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CONFORMATIONAL ANALYSIS WITH LANTHANIDE SHIFT REAGENTS DIFFERENCES IN THE SOLUTION AND CRYSTAL STRUCTURE CONFORMATIONS OF A COMPOUND

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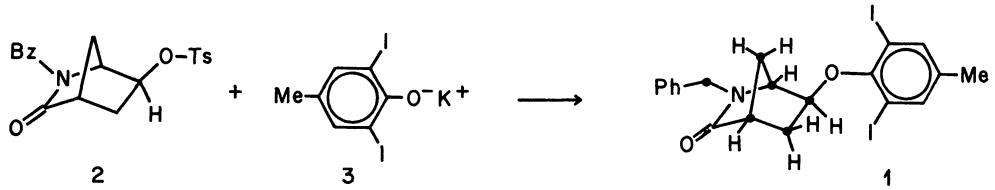
The solid and LSR-determined solution conformations of 2-benzyl-3-oxo-6-exo-(2,6-diiodo-4-methylphenoxy)-2-azabicyclo[2.2.1]heptane are substantially different. The "best" solution conformation contains a close I···H contact of 2.65 Å, in agreement with trends in the ^{1}H chemical shifts in several similar compounds. Crystal structure data may not provide an accurate picture of the major solution conformer in cases where interconversion barriers are low.

The use of NMR - lanthanide shift reagents is now routine for the investigation of various aspects of molecular structure in solution.[1] Application of the LSR technique to conformational analysis has been restricted largely to cases in which there are a small number of reasonable conformations from which to select the major one.[2] In a few instances,[3] more general conformational studies have been carried out by first referencing the "position" of the LSR in the LSR-substrate complex to the positions of several atoms in a rigid portion of the substrate, via their lanthanide induced shifts (LIS's), followed by the use of a fixed LSR position to analyze a conformationally mobile portion of the substrate. Hofer[2] has stated that this procedure is the only reliable one for detailed conformational analysis.

As part of a program to study the conformations of thyroid hormone analogs in solution, we prepared 2-benzyl-3-oxo-6-exo-(2,6-diiodo-4-methylphenoxy)-2-azabicyclo[2.2.1]heptane (1) from tosylate 2 and phenoxide 3.[4] ^{13}C and ^{1}H LIS data for 1 were obtained with Yb(fod)$_3$,[5] and the



2 3 1

Yb was positioned in the LSR-substrate complex by reference to the six carbon (·) and seven hydrogen (H) atoms in the rigid azabicyclo[2.2.1]heptane framework of 1 with the LIS ratio method employed in our laboratory,[6,7] the crystal structure of 1 provided coordinates for the various framework atoms.[8] The 2,6-diiodo-4-methylphenoxy substituent was positioned relative to the "fixed" Yb···bicyclic framework complex by minimization of $\Sigma_i(LIS_i^{obs} - LIS_i^{calc})^2$, for the seven unique substituent LIS's, as a function of the O-C6 and CP1-O rotation angles. The O-C6 angle was cleanly defined, whereas three models were evaluated for CP1-O: (A) a single "best" conformation; (B) unrestricted 0-360° rotation; (C) unrestricted oscillation over an angular range limited to nonbonded contacts between the iodines and framework hydrogen atoms $\geq$ 2.6 Å. Although there are unacceptably short I···H contacts over much of the 0-360° range in (B), the model was included as a "worst possible case" for calibration purposes. The pertinent LIS and shift residual (SR) data given in Table 1 show that models (A) and (C) are substantially better than (B), and that model (D) based on the X-ray crystal structure of 1 is worst of all. Significance testing with the jack-knife method[10] allows the rejection of model (B) relative to (A) at a 96% confidence level. Models (A) and (C) are clearly indistinguishable, and perhaps the best picture is a combined one,

incorporating a mean CP1-O angle of 72° with an angular oscillation amplitude of 10-15°.

Table 1. LIS Data (Hz) for Models (A) - (D) of the 2,6-Diiodo-4-methylphenoxy Substituent in 1.

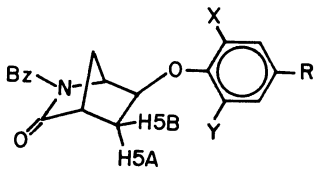
Atom (s)	LIS^{obs}	LIS (A)	LIS (B)	LIS (C)	LIS (D)
CP1	203.45	199.12	197.91	198.95	218.3
CP2, CP6	145.51	152.72	155.90	153.00	176.3
CP3, CP5	108.04	103.02	103.30	103.00	128.3
CP4	101.35	89.13	87.16	88.85	113.8
C, methyl	58.76	59.52	57.65	58.26	81.5
HP3, HP5	143.78	149.37	153.30	149.95	196.3
H, methyl	97.12	98.85	95.43	98.36	138.4
O-C6		-7°	-10.5°	-6.5°	43°
CP1-O		72°	0-180°*	60-98°	72°
SR		0.0487	0.0622	0.0502	0.239

*Because of the substituent's symmetry and required LIS averaging, 0-180° and 0-360° rotations are identical.

The X-ray crystallographic and the model (A) structures are illustrated in Fig. 1, and details of the O-C6 and CP1-O conformations are given in Fig. 2. A balance of intra and intermolecular contacts clearly is responsible for the solid state conformation, in which the several I···H nonbonded distances are in the normal range of 2.9-3.2 Å. The solution conformation of the diiodophenoxy group is substantially different from that found in the crystal by virture of a 50° difference in the O-C6 bond rotation angles. In the crystal structure, the O-C6 rotation swings the phenoxy group toward the Cl side of C6, whereas an opposite rotation, toward C5, is observed in the solution structure. The intramolecular distances between the bicycloheptane and diiodophenoxy groups in the model (A) structure are typical, with the exception of the I···H5B contact of 2.65 Å, which is approximately 0.3 Å less than the I···H closest approaches usually found in crystal structures. Trends in the ^1H chemical shift data reported in Table 2 provide additional evidence for a close contact between I and H5B and thus for model (A). δ(H5B) is smaller than δ(H5A) for the first three compounds listed in the table, but in the case of compound 1, the H5B resonance is shifted downfield until it is equal to that of H5A. A downfield shift of this resonance would be expected to occur as a result of the repulsion of electon density away from H5B by the nearby I atom.

Table 2. Chemical Shifts for H5A and H5B in Four 2-Benzyl-3-oxo-6-exo-(substitutedphenoxy)-2-azabicyclo[2.2.1]heptanes

Substituents	(H5A)*	(H5B)*
R = X = Y = H	134 Hz	110 Hz
R = Me, X = I, Y = H	138	113
R = X = i-Pr, Y = H	130	108
R = Me, X = Y = I (1)	137	137



*These values were obtained by extrapolating δ vs. [LSR]/[substrate] plots to [LSR] = 0.

There are several unanswered questions arising from differences in the crystal and solution structures. For example, why does not the solution molecule adopt a crystal-like structure to minimize the intramolecular I···H contacts? The seemingly "short" contacts in the (A)/(C) structure may not be abnormal in solution under certain conditions, and these conditions might be expected to vary with the natures of the solute and solvent (the solute-solvent interaction). While

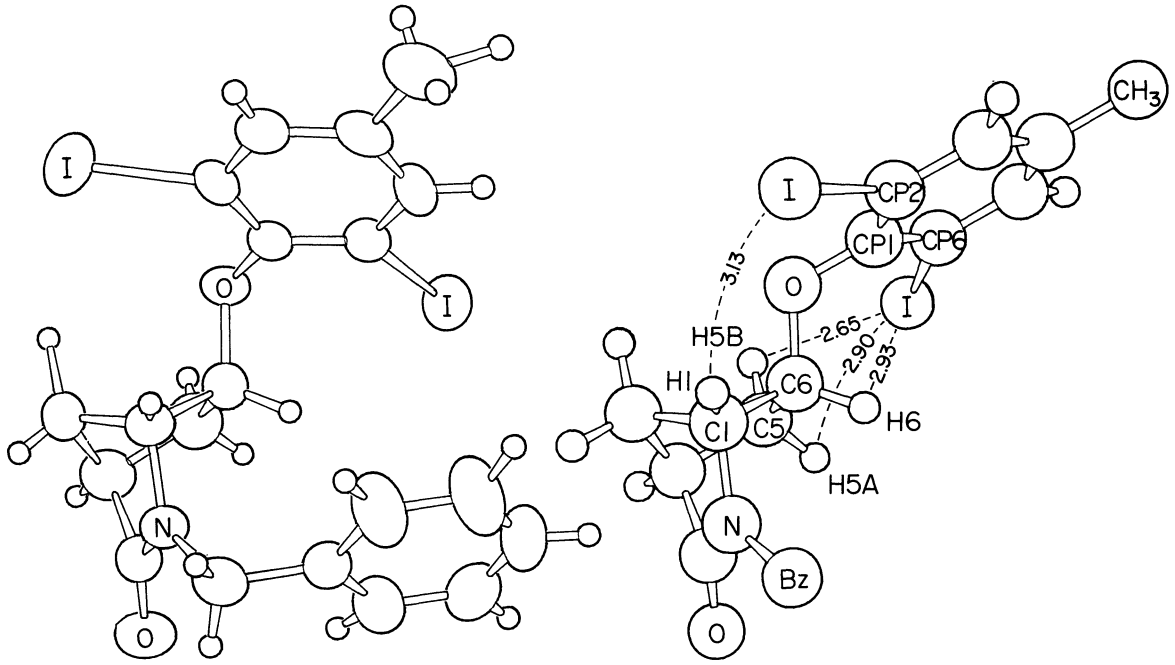


Figure 1. ORTEP drawings of the crystal (left) and model (A) solution (right) structures of compound 1. Several of the shortest I···H intramolecular contact distances (Å) are shown for the solution structure.

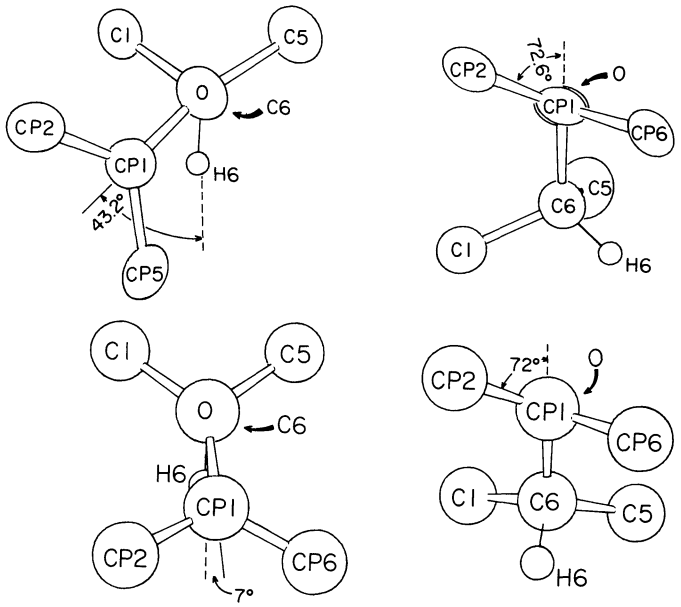


Figure 2. Projections down the O-C6 (left) and CP1-O (right) bonds to describe the diiodophenoxybicycloheptane conformations in the crystal (top) and model (A) solution (bottom) structure of compound 1.

crystal data have been, and will continue to be, of great value for investigations of molecular structure and conformation, we caution that conformations deduced from crystal structure determinations be viewed as such, and that these data not be extrapolated to "look alike" conformations in solution without confirmatory evidence to support the similarily between solid and solution. The potential for significant solid/solution differences is likely to be high in cases in which the barriers to conformational interconversions are small.

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References and Notes

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(4) The reaction takes place with retention of sterochemistry (double inversion). Similar results on a related system have been explained previously (J. W. Huffman, C. B. S. Rao and T. Kamiya, J. Org. Chem., 32, 700 (1967)).

(5) The ^{1}H and ^{13}C spectra were recorded on Varian A-60D (60 MHz) and XL-100 (25.2 MHz) spectrometers, respectively, at ambient temperature. The ^{13}C spectra were taken in the FT-mode with broad band decoupling. The substrate concentrations ranged from 0.2.4-0.4 (for ^{1}H) and 0.4-0.8 M (for ^{13}C) in ca. 0.3 ml $CDCl_3$ (1% TMS). All materials were carefully dried and the LSR was sublimed shortly before each experiment. Small incremental additions of the LSR to the substrate/CDl_3 solution were accomplished with tear-drop shaped weighing bottles, whose openings could fit into the neck of a 5 mm NMR tube; following each addition, the mass of the bottle was determined to correct for LSR remaining in the weighing bottle. The LIS values were obtained from the least-squares determined slopes of the initial linear sections of δ vs. [LSR]/[substrate] plots; the correlation coefficients were in all cases $\geq$ 0.999. The shifted proton δ's were tested according to the procedures of Raber et al. (D. J. Raber, M. D. Johnson, C. M. Campbell, C. M. Janks and P. Sutton, Org. Magn. Reson., 11, 323 (1978)) which indicated that the LIS's were either from a 1:1 LSR-substrate complex, or the ratio $LIS_{1:1}/LIS_{1:2}$ was constant for all atoms. Additionally, experiments were done to demonstrate that LSR complexation occurs exclusively at the lactam oxygen; there is no complexation at the ether oxygen atom.

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(7) Our LSR-positioning computer program minimizes the function $\Sigma_{ij}^{n} (R_{ij}^{obs} - R_{ij}^{calc})^2$, where $R_{ij}^{obs} = LIS_i/LIS_j$ and $R_{ij}^{calc} = (3\cos^2\theta_i-1)r_j^3/(3\cos^2\theta j-1)r_i^3$. Separate summations are done for the ^{1}H and ^{13}C data. The procedure is described in detail in ref. 6a. The ratio residual (RR) for the fit was 0.042.

$$RR = [\Sigma_{ij}(R_{ij}^{obs} - R_{ij}^{calc})^2/\Sigma(R_{ij}^{obs})^2]^{1/2}$$

(8) The crystallographic residual ($\Sigma|F_o - F_c|/\Sigma F_o$) was 0.040. Details will be published elsewhere.

(9) $SR = [\Sigma_i^7 (LIS_i^{obs} - kLIS_i^{calc})^2/\Sigma_i^7(LIS_i^{obs})^2]^{1/2}$. Two separate k's ($k_H$ and k_C) were required to place the ^{1}H and ^{13}C LIS^{calc} values on the LIS^{obs} scale. The k's were evaluated from the bicyclo[2.2.1]heptane framework calculations.

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