mg, 1 mmol) with chloramine T·$3H_2O$ (564 mg, 2 mmol) as described above for the preparation of **6** gave *cis*-**7** (162 mg, 36%) and *trans*-**7** (132 mg, 29%).

cis-**7** had: mp 179–181 °C [from $CHCl_3$–petroleum ether (bp 60–80 °C)]; IR ($CHCl_3$) 2270 (C–D), 1300, 1140, 1085 (SO_2), 968 (S^+–N^-) cm^{-1}; NMR ($CDCl_3$) δ 7.2–8.1 (m, 10, aromatic protons), 7.0–7.2 (m, 2, aromatic protons), 4.96 [s, 1, H(9)], 2.42 (s, 3, toluene ring CH_3); mass spectrum *m/e* 448 (M^+).

trans-**7** had: mp 169–172 °C (from benzene); IR ($CHCl_3$) 2270 (C–D), 1300, 1143, 1088 (SO_2), 968 (S^+–N^-) cm^{-1}; NMR ($CDCl_3$) δ 7.1–8.0 (m, 12, aromatic protons), 5.55 [s, 1, H(9)], 2.38 (s, 3, toluene ring CH_3); mass spectrum *m/e* 448 (M^+).

Thermal Isomerization of *cis*- and *trans*-6. A solution of *cis*-**6** (30 mg) in benzene (3 mL) was refluxed for 10 h. Evaporation of the solvent gave a mixture of *cis*- and *trans*-**6** in a ratio of ~1:3 (by NMR spectroscopy).

Similar treatment of *trans*-**6** gave a mixture of *cis*- and *trans*-**6** in the same ratio.

Reaction of *trans*-6 with Concentrated HCl in Dioxane. A solution of *trans*-**6** (100 mg, 0.23 mmol) in dioxane containing concentrated HCl (0.1 mL) was refluxed for 2 h. The reaction mixture was concentrated, neutralized with 5% NaOH solution, and extracted with $CHCl_3$. The extract was washed with water, dried ($MgSO_4$), and concentrated. The residual oil was chromatographed on silica gel with benzene to give **3** (38 mg, 61%) and 9-hydroxy-9-phenylthioxanthene (**9**; 20 mg, 32%).[8]

Rearrangement of *cis*- and *trans*-6 with DBU in Benzene. To a stirred suspension of *cis*-**6** (100 mg, 0.23 mmol) in benzene (5 mL) was added DBU (34 mg, 0.23 mmol). After stirring at room temperature for 10 min, the reaction mixture was washed with 10% HCl and water and concentrated. The residual oil was purified by preparative TLC on silica gel with benzene as solvent to give 9-phenyl-9-(*N*-*p*-toluenesulfonamido)thioxanthene (**12**; 94 mg, 94%): mp 219–222 °C (from benzene–*n*-hexane); IR ($CHCl_3$) 3350 (NH), 1325, 1150, 1090 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 6.8–7.5 (m, 17 aromatic protons), 5.11 (s, 1, NH), 2.29 (s, 3, toluene ring CH_3).

Analysis was carried out by high-resolution mass spectrometry: calcd for $C_{26}H_{21}NO_2S_2$, 443.1013; found, 443.1061.

Similar treatment of *trans*-**6** (100 mg) gave **12** (85 mg, 85%).

Determination of the Half-life of *cis*- and *trans*-6 in $CDCl_3$ Containing Piperidine as Base at 34 °C. The samples (0.25 M in substrate) were made up in NMR tubes from weighed amounts of *cis*- and *trans*-**6** in $CDCl_3$ with tetramethylsilane as internal standard. The NMR spectrum was then recorded and piperidine (8.5 mg, 0.1 mmol) was added. The spectrum was immediately recorded again at intervals, the temperature being held at 34 °C. The reaction was followed by electronic integration of the H(9) signals. The product was free of decomposition products or byproducts.

Registry No. *cis*-**1a**, 6931-68-6; *trans*-**1a**, 69381-65-3; *cis*-**1b**, 69381-69-7; *trans*-**1b**, 69381-66-4; **3**, 35500-04-0; **4**, 71031-54-4; *cis*-**5**, 71001-68-8; *trans*-**5**, 71001-70-2; *cis*-**6**, 71001-71-3; *trans*-**6**, 71001-72-4; *cis*-**7**, 71001-73-5; *trans*-**7**, 71001-74-6; **9**, 6630-80-4; **12**, 71001-75-7; thioxanthene, 261-31-4; bromobenzene-d_5, 4165-57-5.

Ring Conformations of Proline. Solution Studies Based on Lanthanide Nuclear Magnetic Resonance Shifts and Molecular Mechanics

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Previous studies of ring conformational equilibria of proline based on molecular mechanics computations show the presence of two shallow energy minima: A is a half chair with C^{γ} up and C^{β} down with respect to the average plane of the ring and with the carboxyl group up; B is an envelope with C^{γ} down. Evaluation of available X-ray data showed that in the solid state the reported conformations cluster about one or the other of these conformations of the theoretical minimum energy. The present study concerns the conformational states of the proline ring in solution in $CDCl_3$ and is based on lanthanide NMR shift studies. The shift reagents $Yb(fod)_3$ and $Eu(fod)_3$ gave 25 usable shift values with Ac-L-Pro-OCH_3 and 29 with Bz-Pro-OCH_3.[1] The shift results are consistent with a conformational mixture of roughly 60 parts of A and 40 of B. Assumption of a planar average ring conformation gives a poorer account of the data and the data are inconsistent with a ring having a single intermediate conformation derived from either A or B. In the present study the lanthanide shift data were processed by a molecular mechanics program modified so as to permit simultaneous adjustment of lanthanide parameters, substrate geometry, and conformer mole fractions. Minor adjustment of substrate geometry gave dramatic improvement in the agreement factor between observed and calculated induced shift values, and the observed values have been reproduced to within experimental error. We provide a probable explanation of the variable and unrealistically long lanthanide–oxygen distances commonly reported in LIS studies. This is a consequence of representing a physical system made up of many complexes in rapid equilibrium by one single mathematically averaged complex. The geometry of the substrate is reproduced well by the mathematical model, although this may not closely resemble any individual complex with respect to the lanthanide position nor with respect to the properties of the magnetic tensor.

A previous theoretical evaluation of the conformational energy map for the proline ring based on molecular mechanics calculations showed two shallow minima located at $a_0 = 37°$, $t = 13.3$ (A) and at $a_0 = -36°$, $t = 177.3$ (B).[2] A corresponds to a half chair conformation with C^{β} down and C^{γ} up with respect to the average plane of the ring. B corresponds roughly to an envelope with C^{γ} down. The carboxyl is up. Analysis of the available X-ray data for about 40 proline rings showed that the ring conformations

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(1) (a) IUPAC-IUB Conventions as published in "Amino Acids, Peptides, and Proteins", Vol. 4, G. T. Young, Sr. Reporter, The Chemical Society, London, 1972, p 441; (b) fod is the complexing group derived from 2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedione; dpm is derived from 2,2,6,6-tetramethyl-3,5-heptanedione; (c) LIS, lanthanide induced shift.

(2) D. F. DeTar and N. P. Luthra, *J. Am. Chem. Soc.*, **99**, 1232 (1977).

0022-3263/79/1944-3299$01.00/0

Table I. Observed Chemical Shifts and Observed and Calculated Induced Shifts for Ac-Pro-OCH$_3$ and for Bz-Pro-OCH$_3$

	shift, ppm[a]		induced shift, ppm[b]							
			Ac-Pro-OCH$_3$[c]				Bz-Pro-OCH$_3$[d]			
			Eu(fod)$_3$		Yb(fod)$_3$		Eu(fod)$_3$		Yb(fod)$_3$	
	Ac-Pro-OCH$_3$	Bz-Pro-OCH$_3$	obsd	calcd	obsd	calcd	obsd	calcd	obsd	calcd
H^{α}	4.49	4.68	7.01	6.98	28.11	28.16	8.83	8.83		
H^{β_1}	2.02	2.04	2.47	2.55	9.06	9.00	2.81	2.80	10.16	10.21
H^{β_2}	2.17	2.31	1.79	1.86	7.32	7.07	1.90	1.96	8.35	8.16
H^{γ_1}	1.94	2.02	2.30	2.11	7.72	7.81	2.46	2.42	9.63	9.34
H^{γ_2}	2.02	1.88	1.80	1.73	7.27	6.96	1.99	1.97	8.98	8.81
H^{δ_1}	3.53	3.61	3.82	3.84	14.61	14.59	4.43	4.39	16.39	16.58
H^{δ_2}	3.64	3.55	2.95	3.04	12.91	13.02	3.65	3.80	16.04	16.39
H(Ac)	2.09		6.19	6.18	22.29	22.29				
H(CH$_3$)	3.73	3.78	1.52	1.51	1.91	2.07	1.55	1.50	0.90	0.95
H(ortho)		7.56					4.55	4.32	17.41	17.10
H(meta)		7.41					0.47	0.66	1.58	1.85
H(para)		7.41					0.40	0.43	1.58	1.84
C_1^{α}	58.56	59.16			29.10	28.73			32.79	32.49
C_1^{β}	29.47	29.42			10.97	11.37			12.14	12.68
C_1^{γ}	24.81	25.33			9.86	10.01			11.13	11.47
C_1^{δ}	47.77	49.84			16.87	17.20			19.02	18.95
C_O^{α}	22.20	136.46			34.78	34.68			35.03	
C_O	172.85	172.66			20.74	20.92			24.70	24.53
C_2^{α}	52.10	52.08			4.28	4.06			5.32	
C(ortho)		127.20							17.86	17.90
C(meta)		128.23							5.60	6.04
C(para)		130.00							4.94	4.42
C_O(amide)	169.39	169.55			81.73				85.40	

[a] H downfield from $(CH_3)_4Si$ in $CDCl_3$ at 37 °C; ^{13}C downfield from $(CH_3)_4Si$. [b] Shifts are all downfield. Values reported are defined in eq 3; calculated values are for *s*-trans amide. [c] R value 0.012; $r^2 = 0.99964$. [d] R value 0.020; $r^2 = 0.99912$.

in the solid state cluster about the two theoretical energy minima.

In the present study we examine proline ring conformations in solution in $CDCl_3$ for Ac-L-Pro-OCH$_3$ and for Bz-L-Pro-OCH$_3$.

Lanthanide NMR shift reagents have been used successfully for determination of conformational equilibria in solution.[3] Data are usually evaluated via the equation of McConnell and Robertson[4] (eq 1 below) using cylindrical symmetry to define the magnetic effects of the lanthanide. Earlier evaluations of shift data by the McConnell–Robertson equation have been successful even though rather crude geometries have often been assigned to the substrate and arbitrary locations have been chosen for the shift reagent and for the direction of its magnetic axis.[3,5] More recent LIS studies have used increasingly sophisticated methods for treating geometric factors.[6,7]

A possible problem in using lanthanide shift reagents is complexation that alters the geometry of the substrate.[8] Another cause of concern has been the need to assume relatively long O...lanthanide distances in the complexes, often of the order of 3 Å[9-11] rather than the 2.3–2.5 Å found in X-ray studies.[12-14] Another possible complication is the occurrence of 2:1 complexes such as LS_2.[15] We consider these factors in the Discussion.

Although Eu(fod)$_3$ shows undesirable levels of contact shifts with ^{13}C, it has generally been found that contact terms are not very large with Eu(fod)$_3$ shifts of protons; Yb(fod)$_3$ shows little contact shift with protons and shows appreciable contact shifts with ^{13}C only with the carbon atoms closest to the lanthanide.[13,16,17] Diamagnetic corrections are expected to be negligible for our substrates.[6a,18] The lanthanide magnetic tensor commonly shows cylindrical symmetry, and explanations have been presented for this property.[19]

Previous studies on amides have been evaluated in terms of various lanthanide...O distances from 2.0–2.5 to 2.4–3.2 Å; the lanthanide is found above (or below) the OCN plane and away from the carbon or nitrogen atoms.[10,13,20] Based on limited available data, a lanthanide shift study of H_2^+-Hyp-O$^-$ in D_2O was interpreted as showing a single ring conformation.[21] A study of cyclic proline derivatives was concerned primarily with side-chain conformations, and ring conformations were assigned by means of molecular mechanics energy evaluations.[20,22]

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Table II. Equilibrium Conformations of Proline in $CDCl_3$ at 37 °C

	no shift reagent				in presence of shift reagent			
	Ac-Pro-OCH_3		Bz-Pro-OCH_3		Ac-Pro-OCH_3		Bz-Pro-OCH_3	
	A	B	A	B	A′	B′	A′	B′
mole fraction					0.57	0.43	0.62	0.38
χ_2[a]	35.1	−35.0	35.0	−35.0	36.0	−35.7	33.4	−35.3
d_1	−4.9	−0.5	−5.	−1	0.1	−2.1	−1.8	−0.5
a_0[b]	36.1	35.0	36.6	36	36.0	35.9	33.5	35.3
t	13.4	178.6	11.	177	−0.4	174.2	5.4	178.6
V, kcal/mol[c]	0.3	0	0.3	0	0.7	0.3	0.8	0.2
χ_1	−23.1	28.7	−28.2	29.6	−29.0	30.7	−25.0	28.7
χ_3	−33.3	27.7	−27.9	26.5	−28.8	26.5	−28.7	28.0
χ_4	20.0	−10.3	10.9	−8.4	10.8	−7.5	13.3	−10.3
χ_5	1.9	−11.5	10.8	−13.3	11.5	−14.5	7.4	−11.6
χ_5 - 60 ("ϕ")	301.9	288.5	310.8	286.7	311.5	285.5	307.4	288.4
C_O-N_1-C_1^α-C_1 (true ϕ)[d]	298.6	283.7	302.3	283.0	302.8	280.0	298.0	283.8
N_1-C_1^α-C_1-O_{alk} (ψ)[d]	146.8	157.0	144.3	158.8	111.5	154.6	145.4 (Eu) 144.0 (Yb)	156.5 (Eu) 155.5 (Yb)
C_1-O_2-C_2^α-H (Me ester)[e]	60.2	60.5	60.5	60.5	50.8	61.9	60.3 (both)	60.2 (both)
N_1-C_O-C_O^α-H(acetyl)	75.7	55.9			74.6	56.5		
N_1-C_O-C_{ipso}-C_{ortho}			95.2	90.3			88.8 (Eu) 112.6 (Yb–A)	87.3 (Eu) 87.4 (Yb)

[a] See Figure 1, this paper, and Figure 1, ref 6. [b] Equation 4 and Figure 2, ref 6. Conformation B is the global minimum and conformation A is the other minimum, Figures 1 and 2, ref 6. [c] Energy above global minimum. [d] Reference 1. [e] C_1^α-C_1-O-C_2^α was within 1° of 180° throughout.

Table III. Lanthanide Coordinates

	Ac-Pro-OCH_3		Bz-Pro-OCH_3	
	k^a	$\frac{\partial^2 V^b}{\partial p^2} \times \frac{1}{0.03}$	k^a	$\frac{\partial^2 V^b}{\partial p^2} \times \frac{1}{0.01}$
=O. . .Eu, Å	2.98	12	3.22	12
C=O. . .Eu, deg	142.6	0.03	142.6	0.05
N-C=O. . .Eu, deg	246.0	0.02	254.5	0.03
=O. . .Eu. . .Eu′, deg	186.8	0.3	174.5	0.3
C=O. . .Eu. . .Eu′, deg	187.8	0.007	−2.3	0.007
=O. . .Yb, Å	2.66	830	3.01	725
C=O. . .Yb, deg	130.3	0.5	138.7	0.6
N-C=O. . .Yb, deg	252.3	0.3	264.9	0.2
=O. . .Yb. . .Yb′, deg	174.3	6	174.0	5
C=O. . .Yb. . .Yb′, deg	223.4	0.1	232.5	0.1
k(Eu. . .^{1}H), ppm	766	0.0003	945	0.0004
k(Yb. . .^{1}H), ppm	2203	0.0007	2854	0.0003
k(Yb. . .^{13}C), ppm	2099	0.001	2588	0.0008
mole fraction	0.57	76	0.62	63

[a] Distances in angstroms, angles and torsions in degrees, shift constants (k) in ppm. [b] Second partial derivative of steric energy with respect to the parameter; these values are the effective "force constants" in a Hooke's law expression $V_{partial} = {}^1/_2\, k(p - p_0)^2$. The 0.03 and 0.01 are the energy equivalents of the shift error. (Similar results from 0.05 down to 0.0005.) Units are mdyne-Å/molecule, 1 mda/molecule = 143 kcal/mol.

Results

We have derived shift values and induced shift values from ^1H and ^{13}C NMR spectra of the pure substrates Ac-Pro-OCH_3 and Bz-Pro-OCH_3 in solution in $CDCl_3$ and mixtures of these respective substrates with various molar ratios of either Eu(fod)$_3$ or Yb(fod)$_3$. (See footnote 1 for definitions of abbreviations.) The reported shift values have been calculated for a 1:1 ratio of a 1:1 complex; the experimental molar ratios of L/S actually ranged from 0 to 0.6. The statistical procedure we used for obtaining shift values is described in the Experimental Section.

The observed induced shift values are to be reproduced by values calculated from the McConnell and Robertson equation[4]

$$\Delta_{ij} = k_j(3 \cos^2 \theta_i - 1)r_i^{-3} \qquad (1)$$

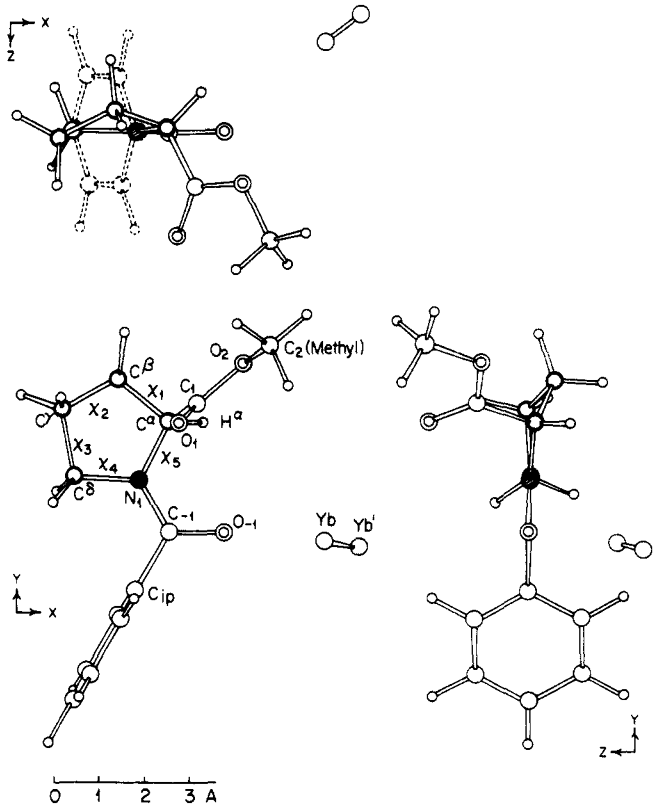

Figure 1. Orthographic projections of the Yb complex with Bz-Pro-OCH_3; ring conformation B. The figure was traced from ORTEP[29] drawings.

Δ_{ij} is the observed shift for nucleus i and shift reagent j; r_i is the distance between lanthanide and nucleus i and θ_i is the angle between the magnetic vector and the vector along r_i. A series of preliminary calculations showed that the data required the lanthanide to be located in the general region reported for other amides;[10,13,20] this position is shown in orthographic projection in Figure 1 for Yb and Bz-Pro-OCH_3.

In the final calculations, summarized in Tables I–III and in Tables IS and IIS of the supplementary material, we treated all shift and conformational data together. In the next few paragraphs we summarize the logistics involved.

For a given substrate we have three independent sets of shift data: ^{1}H–Eu, ^{1}H–Yb, and ^{13}C–Yb. There were 25 total values for Ac-Pro-OCH$_3$ and 29 for Bz-Pro-OCH$_3$. Most of our models of the substrate were based on two independent conformations A and B and on an adjustable mole fraction of A (or of B). From the standpoint of substrate any single set of calculated shift values was derived from one specific A-type conformer and one specific B-type conformer and on a fixed mole fraction; all 25 or all 29 calculated shift values were computed from this one specific mixture of conformers. There is a single exception to this generalization in that we found it necessary to use two separate orientations of the phenyl ring for the A conformation, one ring orientation with Yb and a different one with Eu.

From the standpoint of shift reagent we made no arbitrary assumptions about the average position of the lanthanide atom nor about the average direction of the magnetic axis. It takes three parameters to locate the lanthanide, two parameters to define the direction of the magnetic axis, and one parameter to define k_j of eq 1 for a given lanthanide–nucleus pair. We therefore used six adjustable parameters for Eu, but we used only seven adjustable parameters for Yb. The Yb position and the Yb magnetic axis must be identical for the ^{1}H and for the ^{13}C data, although the experimental need to use different concentration ranges for ^{1}H and for ^{13}C spectra could lead to minor divergences. We used separate k_j values, however, for Yb–^{1}H and for Yb–^{13}C.

Strictly speaking we should have shown θ_{ij} and r_{ij} in eq 1, since the Yb and Eu positions are not coincident, but θ_i and r_i are identically the same for ^{1}H–Yb and ^{13}C–Yb for all nuclei.

The procedure used for obtaining average shift values was as follows: for a unique atom such as the H$^\alpha$ and a given lanthanide such as Eu

$$\Delta_{ij} = \Delta_{ijA} f_A + \Delta_{ijB}(1 - f_A)$$

where f_A is the mole fraction of conformation A and Δ_{ijA} is the calculated shift value for H$^\alpha$ for conformation A and similarly Δ_{ijB} is the value for H$^\alpha$ of conformation B. If a given Δ_i arises from thermal averaging over several atoms as over the three hydrogen atoms of the rotatable methyl group, a separate Δ_{ijkA} was calculated for each of the k = 1–3 hydrogen atoms, each assumed to be in a fixed rotational position and the group value $\Delta_{ijA} = {}^1/_3 \sum \Delta_{ijkA}$. These procedures are valid, since rotational or other barriers tend to confine the position of any given nucleus to a relatively small spatial volume that can be represented by a static average position.

From an assumed starting set of 13 parameters for the lanthanides we carried out an adjustment of all 13 to find the parameter values that minimize S^2 and hence of R^2 (eq 2 and 3). The R^2 term is the Hamilton agreement factor.[23]

$$S^2 = \sum(\Delta_{ij(\text{obsd})} - \Delta_{ij(\text{calcd})})^2 \quad (2)$$

$$R^2 = S^2 / \sum \Delta_{ij(\text{obsd})}{}^2 \quad (3)$$

For the present relatively complex system of nuclei, the calculated Δ_{ij} values are sensitive to minor changes in the geometries assumed for the substrate. We therefore refined the calculations by performing a simultaneous adjustment of the lanthanide parameters and a reminimization of the conformational energy by molecular mechanics. The rationale is that the energy minima are shallow, thus permitting perturbation of conformations from the position of minimum at little cost in energy. In fact the X-ray data show a considerable spread of conformations about the minima.[2]

The refined mode of calculation in effect allows the shift error term to drive the conformations to new positions on the *a–t* map.[2] The computation is performed by defining some fractional value of S^2 to be an energy term. This assignment requires some care, since too large a fractional value will give a very low value of S^2 at the expense of a distorted molecule. There is, however, a range of values for the fraction, around 0.01 for our force field, which gives excellent agreement factors with negligible disturbances of the proline conformational geometries. As indicated in footnote *b* of Table III, values from 0.0005 to 0.05 gave comparable results.

Table II reports the equilibrium conformations we obtained by this procedure. Examination of the individual torsional values shows the minor extent to which the present shift study conformations differ from those reported previously for the energy minima. We may amplify further by comparisons based on the more than 65 torsions applicable to Bz-Pro-OCH$_3$.[24] For the B set of torsions the conformation of minimum energy and the conformation of minimum shift error show torsional differences which may be described as a standard deviation of 1.8° and a maximum difference of 4°. For the A set the values are 2.7° and 7.5°. The conformational perturbation required to improve the shift agreement is therefore much smaller than the perturbations observed in most of the X-ray studies.

Examination of Table I shows that the agreement between observed and calculated shift values is excellent. The *R* values are unusually small, and particularly so for the simultaneous treatment of so many shift values. This excellent agreement attests to the applicability of the McConnell and Robertson equation and it attests also to the validity of the computations and of the experimental data. We present a fuller analysis of the errors below.

The NMR curves showed the presence of s-cis conformer of the amide group amounting to 20–25%, but with the data in hand there were not enough induced shift values to permit a separate analysis of the proline ring conformation for the s-cis form. Kessler and Molter observed perturbation of the s-cis to s-trans ratios in some peptide systems upon complexation with shift reagents.[8] We find no such changes in the proline systems. One difference is that we are working with a disubstituted amide while the other peptides had monosubstituted amide groups.

We carried out a number of other computations to determine the agreement possible if we assume alternative models having a single conformation for the proline ring. For Ac-Pro-OCH$_3$ R^2 for a planar ring is 6.3 times the value reported in Table I. For any single adjusted conformation starting from either A or B the R^2 value is even larger.

We have carried out a sensitivity evaluation of the values of the mole fractions. For Ac-Pro-OCH$_3$ the best mole fraction is 0.62 of conformation A. If this mole fraction is held constant at 0.73 or at 0.36, then R^2 is 2.3 times larger; at 0.82 or at 0.25 R^2 is 4 times larger.

Although the statistical distribution of R^2 is known, the derivation of statistical limits depends on having information about the degrees of freedom. Since we adjusted

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[23] $R = [\sum(\Delta_{i(\text{obsd})} - \Delta_{i(\text{calcd})})^2 / \sum(\Delta_{i(\text{obsd})})^2]^{1/2}$; W. C. Hamilton, "Statistics in Physical Science", Ronald Press, New York, 1964, p 157. The square of the correlation coefficient, r^2, is a more widely used measure of goodness of fit; $r^2 = [1 - \sum(\Delta_{i(\text{obsd})} - \Delta_{i(\text{calcd})})^2 / \sum(\Delta_{i(\text{obsd})} - \Delta_{i(\text{avg})})^2]$. Actually R^2 is not much different from $1 - r^2$; in the present examples R^2 is about 40% smaller.

[24] Details are presented in the Ph.D. dissertation of N. P. Luthra, Florida State University, 1977.

some 90 parameters in minimizing the energy of the two proline conformers, it could be argued that no degrees of freedom remain. On the other hand the actual extent of conformational adjustment was minute, and only a few parameters exert much control. From arguments too long to warrant detailed presentation we conclude that the effective degrees of freedom would be about five and that R_a^2/R_b^2 ratios which exceed 2.3 are then significant at the 5% confidence level.

Discussion

Application of the McConnell–Robertson equation to LIS data places each shift atom on a cone of revolution whose axis is the apparent magnetic axis of the lanthanide atom and at a defined distance from the apex, which coincides with the apparent position of the lanthanide. In other words LIS data define a locus for each shift atom on the circumference of a circle.

The shift atoms of the substrate are also constrained to obey molecular forces which place limits on bond lengths, angles, and torsions. The degree of reliability with which a given LIS study defines a substrate geometry depends therefore on the interplay of these several restrictive factors. The precision with which the circular loci are defined will be determined primarily by the agreement between observed and calculated shift values. It will depend also on finding all mathematically possible locations for the shift reagent; the possibilities for multiple locations drop sharply as the number of observed shift nuclei increases and as their spatial distribution becomes unsymmetrical.

For reasons presented below we conclude that most LIS studies, including the present study, are concerned with mobile equilibria among a very large number of complexes. Further, we conclude that this complication does not matter, nor does the occurrence of LS_2 or other multiple complexes matter, providing only that for the experimental system it is possible to find an apparent location of the lanthanide and an apparent direction for the magnetic axis which accurately reproduces the shift values. LIS studies are therefore not generally useful in describing the geometry at the lanthanide center because it is not possible to examine properties of individual complexes, but LIS studies can provide additional and important information about substrate geometry.

From these above considerations we conclude that the most generally useful approach in LIS studies will be to adjust the lanthanide position and its magnetic axis and scaling factor while simultaneously allowing alteration of substrate geometry subject to force field constraints. Under various sets of assumptions we could specify how closely we know the circular locus of each given shift atom. However, such estimates depend on rather arbitrary definitions and we believe that it is more useful to examine alternative models in terms of the overall agreement of the observed and calculated shift values, the Hamilton R.[23]

Our overall conclusion with respect to Ac-Pro-OCH_3 and Bz-Pro-OCH_3 in $CDCl_3$ at about 35 to 40 °C is that the conformations of the proline ring average to about 60 parts of A and 40 parts of B as summarized in Table II. This agrees both with the conformations observed in X-ray studies and it agrees with theoretical calculations.[2]

We find it possible to define an apparent location for the lanthanide, an apparent magnetic axis and a scaling factor which causes the McConnell–Robertson equation to reproduce observed shift data within experimental error. For the number of shift atoms treated, we have obtained for our systems better agreement than has previously been reported.

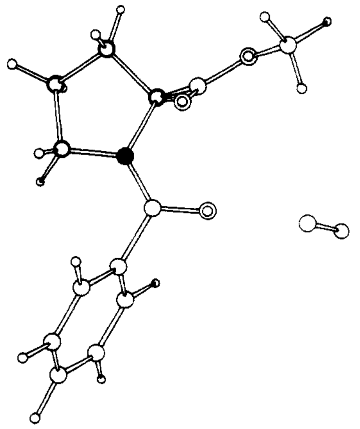

Figure 2. Yb complex with ring conformation A. The figure was traced from ORTEP[29] drawings.

The statistical computation of the shift values reported in Table I (see Experimental Section) shows that the scalar standard deviation of the observed Eu values for Ac-Pro-OCH_3 is 0.15 ppm while the scalar standard deviation between observed and calculated shift values is 0.09. That the calculations show a slightly smaller error than observation is not statistically significant. In the Experimental Section there are similar comparisons for the other five data sets. The largest discrepancy is in the Yb–^{1}H set for Bz-Pro-OCH_3 for which the scalar standard deviation of observed values is 0.1 and the difference between observed and calculated values is 0.25. This difference arises in large measure from our use of unit weighting in the calculations even though experimental errors in the Yb–^{13}C data are considerably larger than in any other set. While we believe that the distribution of scalar error is more nearly normal than is the distribution of relative error, we reach similar conclusions based on minimizing the relative error.

Turning next to the three possible complications discussed at the beginning, the first concerns steric perturbation of the conformation on complexation of substrate with the very large lanthanide complex. We do find such perturbation in the rotational position of the phenyl ring of the benzoyl group of Bz-Pro-OCH_3 with $Yb(fod)_3$. The phenyl ring of the B conformer with $Yb(fod)_3$ is shown in Figure 1 and the central ring of the A conformer with $Yb(fod)_3$ is shown in Figure 2. For reasons discussed below we find that the conformational multiplicities that arise with $Yb(fod)_3$ and $Eu(fod)_3$ make a detailed theoretical analysis impractical. The canted orientation is seemingly the opposite from that expected for a "push". We have found one other example of a "pull" in the literature.[25]

The fact that the computations show a mixture of proline ring conformations close in composition to the mixture calculated from energy considerations alone suggests that the lanthanide does not cause significant perturbation of the proline ring. The phenyl ring example shows that our procedures are capable of picking up perturbations where they are present.

The second possible complication concerns the nature of the lanthanide complexes. First we take up the facts. The optimal lanthanide–O distances reported in Table III range from 3 to 3.2 Å for Eu and from 2.7 to 3.0 Å for Yb. The direction of the magnetic axis =O...Eu...Eu′ or =O...Yb...Yb′ is not very far from the collinearity usually observed (180°). Other geometric parameters also do not differ very much from one lanthanide–substrate pair to

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[25] B. L. Shapiro, M. D. Johnston, Jr., and M. J. Shapiro, *Org. Magn. Reson.*, **5**, 21 (1973).

another. Also the shift constants for Yb–^{1}H and for Yb–^{13}C are nearly the same. We report the depth or shallowness of fit due to a given lanthanide parameter in terms of second partial derivative; these are equivalent algebraically to Hooke's law force constants.

In summary the lanthanide parameters we have calculated are closely comparable to those normally observed in other systems, including amide systems.[12,13,20]

We postulate that the long lanthanide–oxygen distances are a consequence of using one single mathematically averaged complex as a model for a system consisting of a large number of complexes present in mobile equilibrium. We have carried out preliminary computations to test the postulate. First we calculated the shift values that would result from a single Ac-Pro-OCH$_3$ conformer and a hypothetical complex having a given lanthanide–oxygen distance and magnetic axis. We obtained a second calculated set by defining a second complex having a different direction for the magnetic axis but with all else the same. We then synthesized shift data by taking averages of these two sets. And finally, we introduced these synthetic data as though they were observed data in our standard calculation. The calculation gave a good account of the synthetic data but required a new lanthanide–oxygen distance longer than used in the two hypothetical complexes. The substrate geometry and the fraction of substrate conformers corresponded closely to the values used in the hypothetical complex. In the communication which describes the origin of cylindrical symmetry of the magnetic axis Horrocks alludes to this tendency for averaging to give apparent long lanthanide–substrate bonds.[19]

If Eu(fod)$_3$ formed a stable Eu–oxygen bond with the substrate there would then be at least 12 possible stereoisomers with Ac-L-Pro-OCH$_3$ and at least 24 with a racemic substrate. This may be worked out as follows. An octahedral complex with three A–B ligands is representable as one stereoisomer among three *dl* pairs. When Eu(fod)$_3$ combines with a seventh ligand, the Eu site may be adjacent to three A groups, to three B groups, to two A plus B, or to two B plus A.

It has been established that shift reagents may form LS$_2$ complexes as well as LS complexes and that the shift values differ.[26] However, it is not clear that this circumstance makes much difference in the complexity already present, nor that separate evaluation of data for the two stoichiometric complexes will give a different substrate geometry.

We can now complete our evaluation of discrepancies between observed and calculated shift values in the present study. The largest, and these are not very large, all have to do with the torsional position of the phenyl ring of Bz-Pro-OCH$_3$, and there are three probable explanations. (1) The various complexes present may be perturbing the phenyl ring to different orientations which are not properly representable in terms of a single averaged orientation. (2) The ring orientation is at such an angle with respect to the average direction of the magnetic axis that small torsional changes or small changes in direction of the magnetic axis lead to large changes in calculated shift values. (3) Partly in consequence of this sensitivity, there may be no single average position of lanthanide and direction of magnetic axis which represents the population of physical complexes with respect to the phenyl ring.

The focus of the present study is on the conformational equilibria of the proline ring, and examination of the data in Table I shows that there is very good agreement between observed and calculated induced shift values for the hydrogen atoms and carbon atoms of the proline ring.

As a general proposition we conclude that lanthanide shift studies will prove a valuable standard tool for probing conformational equilibria with proper regard for the limitations summarized here and elsewhere.[3]

Experimental Section

Ac-Pro-OCH$_3$. Ac-Pro-OH was prepared in 70% crude yield by adding acetic anhydride and sodium hydroxide to a solution of proline in sodium bicarbonate at 5 °C. Recrystallization from isopropyl alcohol gave a 75% recovery. Esterification with diazomethane gave a product which was purified by distillation: bp 142 °C (10 torr).

Bz-Pro-OCH$_3$. H-Pro-OCH$_3$ was prepared by esterification of a suspension of proline in methanol by addition of thionyl chloride. The resultant hydrochloride was dissolved in water, made slightly alkaline with sodium hydroxide, and acylated by adding benzoyl chloride and sodium bicarbonate. The crude product (78%) was recrystallized from a mixture of ethyl acetate and hexane: mp 94–94.5 °C (lit. 91–92 °C).[27]

Other Reagents. These were purchased. Eu(fod)$_3$ was sublimed at 170 °C (0.1 torr) and Yb(fod)$_3$ at 140 °C. These were stored over phosphorus pentoxide under nitrogen and were used within 24 h after sublimation. The NMR tubes were dried at 110 °C before use.

NMR. In each of six dried vials was placed about 20 mg (accurately weighed) of Bz-Pro-OCH$_3$. Then shift reagent was added under nitrogen, the amount ranging from 6 to 75 mg. Then 0.5 mL of CDCl$_3$ was added, along with vapors of (CH$_3$)$_4$Si as internal standard. The tubes were frozen in liquid nitrogen, outgassed, and sealed. They were kept in the dark. For ^{13}C NMR, a 343-mg sample of Bz-Pro-OCH$_3$ was weighed into a 10-mm NMR tube and dissolved in degassed CDCl$_3$. Then Eu(fod)$_3$ was added in portions of 120 to 750 mg. Solutions with Yb(fod)$_3$ were similarly prepared using 74 mg of Bz-Pro-OCH$_3$ and 15–70 mg of Yb(fod)$_3$. The liquid Ac-Pro-OCH$_3$ was handled as a stock solution.

Spectra were run on a Bruker HX-270 spectrometer operated at 270 MHz for protons and at 67.9 MHz for carbon-13. For protons a sweep width of 3012 Hz was generally used. Free induction decays of about 32 scans were accumulated and Fourier transformed to yield 16K data points. This gave 8K of real points for a resolution of about 0.4 Hz. In some runs 16K of real points were used. Chemical shifts were measured numerically. For broadened peaks averages were taken at three positions. For ^{13}C the sweep width was 15 KHz for 8000 real points. Proton decoupled spectra were used except that off resonance spectra were used as an aid to identification.

Computation of the Shift Values, Δ_i. For the present study we require relative shift values for the various nuclei. To minimize the effects of minor errors in concentrations and of minor impurities, we computed relative shifts Δ_i as defined in eq 4 and 5.

$$\nu_{ij} = \nu_i^0 + \Delta^0 f_i (L/S)_j \qquad (4)$$

$$\Delta_i = \Delta^0 f_i \qquad (5)$$

The resonance position for nucleus i in solution j is ν_{ij}. This is taken to be a linear function of the L/S ratio; (L/S)$_j$ is the molar ratio of lanthanide complex to substrate in solution j. For nucleus i the resonance position in the absence of shift reagent is at ν_i^0. The slope of the line is $\Delta^0 f_i$, where Δ^0 is the shift experienced by a reference nucleus (taken as H$^\alpha$) at L/S = 1. For the reference nucleus $f_i \equiv 1$. The lines showed no curvature over the range of concentration treated, maximum L/S = 0.6.

For *m* solutions (*m* = 6) including pure substrate and substrate plus various L/S ratios of lanthanide there are up to *m* values of ν_{ij} for each of the *n* nuclei. A few values of ν_{ij} were unavailable because of overlapping peaks or because of excessive broadening. We held the *n* values of ν_i^0 constant and adjusted the *n* − 1 values

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(26) B. L. Shapiro and M. D. Johnston, Jr., *J. Am. Chem. Soc.*, **94**, 8185 (1972).

(27) L. F. Johnson, A. V. Robertson, W. R. J. Simpson, and B. Witkop, *Aust. J. Chem.*, **19**, 115 (1966).

of f_i and the value of Δ^0. The least-squares criteria minimized the $\sum(\nu_{ij(obsd)} - \nu_{ij(calcd)})^2$ for all data for a given substrate-shift reagent set for a given type of nucleus ^{1}H or ^{13}C; we used the computer program GENLSS.[28]

The results are summarized in Tables 6-1(a) through 6-1(f) of ref 24.

The scalar errors of the slopes are nearly constant for a given data set. In carrying out the minimization which gave the data in the tables, the scalar error in the directly observed shift data, the ν_{ij} values were minimized. This does not automatically result in scalar errors for the Δ_i. Some authors have used relative errors for the Δ_{ij};[25] this may have been the correct choice but hardly for the reasons advanced. The form of error distribution can readily be ascertained by standard techniques.

There is a close correspondence between the scalar standard deviations of the observed shift values, the first number listed (based on GENLSS runs), and the scalar standard deviations of the calculated shift values, the second number (based on the data in Table I): for Bz-Pro-OCH$_3$ and Eu (0.13, 0.11), Yb–^{1}H (0.1, 0.25), and Yb–^{13}C (0.5, 0.4); for Ac-Pro-OCH$_3$ and Eu (0.15, 0.09), Yb–^{1}H (0.24, 0.16) and Yb–^{13}C (0.23, 0.3).

Computations. Least-squares evaluations of Δ_i were performed by use of GENLSS.[28] Figures 1 and 2 were prepared by ORTEP.[29] Molecular mechanics computations utilized MOLMEC[30] and the force field previously described.[2]

Acknowledgment. This work was supported in part by U.S. Energy Research and Development Administration contract No. (40-1)-2690 with the Institute of Molecular Biophysics. We are also grateful to the Computing Advisory Committee for a grant of computing time which made this work possible.

Registry No. Ac-Pro-OCH$_3$, 27460-51-1; Bz-Pro-OCH$_3$, 5493-38-9; acetic anhydride, 108-24-7; proline, 147-85-3; H-Pro-OCH$_3$, 2577-48-2.

Supplementary Material Available: Observed and calculated ^{1}H and ^{13}C shift values for *S-trans*-Bz-Pro-OCH$_3$ and for *S-trans*-Ac-Pro-OCH$_3$ (5 pages). Ordering information is given on any current masthead page.

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Regiospecific Electroacetoxylation of 4-Methylphenyl Acetate to Form 4-Acetoxybenzyl Acetate. A Significant Procedure for Vanillin Synthesis Involving Novel Etherification Methods of Aryl Bromides

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Electroacetoxylation of 4-methylphenyl acetate (**1**) was carried out in AcOH–*t*-BuOH (9:1 v/v) in in the presence of copper(II) acetate by using carbon electrodes to give the side-chain-oxidized products in 88% selectivity (90% conversion), i.e., 4-acetoxybenzyl acetate (**2a**, 69%), 4-acetoxybenzaldehyde (**4a**, 8%), and 4-acetoxybenzylidene diacetate (**3**, 3%). The electrolysis products **2a**, **3**, and **4a**, either by platinum oxide catalyzed oxygen oxidation or by acid-catalyzed hydrolysis, were smoothly converted to 4-hydroxybenzaldehyde (**4b**) whose bromination provided 3-bromo-4-hydroxybenzaldehyde (**5a**, 90%) as well as 3,5-dibromo-4-hydroxybenzaldehyde (**5b**, 4.5%). Treatment of **5a** with either ROH–NaOH–CaO/DMF–CuCl$_2$ or ROH–BaO–DMF–CuCl$_2$ resulted in vanillin (**6a**, 94%) and ethyl vanillin (**6b**, 93%), respectively. On the other hand, acid-catalyzed hydrolysis of **2a** gave 4-hydroxybenzyl alcohol (**11**, 89%), and acid-catalyzed alcoholysis of **2a** furnished 4-hydroxybenzyl ethers **8a** (100%) and **8b** (99%). The oxygen oxidation of both **8** and **11** can produce **4b** in good yield. 4-Hydroxy-3-methoxy(or ethoxy)benzyl ether (**10**), another key precursor for the vanillin synthesis, was prepared from both **8** and **11** by bromination followed by etherification with ROH–BaO–DMF–CuCl$_2$ in good yield.

Our interest in the electrolytic side-chain oxidation of 4-cresol homologues was stimulated by the good results obtained from the chemical oxidation of 2,6-dialkyl-4-methylphenols into the corresponding 3,5-dialkyl-4-hydroxybenzaldehydes.[1] Basically, if the preparation of 4-hydroxybenzyl alcohol (**11**) and/or 4-hydroxybenzaldehyde (**4b**) could be accomplished by electrochemical oxidation of 4-cresol, the procedure would be of remarkable utility since the oxidized products can be widely used as important chemicals in the organochemical industry.

The lack of the regioselectivity in the anodic oxidation of nonmasked phenols[2] enables us to choose 4-methylphenyl acetate (**1**) for our present work. However, some patents on the chemistry of the catalytic oxygen oxidation of **1**[3] reveal that the conversion of **1** into **4a** (Y = Ac) has been shown to occur with less than 31% selectivity (ca. 63% conversion). Our aim, based on electroacetoxylation of the methyl group of **1**, was to generate 4-acetoxybenzyl acetate (**2a**), prior to the formation of **4b**. Additionally, we examined several approaches to vanillins (**6**) from the acetate **2a** as outlined in Schemes I and II, which involve novel alkoxylation reactions of 2-bromophenols **5**, **9**, and **12**.

Electroacetoxylation of 4-Methylphenyl Acetate (1). The anodic side-chain acetoxylation of aromatic compounds has been carried out in a variety of solvent-supporting electrolyte-additive systems: AcOH–Ac$_2$O–AcONa,[4] AcOH–AcOK–Co^{2+},[5] AcOH–Me$_4$NOTs,[6] AcOH–

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