t*-$BuP(O)PCl_2$; for **7,** mp 165–166 °C. (All melting points are uncorrected.)

Anal. Calcd for $C_{11}H_{23}PO_3$: C, 56.40; H, 9.90; P, 13.22. Found: C, 56.45; H, 9.94; P, 13.05.

Lanthanide-induced shift measurements were performed with Eu(fod)$_3$ or Eu(dpm)$_3$. Spectra of about 5% $CDCl_3$ solutions (Me_4Si as internal reference) containing 0–0.3 mol of ligand (L) per mole of substrate (S) were obtained at 60 MHz (Varian A-60-D instrument). The lanthanide shift reagent was added stepwise from a stock solution with the help of a 50-μl. syringe. Each signal in the spectra was followed, and the LIS were found to be directly proportional to the (L)/(S) ratio present up to a value of ca. 0.4 mol/mol. A least-squares fit to the experimental points was used to obtain the observed molar LIS. Calculations relative to the simulation of the experimental LIS data were performed on a CDC-6600 digital computer.

Interatomic distances and bond angles were taken from pertinent x-ray data for **3**[21] and similar derivatives,[22] with simple coordinate transformations being applied by the computer to place the molecule properly in the dipolar field of the lanthanide shift reagent. For compounds bearing a methyl, this group was treated as a point methyl group (i.e., averaged positions).[2,6] For compounds **4** and **6** in which the phenyl group possesses a local C_{2v} axis coincident with its bond to the phosphorus atom, calculations of the coordinates of the ortho and meta protons were performed by positioning the Ld–O–P plane coplanar with the aryl ring and averaging the geometrical factors of the two ortho protons. Total neglect of phenyl ring protons gave nearly identical results for H-1 through H-3.

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References and Notes

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Aqueous Solution Conformation of Rigid Nucleosides and Nucleotides

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Abstract: The aqueous solution conformations of 18 different nucleoside derivatives in which various segments of the molecules were locked were investigated by NMR spectroscopy. In one set of the compounds the exocyclic linkage and the ribose were frozen; in another set the base and the ribose moieties were fused. Within these two broad categories conformations of the derivatives related to each other as enantiomers, α,β anomers and oxy and deoxy analogues were examined. Even though significant differences exist in the intimate details of their conformations, in general it was found that when the exocyclic linkage and the ribose were frozen the sugar ring exhibited ^3E conformation and the cyclic phosphate a chair form, the base showing accessibility of syn conformation. In those cases when the base and the ribose were fused, the sugar ring displayed ^2E pucker for the β derivatives and ^3E pucker for α derivatives with the magnitude of the sugar–base torsion angle being the same in both cases ($\chi \simeq 290°$). In addition, strong intramolecular perturbation between the phosphate backbone and the base was detected in the β cyclic series, while it was absent in the α cyclic series. As expected, the enantiomeric pairs displayed identical conformational features. In the case of 2′-deoxy-3′,5′-cyclic AMP, the possibility of the ribose ring existing as an unusual $^3E \rightleftarrows {}^0E$ equilibrium is discussed.

Introduction

Nuclear magnetic resonance spectroscopy has been used as a powerful tool (comparable to the use of x-ray crystallography in solid state) to obtain direct molecular parameters in solution. When the flexible molecules are studied in solution, their conformations are interpreted as states of dynamic equilibrium between the energy minimal conformers. For instance, in the conformational studies of nucleosides and nucleotides in recent years,[1-17] the glycosidic conformation has been described as syn $\rightleftarrows$ anti, the ribofuranose ring as $^2E \rightleftarrows {}^3E$, the C(4′)–C(5′) bond as gg $\rightleftarrows$ g/t, and the C(5′)–O(5′) bond as g′g′ $\rightleftarrows$ g′/t′ equilibrium with preference for one or the other conformer. In this paper, NMR studies are presented of several rigid nucleosides and nucleotides in which either the exocyclic linkage and the ribofuranose ring are fixed (e.g., 3′,5′-cyclic nucleotides I and II) or the base moiety and the sugar ring are fused (e.g., β-D- (or L-) 2′,O^2-cyclic arabinonucleosides (III) and α-D-2′,O^2-cyclic nucleosides (IV)). Several novel compounds, α-nucleosides and nucleotides, were also studied. As usual, the conformations about the flexible regions of the molecules were expressed in terms of dynamic equilibrium between the minimum energy conformers. The conformations of the inflexible portions (except for the base) of the molecules were described in terms of dihedral angles computed from the appropriate Karplus equations. The pure ^2E and ^3E conformations observed in the present case were compared with the models postulated in pseudorotational pathway.[18,19] Comparative studies of the interactions between the base and the exocyclic backbone were also undertaken. A comparison of the data of oxy and deoxy 3′,5′-cyclic nucleotides was made to obtain information about the anisotropic effect of hydroxyl groups. Among the 18 different nucleoside deriv-