ion intermediate thus formed (eq 1 and 2).

$$\underset{\mathbf{1}}{C_6H_5CH{=}C(SCH_3)_2} + H_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\mathbf{2}}{C_6H_5CH_2\overset{+}{C}(SCH_3)_2} + H_2O \quad (1)$$

$$\mathbf{2} + 2H_2O \xrightarrow{k_2} \underset{\mathbf{3}}{C_6H_5CH_2COSCH_3} + CH_3SH + H_3O^+ \quad (2)$$

Figure 1 shows $^1H$ NMR spectral changes during the reaction of **1** in 90% $CD_3CN/D_2O$ containing about 2 mM DCl at 35 °C.[10] Spectrum A was recorded before the addition of enough acid, the olefinic hydrogen resonance of **1** appearing at 6.69 ppm in the integral intensity of 1 H. In 100 min (spectrum B), the signal at 6.69 ppm disappeared almost completely, while the $CH_3S$ signals at 2.32 and 2.39 ppm remained in about 80% of the original intensity. The signals for the products (arrows) showed up correspondingly in intensity equivalent to ca. 20% conversion. Spectrum C (20 h) shows the formation of methyl phenylthioacetate (**3**) ($CH_3S$ resonance at 2.23 ppm) and methyl orthophenylthioacetate (**4**) ($CH_3S$ resonance at 2.08 ppm) in the ratio of 5:1. The methylene resonances of these products cannot be perceived; the one for **3** is only barely discernible at 3.84 ppm (arrow). The $CH_3S$ resonances of **1** are still observable (eq 3).

$$\mathbf{1} \overset{D_3O^+}{\rightleftharpoons} \underset{\mathbf{2'}}{D{-}\overset{H}{\overset{|}{C}}(C_6H_5){-}{}^+C(SCH_3)_2} \rightleftharpoons \underset{\mathbf{1}\text{-}d_1}{C_6H_5CD{=}C(SCH_3)_2} \longrightarrow \underset{\mathbf{3'}}{C_6H_5CD_2COSCH_3} \quad (3)$$

These observations evidently indicate that the carbon protonation (eq 1) is reversible and that the decay of the intermediate **2** (eq 2) is rate determining ($k_{-1} > k_2$). The rate of the H–D exchange estimated from the disappearance of the olefinic hydrogen was about 10 times greater than that of the hydrolysis. The product **4** must have arisen from the nucleophilic trapping of **2** by $CH_3SH$ liberated on the formation of **3** (eq 4).

$$\mathbf{2} + CH_3SH \rightarrow \underset{\mathbf{4}}{C_6H_5CH_2C(SCH_3)_3} + H_2O \quad (4)$$

Kinetic measurements for the hydrolysis were made spectrophotometrically at 295 nm with a Shimadzu UV 200 spectrophotometer. The reactions were carried out at 30 °C in aqueous acetonitrile (10 vol %), the ionic strength being maintained at 0.45 with added KCl. The reaction was found to be catalyzed by general acids ($ClCH_2CO_2H$, $HCO_2H$) as well as $H_3O^+$ ($k_{H_3O^+} = 0.126\ M^{-1}\ s^{-1}$). The hydration of **2** (eq 2) must be catalyzed by a general base.

The reaction was greatly accelerated by the addition of a thiol, 2-hydroxyethanethiol. In 0.05 M aqueous HCl containing a constant 10 vol % of organic components ($CH_3CN$ + $HOCH_2CH_2SH$), the rate was linearly increased with thiol concentrations, $k_{obsd}$ ($s^{-1}$) = $4.68 \times 10^{-3} + 3.84 \times 10^{-3}$ · [$HOCH_2CH_2SH$]. The control experiments with *p*-methoxyphenyl vinyl ether, which is hydrolyzed through the rate-determining protonation,[11] showed that the rate of its hydrolysis was not affected by the addition of up to 0.5 M thiol. The acceleration observed further substantiates that the nucleophilic trapping of the intermediate **2** is rate determining. The relative nucleophilicity ($HOCH_2CH_2SH/H_2O$) of about 40 deduced here is reasonable as compared with that estimated from the reaction with a stable carbonium ion.[12]

Pseudo-first-order plots for the reaction of **1** in 10% $CH_3CN/D_2O$ (0.05 M DCl) curved markedly from an initial slope (within 1 min) of $2.26 \times 10^{-3}\ s^{-1}$ to an ultimate slope of $3.15 \times 10^{-3}\ s^{-1}$. This is undoubtedly due to the initial H–D exchange at the 2 position of **1** and to the greater hydrolysis rate of the deuterated substrate **1**-$d_1$ as compared to the undeuterated **1**. In fact, the reaction of the isolated 2-deuterio substrate **1**-$d_1$[13] under the same conditions gave excellent linear plots with a slope ($3.16 \times 10^{-3}\ s^{-1}$) close to the approximate ultimate slope. The hydrolysis of **1**-$d_1$ in 10% $CH_3CN/H_2O$ (0.05 M HCl) was slightly decelerated at a later stage of reaction. The linear plots obtained within a first half-life gave $k_{obsd} = 6.46 \times 10^{-3}\ s^{-1}$, which is 1.38 times greater than that for **1** obtained in 10% $CH_3CN/H_2O$ and 2.04 times that for **1**-$d_1$ in 10% $CH_3CN/D_2O$.

That is, the rate constants obtained above give the secondary isotope effect $k_D/k_H = 1.38$ and the solvent isotope effect $k_{H_2O}/k_{D_2O} = 2.04$. The former is close to the typical value estimated for the hybridization change ($sp^2$ to $sp^3$) of the carbon carrying the isotope.[14] Thus, it is compatible with the mechanism involving equilibrium formation of the intermediate **2**. The normal solvent isotope effects observed agree with the apparent general acid catalysis. The rate-determining step must involve proton transfer from a nucleophilic water molecule to a general base.

All the evidence presented above points to the mechanism involving the preequilibrium carbon protonation (eq 1 and 2). Further studies on the details of the kinetics are in progress.

**Acknowledgment.** We thank H. Okuda for recording NMR spectra and A. Oshio for technical assistance.

(10) The reaction was carried out in an NMR sample tube on a JNM-MH-100 spectrometer.

(11) Fueno, T.; Matsumura, I.; Okuyama, T.; Furukawa, J. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 818–823.

(12) Ritchie, C. D. *J. Am. Chem. Soc.* **1975**, *97*, 1170–1179. Ritchie, C. D.; Gandler, J. *Ibid.* **1979**, *101*, 7318–7323.

(13) Obtained by the reaction of **1** in acidic $CH_3CN/D_2O$ solution, isotopic purity being ca. 94% by NMR spectroscopy.

(14) Streitwieser, A., Jr.; Jagow, R. H.; Fahey, R. C.; Suzuki, S. *J. Am. Chem. Soc.* **1958**, *80*, 2326–2332. Ritchie, C. D. "Physical Organic Chemistry"; Marcel Dekker: New York, 1975; pp 223–224.

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## Structure Elucidation with Lanthanide-Induced Shifts. 8. Geometry of Europium–Ketone Complexes[1]

*Sir:*

Since the initial discovery that tris(β-diketonate) complexes of europium(III) can cause substantial chemical shift changes in the NMR spectra of organic compounds,[2] considerable effort has been expended in attempts to understand and utilize these lanthanide-induced shifts (LIS).[3] We have previously demonstrated that lanthanide-induced shifts can be used for rigorous structure evaluation of nitriles.[1,4,5] For that class of compounds, interpretation of experimental data is greatly simplified by the expectation that the resulting lanthanide complex will have a nearly linear carbon–nitrogen–lanthanide array.[4-7] We next turned our attention to functional groups for which this simplifying assumption could not be made. In the case of the carbonyl group, the LIS were expected to result from the time-average shifts of two discrete complexes corresponding to coordination at each of the lone pairs of electrons on oxygen (i.e., C–O–Eu bond angle

(1) Part 7: D. J. Raber, C. M. Janks, M. D. Johnston, Jr., and N. K. Raber, *Org. Magn. Reson.*, in press.

(2) (a) C. C. Hinckley, *J. Am. Chem. Soc.*, **91**, 5160 (1969); (b) J. K. M. Sanders and D. H. Williams, *J. Chem. Soc. D*, 422 (1970).

(3) For reviews, see: (a) O. Hofer, *Top. Stereochem.*, **9**, 111–197 (1976); (b) M. R. Willcott, III and R. E. Davis, *Science (Washington, D.C.)*, **190**, 850 (1975); (c) A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackham, *Chem. Rev.*, **73**, 553 (1973); (d) B. C. Mayo, *Chem. Soc. Rev.*, **2**, 49 (1973); (e) J. Reuben, *Prog. Nucl. Magn. Reson. Spectrosc.*, **9**, 1 (1973).

(4) M. D. Johnston, Jr., D. J. Raber, N. K. DeGennaro, A. D'Angelo, and J. W. Perry, *J. Am. Chem. Soc.*, **98**, 6042 (1976).

(5) (a) D. J. Raber, M. D. Johnston, Jr., J. W. Perry, and G. F. Jackson, III, *J. Org. Chem.*, **43**, 229 (1978); (b) D. J. Raber, M. D. Johnston, Jr., and M. A. Schwalke, *J. Am. Chem. Soc.*, **99**, 7671 (1977).

(6) R. E. Davis, M. R. Willcott, III, R. E. Lenkinski, W. v. E. Doering, and L. Birladeanu, *J. Am. Chem. Soc.*, **95**, 6846 (1973).

(7) The linearity of coordination is in fact only approximate. For a detailed discussion, see ref 1.

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Table I. Experimental Bound Shifts of Adamantanones

| H type | bound shifts 1 | 2 | 3 |
|---|---|---|---|
| a | 15.67 ± 0.22 | 16.16 | 16.10 |
| a' | | | 17.99 |
| b | 8.12 ± 0.10 | 8.36 | 8.38 |
| b' | | 9.65 | 9.31 |
| b'' | | | 8.43 |
| c | 5.18 ± 0.06 | 5.09 | 4.95 |
| c' | | 5.87 | 4.83 |
| c'' | | | 5.02 |
| d | 4.39 ± 0.06 | 4.72 | 4.52 |
| d' | | | 4.52 |
| e | 3.67 ± 0.05 | 4.01 | 3.98 |
| e' | | 4.01 | 4.62 |
| $CH_3$ | | 11.28 | 7.54 |
| $CH_3'$ | | | 3.89 |

$\simeq$ 120°). In this paper, we report the successful extension of our methodology to the rigorous structure evaluation of ketones by using Eu(fod)$_3$.[8] Moreover, we present evidence showing that *only a single complex is formed, which in the absence of structural perturbations has a carbon–oxygen–europium bond angle of 180°.*

In those cases for which contact shifts are negligible,[9] the LIS are generally considered[3] to be given by the dipolar form of the pseudocontact equation[3,10] (eq 1). The LIS is the change in

$$\mathrm{LIS} = \frac{k(3\cos^2\theta - 1)}{r^3} \qquad (1)$$

chemical shift caused by complexation with the lanthanide shift reagent, and $k$ is a constant which describes the magnitude of the induced magnetic dipole of the lanthanide ion. Under the commonly used assumption of axial symmetry,[11a] the other parameters in eq 1 describe the structure of the lanthanide–substrate complex. Thus, $r$ is the length of a line segment connecting the lanthanide nucleus and the proton under consideration, and $\theta$ is the angle between this line and the bond between the lanthanide ion and the donor atom of the substrate.

The interaction between shift reagent and substrate involves rapid equilibria, and any attempt to correlate observed shifts with eq 1 requires the circumvention of several formidable barriers: (1) The observed chemical shifts are a weighted time average of those from both free and complexed substrate, and complexes of 2:1 as well as 1:1 stoichiometry are typically formed.[12-14] (2) The structural details for the appropriate complex are unknown, yet atomic coordinates are needed for the europium and all relevant hydrogen atoms.

The first problem can be solved by using the bound shifts obtained by nonlinear regression analysis of the dependence of the induced shifts on europium concentration.[12] In addition, we have restricted our work to the 1:1 complex since this must approach more closely the required threefold symmetry (especially on a time-average basis).[11a] The second problem is more difficult. Although reliable geometric parameters for the substrate moiety

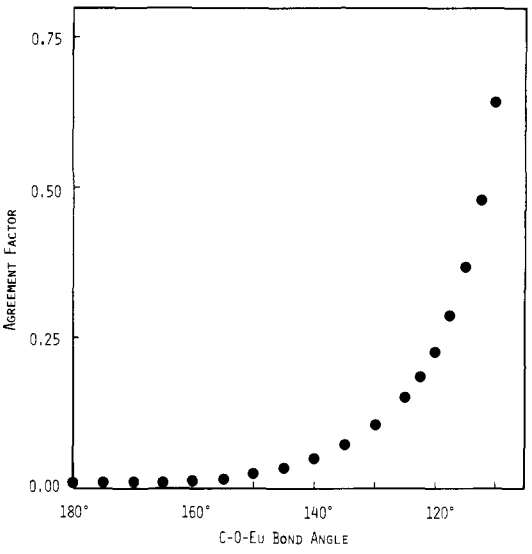
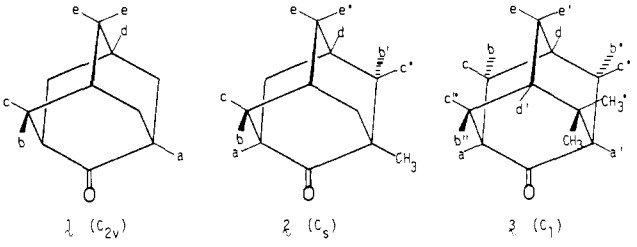
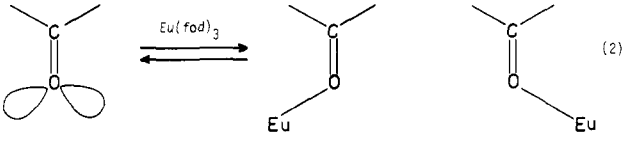



**Figure 1.** Plot of statistical agreement between calculated and experimental LIS for the two-site model as a function of the carbon–oxygen–europium bond angle for adamantanone (**1**).

can be obtained from molecular mechanics calculations,[15] the structural parameters (bond lengths and angles) involving europium remain unknown. We have rejected[1,4] the commonly used approach[3] of simply using that geometry which affords the best fit between calculation and experiment since that method yields results which lack consistency (and are sometimes chemically unreasonable). Instead, we have utilized the chemically reasonable idea that these structural parameters will be essentially constant for a particular functional group. As in the case of our earlier work with nitriles,[1,4] we took advantage of the symmetry and structural rigidity of the adamantane skeleton and initiated our studies with adamantanone (**1**) and the two methyl-substituted derivatives **2** and **3**.




The bound shifts of **1**–**3** are reported in Table I. We proceeded to calculate the LIS with eq 1 according to the bonding arrangement depicted by eq 2 in which the europium coordinates in the plane of the carbonyl group to yield two discrete complexes.




Since $k$ should to a first approximation be a property only of the shift reagent,[11b] we used the value of $k$ = 976.6 which had previously been determined in our study of nitriles.[1] As in the previous study,[1] the statistical comparison of experimental and calculated LIS proved inadequate for evaluating the europium–oxygen bond length. For example, calculations with adamantanone (**1**) afforded agreement factors[16] which were essentially unchanged

(8) Tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octadionato)europium is commercially available (Aldrich, No. 16,0938).

(9) In our experience,[1,4,5] contact contributions to the LIS are negligible for all hydrogens separated from the binding site by two or more saturated carbon atoms. Those protons which are nearer to the binding site (e.g., the type a hydrogens of the adamantanone derivative in this paper) suffer substantial contact contributions and have been excluded from our calculations.

(10) H. M. McConnell and R. E. Robertson, *J. Chem. Phys.*, **29**, 1361 (1958).

(11) (a) For a complete discussion, see ref 1. (b) No major changes are expected in the magnetic properties of the europium ion as a result of variations in a neutral monodentate ligand. Indeed, if treated as an adjustable parameter, the same value of $k$ ($\simeq 10^3$) is found for ketones and nitriles.

(12) (a) B. L. Shapiro and M. D. Johnston, Jr., *J. Am. Chem. Soc.*, **94**, 8185 (1972); (b) M. D. Johnston, Jr., B. L. Shapiro, M. J. Shapiro, T. W. Proulx, A. D. Godwin, and H. L. Pearce, *ibid.*, **97**, 542 (1975).

(13) (a) J. Reuben, *J. Am. Chem. Soc.*, **95**, 3534 (1973); (b) J. W. ApSimon, H. Beierbeck, and A. Fruchier, *ibid.*, **95**, 939 (1973).

(14) D. J. Raber, M. D. Johnston, Jr., C. M. Campbell, C. M. Janks, and P. Sutton, *Org. Magn. Reson.*, **11**, 323 (1978).

(15) (a) N. L. Allinger, *Adv. Phys. Org. Chem.*, **13**, 1–82 (1976); (b) N. L. Allinger, *QCPE*, **11**, 318 (1976).

(16) The agreement factor is defined by the following equation, which was first introduced to shift reagent work by R. E. Davis and M. R. Willcott, III, *J. Am. Chem. Soc.*, **94**, 1744 (1972).

$$\mathrm{AF} = \frac{\sum(\mathrm{LIS_{obsd}} - \mathrm{LIS_{calcd}})^2}{\sum(\mathrm{LIS_{obsd}})^2}$$

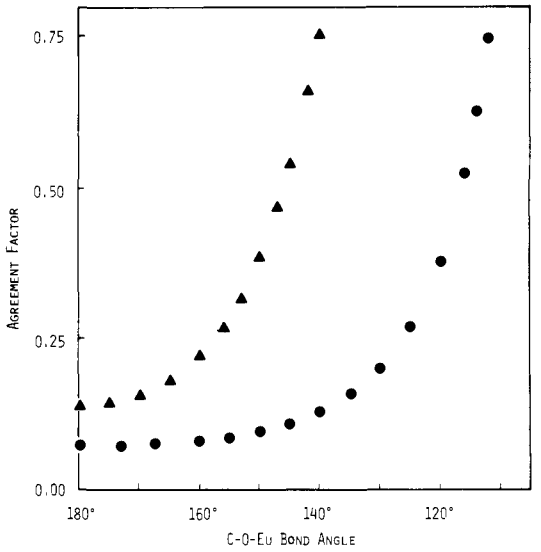



**Figure 2.** Plot of statistical agreement between calculated and experimental LIS for the two-site model as a function of the carbon–oxygen–europium bond angle [**2** (▲); **3** (●)].

Table II. Structural Data for the One-Site Model of Eq 3[a]

| compd | linear structure agreement factor | optimum structure agreement factor | optimum structure Eu–O–C angle,[b] deg |
|---|---|---|---|
| 1 | 0.01 | 0.01 | 180 |
| 2 | 0.14 | 0.03 | 163 |
| 3 | 0.07 | 0.03 | 170 |

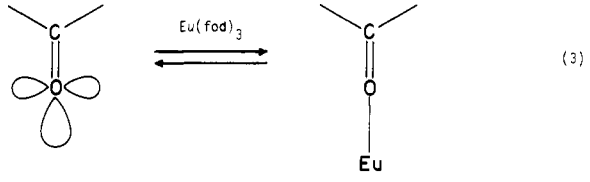
[a] Footnote 22a. [b] The nonlinear distortion is in the direction away from the methyl substituents.

over a range of bond lengths from 2.3 to 3.3 Å. Consequently, we again turned to the crystallographic literature on tris(β-diketonate)–lanthanide(III) complexes[17] which permitted the conclusion that 2.50 Å represents the most appropriate value for the europium–oxygen bond length with ketones.[11,18,19]

According to the "two-site model"[20] depicted in eq 2, the best agreement between experiment and calculation (i.e., a minimum agreement factor) should be for a carbon–oxygen–europium bond angle in the vicinity of 120°. However, Figure 1, which summarizes the results for adamantanone, clearly shows the absence of any minimum in this region. The results for the methyl-substituted adamantanones **2** and **3** (Figure 2) similarly show no minimum anywhere near 120°.[21] These results suggest that the two-site model is incorrect and led us to the hypothesis that *coordination of lanthanide shift reagents to the carbonyl group of a ketone involves only a single coordination site with a carbon–oxygen–europium geometry which is approximately linear*!

The lower symmetry of **2** and **3** precludes complexes which are *exactly* linear, and this is reflected in the relatively large agreement factors found for a carbon–oxygen–europium angle of 180° (Figure 2). However, optimization of the structure of the complex by permitting distortion[22] from linearity results in a dramatic decrease in the agreement factor as shown in Table II. The optimized structures all have agreement factors of 0.03 or smaller (a value which we have found to provide a convenient upper limit for acceptability of a structure[1]), and the distortions from linearity are relatively small (≤20°). Even when additional variable parameters are introduced into the two-site model, it is not possible to achieve agreement between prediction and experiment which is superior to that found for a *single* optimum coordination geometry.[21]

The preferred (approximate) linear geometry may seem surprising in view of the conventional representation of the lone pairs of electrons on oxygen (eq 2). However, the σ bond between carbon and oxygen requires a hybrid of only the 2s and a single 2p orbital on oxygen, and a second p orbital is needed for the corresponding π bond.[23] This leaves an sp hybrid for interaction with europium via a *linear* σ bond (eq 3).[24] In addition, the empty




(3)

5d orbitals on europium have the appropriate symmetry and size[25] for interacting with the remaining p orbital on oxygen in a π fashion. The presence of two *nonequivalent* lone pairs of electrons—even on completely symmetrical carbonyl groups—is fully borne out by *both* theory[26] and experiment.[27]

(17) (a) J. A. Cunningham and R. E. Sievers, *J. Am. Chem. Soc.*, **97**, 1586 (1975); (b) C. S. Erasmus and J. C. A. Boeyens, *Acta Crystallogr., Sect. B*, **B26**, 1843 (1970); (c) J. P. R. de Villiers and J. C. A. Boeyens, *ibid.*, **B27**, 692 (1971); (d) E. D. Watkins, II, J. A. Cunningham, T. Phillips, II, D. E. Sands, and W. F. Wagner, *Inorg. Chem.*, **8**, 29 (1969); (e) T. Phillips, II, D. E. Sands, and W. F. Wagner, *ibid.*, **7**, 2295 (1968); (f) J. A. Cunningham, D. E. Sands, W. F. Wagner, and M. F. Richardson, *ibid.*, **8**, 22 (1969); (g) F. A. Cotton and P. Legzdins, *ibid.*, **7**, 1777 (1968); (h) A. Zalkin, D. H. Templeton, and D. G. Karraker, *ibid.*, **8**, 2680 (1969).

(18) For a variety of different complexes reported in ref 17, the bond length of a ligand which is coordinated to the lanthanide via a *neutral* oxygen is longer than the corresponding bond to one of the β-diketonate oxygens by ca. 0.1 Å.

(19) (a) While this value may not be the precise bond length, we have already demonstrated that a good agreement between observed and calculated LIS values can be obtained by using bond lengths which vary over a range of at least 1 Å. Consequently, any error introduced by the use of 2.50 Å should be small and should be removed in the final structural refinement by scaling of the experimental shifts.[11] The scaling factor is small for **1**–**3** (1.0 ± 0.1). (b) Clearly, the use of a single bond length for all ketone complexes is an approximation. However, it appears to be a good approximation on the basis of the available X-ray data.[17,18] In any case, it seems fully justified by the accuracy and consistency of our results.

(20) (a) R. J. Abraham, D. J. Chadwick, and F. Sancassan, *Tetrahedron Lett.*, 265 (1979); (b) B. H. S. Liĕnard and A. J. Thomson, *J. Chem. Soc., Perkin Trans. 2*, 1390 (1977); (c) R. E. Lenkinski and J. Reuben, *J. Am. Chem. Soc.*, **98**, 4065 (1976); (d) P. Finocchiaro, A. Recca, P. Maravigna, and G. Montaudo, *Tetrahedron*, **30**, 4159 (1974); (e) R. H. Newman, *ibid.*, **30**, 969 (1974). (f) For the advocacy of a four-site model, see: R. J. Abraham, D. J. Chadwick, L. Griffiths, and F. Sancassan, *Tetrahedron Lett.*, 4691 (1979).

(21) (a) As a consequence of the lower symmetry of **2** and **3**, the use of equal weights and equal bond angles for the two complexes in eq 2 is an approximation. Unfortunately, the use of any additional variable parameters in the calculations would invalidate the statistical comparisons. (b) We have nevertheless carried out an extensive evaluation of the data for **2** by using the two-site model but allowing the two complexes to have different C–O–Eu bond angles (although maintaining $C_s$ symmetry) and unequal populations. Despite the introduction of *three additional variable parameters*, it was not possible to achieve an agreement factor lower than the optimum value found with the one-site model. (c) At the specific suggestion of a referee, we have also evaluated the two-site model with a C–O–Eu angle of 120° for different O–Eu distances. Over the range of 2.0–3.5 Å, the agreement factor decreases uniformly with increasing O–Eu distance for each compound. However, even with the inclusion of unequal populations, none of the agreement factors is ever below 0.12.

(22) The O–Eu bond length was maintained at 2.50 Å, and the C–O–Eu angle was varied freely. The symmetry (if any) of the complex was restricted to that of the corresponding ketone.

(23) Cf.: W. L. Jorgensen and L. Salem, "The Organic Chemist's Book of Orbitals", Academic Press, New York, 1973. See particularly pp 42–43.

(24) The "one-site model" has been used on occasion, but this has typically been only a computational simplification rather than a structural proposal. Cf.: O. Hofer, *Monatsh. Chem.*, **110**, 745 (1979); P. Földesi and O. Hofer, *Tetrahedron Lett.*, 2137 (1980).

(25) (a) T. Moeller, *MTP Int. Rev. Sci.: Inorg. Chem., Ser. One*, **7**, 275–298 (1971); (b) T. J. Marks, *Prog. Inorg. Chem.*, **24**, 51–107 (1978).

(26) Reference 23. The drawings on pp 84, 141–142, 147–148, and 213–215 illustrate the nonequivalent nonbonding orbitals for formaldehyde, acetaldehyde, formyl fluoride, and acetone, respectively.

(27) (a) H. Ogata, J. Kitayama, M. Koto, S. Kojima, Y. Nihei, and H. Kamada, *Bull. Chem. Soc. Jpn.*, **47**, 958 (1974); (b) D. Chadwick and A. Katrib, *J. Electron Spectrosc. Relat. Phenom.*, **3**, 39 (1974); (c) D. Chadwick, *Can. J. Chem.*, **50**, 737 (1972); (d) L. S. Cederbaum, W. Domcke, and W. v. Niessen, *Chem. Phys. Lett.*, **34**, 60 (1975); (e) R. Hernandez, P. Masclet, and G. Mouvier, *J. Electron Spectrosc. Relat. Phenom.*, **10**, 333 (1977); (f) W.-C. Tam, D. Yee, and C. E. Brion, *ibid.*, **4**, 77 (1974); (g) C. R. Brundle and D. W. Turner, *Chem. Commun.*, 314 (1967).

Little experimental data are available regarding the coordination geometry of Lewis acids to organic carbonyl groups. While the available evidence for coordination with $H^+$ indicates a geometry corresponding to eq 2 (H-O-C = 115°),[28] calculations indicate that $Li^+$ prefers a linear geometry (eq 3).[29] We have carried out extensive calculations at the STO-3G and STO-3/21G levels for the interaction of formaldehyde with various first and second row Lewis acids, and the results indicate that a *linear geometry is preferred* when the cation can act as both a $\sigma$ and $\pi$ acceptor.[30]

The origin of the nonlinear distortion has not yet been adequately determined. Molecular orbital calculations at the INDO[31,32] level fail to detect any distortion of the "lone-pair" orbitals of **2** and **3**. However, the direction of nonlinear deviation found for a variety of bridged and cyclic ketones in addition to **2** and **3** suggests a steric effect. Although steric repulsion between the shift reagent and substituents on the substrate moiety appears to be unimportant for nitriles,[1,5] the C-O-Eu distance for ketones (ca. 3.7 Å) is shorter than the C-C-N-Eu distance (ca. 5.1 Å) for nitriles by approximately 1.4 Å. In any case, the concept of steric interactions provides a useful device for interpreting and predicting distortions from an otherwise linear arrangement.

**Acknowledgment.** This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society, by grants from the Research Corporation, and by a Fellowship (to D.J.R., 1978-1979) from the Alexander von Humboldt Foundation. Much of the computational work was carried out at the Universität Erlangen-Nürnberg; D.J.R. and N.K.R. express their appreciation to Professor Paul v. R. Schleyer and the Rechenzentrum der Universität Erlangen-Nürnberg for providing working facilities and generous amounts of computing time.

(28) (a) A. M. White and G. A. Olah, *J. Am. Chem. Soc.*, **91**, 2943 (1969); (b) W. A. Lathan, L. A. Curtiss, W. J. Hehre, J. B. Lisle, and J. A. Pople, *Prog. Phys. Org. Chem.*, **11**, 175 (1974).

(29) (a) T.-K. Ha, U. P. Wild, R. O. Kühne, C. Loesch, T. Schaffhauser, J. Stachel, and A. Wokaun, *Helv. Chim. Acta*, **61**, 1193 (1978); (b) J. E. Del Bene, *Chem. Phys.*, **40**, 329 (1979).

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(32) For example, the orbital coefficients at oxygen of the highest occupied molecular orbital of **2** are -0.002 (2s), 0.580 ($2p_x$), 0.000 ($2p_y$), and 0.000 ($2p_z$) where the C-O bond defines the $z$ axis and the carbon atom of the methyl group lies in the $xz$ plane. Clearly, this "lone-pair" orbital corresponds to an essentially unperturbed $p_x$ orbital, i.e., the orbital shown in eq 3 which is perpendicular to the C-O bond.

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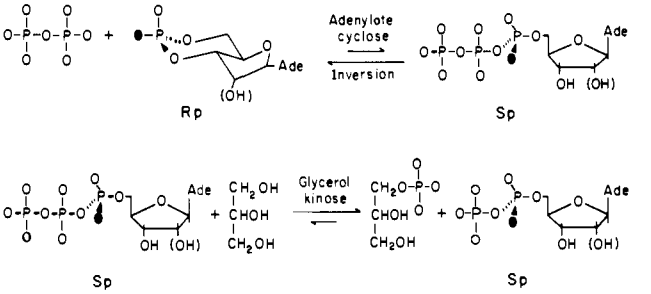
## Oxygen Chiral Phosphodiesters. 2. Enzymatic Synthesis and Configurational Analysis of [$\alpha$-$^{18}$O]-2′-Deoxyadenosine 5′-Diphosphate

*Sir:*

The mechanistic investigation of enzymes which catalyze reactions involving nucleoside di- and triphosphates has been facilitated by the use of diastereomeric phosphorothioate analogues in which a nonbridging oxygen atom of a phosphate group is replaced by a sulfur atom.[1,2] For example, the separated diastereomers of ATP$\alpha$S[3,4] have been used to probe the stereochemical course of a number of adenylyl transfer reactions, thereby providing important information regarding the formation of an adenylated enzyme intermediate during catalysis. The separated diastereomers of ATP$\beta$S[3,5-8] have been used to examine the nature of metal ion coordination to the nucleotide, since the stereoselectivity of an enzymatic reaction involving ATP$\beta$S often depends on the identity of the divalent metal ion used to promote catalysis. However, mechanistic ambiguity can result, since phosphorothioates are often poor substrates for enzymes. Experiments employing nucleotides which are oxygen chiral at either the $\alpha$- or $\beta$-phosphorus atom would not be subject to this problem. In this communication, we report the syntheses of the first oxygen chiral nucleoside diphosphates, the $R_P$ and $S_P$ diastereomers of [$\alpha$-$^{18}$O]-2′-deoxyadenosine 5′-diphosphate ([$\alpha$-$^{18}$O]dADP); these materials were prepared from the $S_P$ and $R_P$ diastereomers, respectively, of cyclic [$^{18}$O]-2′-deoxyadenosine 5′-monophosphate (cyclic [$^{18}$O]dAMP)[9] by using the adenylate cyclase from *Brevibacterium liquefaciens*[10] as a stereospecific catalyst. We also describe a simple, sensitive, and general method for the determination of the absolute configuration of nucleoside polyphosphates which are oxygen chiral at either the $\alpha$- or $\beta$-phosphorus atom. Our experiments illustrate that the stereochemical course of the reaction catalyzed by the bacterial adenylate cyclase is inversion of configuration whether phosphorothioates[11] or oxygen chiral substrates are used.

Scheme I




[a] Enzymatic synthesis of [$\alpha$-$^{18}$O] dADP (or ADP) from cyclic [$^{18}$O] dAMP (or AMP). The example shown is the preparation of the $S_p$ diastereomer of [$\alpha$-$^{18}$O] nucleoside diphosphate from the $R_p$ diastereomer of cyclic [$^{18}$O] nucleoside monophosphate. ● represents $^{18}$O.

The strategy for the stereospecific synthesis of oxygen chiral [$\alpha$-$^{18}$O]dADP (or [$\alpha$-$^{18}$O]ADP) from oxygen chiral cyclic [$^{18}$O]dAMP (or cyclic [$^{18}$O]AMP) is summarized in Scheme I. The adenylate cyclase from *B. liquefaciens* (ATCC 14929) catalyzes the cyclization of ATP (or dATP) to yield cyclic AMP (or cyclic dAMP) and pyrophosphate.[10] At neutral pH, the reaction catalyzed by this enzyme is reversible, with the velocity for the production of ATP from cyclic AMP and pyrophosphate being maximal at pH 7.3. At this pH and in the presence of 5 mM $MgSO_4$, the equilibrium constant for the reaction written in the direction of ATP synthesis is 8 $M^{-1}$.[12] At millimolar concentrations of reactants and products, the reaction favors the synthesis of cyclic AMP. To favor production of chiral acyclic nucleotide, we have chosen to couple nucleoside triphosphate production to the glycerol kinase reaction.[13]

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