gas-phase basicities of the amines increase in the order ammonia, methylamine, dimethylamine, and trimethylamine, *i.e.*, with increasing methyl substitution. This is the order that can be expected on the basis of the electron-donating effect of the methyl groups. This simple order is not observed in aqueous solution (see last column of Table I).

Aniline and pyridine are stronger gas-phase bases than ammonia, while aniline and pyridine are much weaker bases in aqueous solution. Most organic chemistry textbooks explain the relative weak aqueous basicity of aniline by the resonance[6] and the electron-withdrawing inductive effect of the phenyl group. Both of these are intrinsic molecular properties which should show up in the gas phase. Since this is not the case, the low basicity of aniline (relative to ammonia) is largely due to solvent effects. Perhaps it is more appropriate to compare aniline to an amine of similar size, *i.e.*, cyclohexylamine. A preliminary determination shows that $\Delta G^\circ \simeq 11$ kcal/mol for proton transfer from cyclohexylamine to aniline. The much greater base strength of cyclohexylamine thus is in qualitative agreement with a relative electron withdrawal from the N atom in aniline.

Arnett[7] has recently proposed a simple thermodynamic cycle treatment based on gas-phase basicities which promises to lead to a meaningful separation of solvent and intrinsic molecular effects.

The above measurements were completed before we learned that similar organic bases have recently been investigated by the ion-cyclotron resonance technique.[8] The results from these measurements which were done at room temperature and pressures of around 10^{-5} Torr are in good agreement with the present findings.

(6) G. W. Wheland, "Resonance in Organic Chemistry," Wiley, New York, N. Y., 1965, pp 355–357.

(7) E. M. Arnett, "Thermodynamic Properties for Ionization and Solvation of Amines and Their Conjugate Ions," paper presented at 3rd Conference of Structure Energy Relationships, Tallahassee, Fla., Feb 17–19, 1972. A very similar cycle was used earlier for the related proton transfer $HA + B^- = A^- + BH$ [J. D. Payzant, R. Yamdagni, and P. Kebarle, *Can. J. Chem.*, **49**, 3308 (1971)].

(8) (a) M. Taagepera, W. H. Henderson, R. T. C. Brownlee, J. L. Beauchamp, D. Holtz, and R. W. Taft, results quoted at the 3rd Conference of Structure Energy Relationships, Tallahassee, Fla., Feb 17–19, 1972. (b) R. T. McIver, and R. W. Taft, ref 8a.

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Analysis of Steroid Nuclear Magnetic Resonance Spectra Using Paramagnetic Shift Reagents

Sir:

Recent publications have indicated the potential utility of the so-called shift reagents in interpreting nmr spectra of steroids.[1-3] In such studies, assignment of resonances is generally made by following changes in the chemical shifts for protons of the steroid as the concentration of the shift reagent is increased in the solution under observation. These changes in chemical shifts, $\Delta\delta$, are assumed to be linear and usually to lower field with increasing concentration of shift reagent. In most cases $\Delta\delta$ has been interpreted as arising from a contact interaction, pseudocontact interaction, or combination of the two, between the shift reagent and the substrate. In the case of pseudocontact interaction, the magnitude of $\Delta\delta$ has been assumed to be inversely proportional to the cube of the distance between the metal ion of the shift reagent and the proton giving rise to the resonance in question.[3]

Recently, our laboratory had occasion to apply this technique to an attempt to analyze the stereochemistry of several cholesterol derivatives. Before proceeding with the analysis of the derivatives, the spectrum of cholesterol itself in the presence of a shift reagent was examined. The present communication reports the findings of this experiment.

A 0.131 *M* solution of cholesterol in $CDCl_3$–TMS was prepared volumetrically. The shift reagent tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione)europium(III) was weighed into the volumetric flask before bringing the solution to final volume. The amount added was such that the final solution was 0.128 *M* in the shift reagent. Thus, the molar ratio of shift reagent to steroid, *f*, was 0.98 in this solution.

An aliquot of the solution was used to obtain its spectrum at 100 MHz.[4] After removal of the aliquot, the remaining solution was weighed and a further solution *with identical value of f* was prepared by dilution. By repeating this process, spectra of cholesterol in the presence of shift reagent were obtained for various concentrations of cholesterol, all at identical molar ratios of shift reagent:cholesterol.

Assignments of resonances were made by comparison with Hinckley's data[1] and by consideration of the expected coupling patterns for the methylene protons of ring A of cholesterol. A plot of the chemical shifts, δ, *vs.* molar concentration of cholesterol, *C*, is shown in Figure 1. It is seen that the variation of δ with *C* is not linear, even though *f* is constant throughout the entire range of *C* examined. Furthermore, it is obvious that even at the highest concentration of cholesterol investigated, the value of δ is still increasing. A similar observation of nonlinearity of δ with respect to concentration of substrate has been reported by Tomic, *et al.*, in a study of cyclopropylmethanols and the shift reagent tris(dipivalomethanato)praseodymium(III).[5]

The nature of this variation of δ with *C* is reminiscent of the variation of δ OH with concentration of alcohols in solution, which is attributed to the rapid equilibrium of hydrogen bonding in such cases.[6] If it is assumed that in the present case complex formation between substrate S and europium chelate E involves a rapid equilibrium with the complex SE (as in (1)), the equi-

$$S + E \rightleftharpoons SE \quad (1)$$

(1) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969).

(2) P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *ibid.*, **92**, 5737 (1970).

(3) C. C. Hinckley, M. R. Klotz, and F. Patil, *ibid.*, **93**, 2417 (1971).

(4) The cholesterol used in this experiment was obtained from Nutritional Biochemicals Corp., Cleveland, Ohio. The shift reagent was obtained from Alfa Inorganics, Beverly, Mass., and was kept in a sealed ampoule in a desiccator until used. Spectra were obtained on a Varian Associates HA-100-15 spectrometer using a 5-mm sample tube. In some cases spectra were recorded after several scans using a time-averaging computer. The temperature at which the experiment was performed was 37 ± 0.5°.

(5) L. Tomic, Z. Majerski, M. Tomic, and D. E. Sunko, *Chem. Commun.*, 719 (1971).

(6) J. W. Emsley, J. Feeney, and L. H. Sutcliff, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, New York, N. Y., 1965, Chapter 9, and references therein.

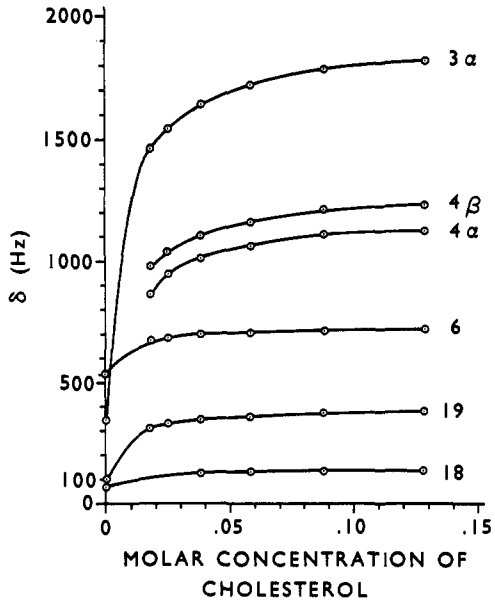

Figure 1. Observed variation of chemical shift (δ) with concentration of cholesterol in solution containing a fixed ratio shift reagent: cholesterol.

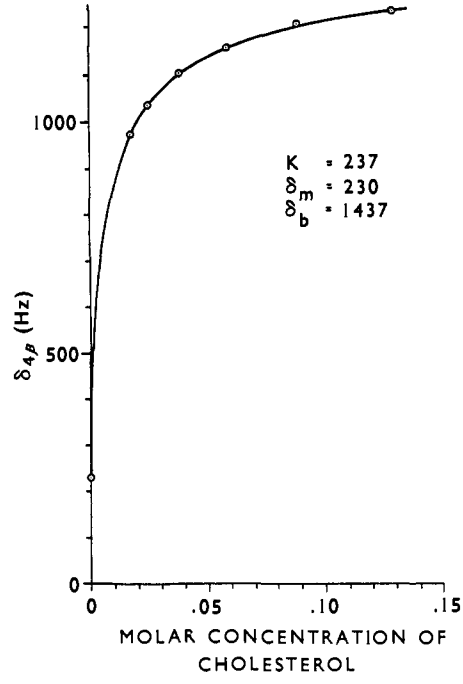

Figure 2. Comparison of experimental data for 4β proton of cholesterol with curve calculated using eq 4.

librium constant K, then an expression for the chemical shift in terms of concentration of the substrate (in the present case, cholesterol), can be derived in a manner similar to the derivation of expressions for the hydrogen-bonding systems cited above.[7] Thus, if δ_m is the chemical shift of a given proton in the uncomplexed substrate S, and δ_b is the chemical shift of that same proton in the complex SE, then the observed chemical shift δ for that proton at any *total* molar concentration (C) under conditions of rapid exchange is given by (2) where M is the molar concentration of uncomplexed substrate in the equilibrium solution. The value of M

$$\delta = (M/C)(\delta_m - \delta_b) + \delta_b \quad (2)$$

may be expressed in terms of C, K, and f. In this case (2) becomes (3). From (3) it is obvious that even when

$$\delta = \frac{(1-f)CK - 1 + (((f-1)CK + 1)^2 + 4CK)^{1/2}}{2CK} \times (\delta_m - \delta_b) + \delta_b \quad (3)$$

$f = 1$, *i.e.*, when the molar ratio of shift reagent to steroid is unity, the observed chemical shifts for cholesterol will still be a nonlinear function of the molar concentration of steroid. This is shown in (4).

$$\delta = \frac{-1 + (1 + 4CK)^{1/2}}{2CK}(\delta_m - \delta_b) + \delta_b \quad f = 1 \quad (4)$$

In order to test this approach, the chemical shift data for one proton, namely the 4β proton of cholesterol, were used with (4) to calculate a value of $K = 237$ for the equilibrium between cholesterol and the shift reagent. The error in the equilibrium constant amounted to $\pm 5.6\%$. Using a value of $\delta_m = 230$ Hz for the 4β proton (obtained from the spectrum of cholesterol in the absence of shift reagent), the value $\delta_b = 1437$ was obtained for this proton. The error in δ_b was $\pm 0.8\%$. These values, when used with the experimental concentration in (4), lead to the plot shown in Figure 2. The circles represent the experimental data which agree with the calculated within ± 2.6 Hz. We are presently preparing computer programs based upon eq 3 to analyze all of the data, which should give K as well as δ_m and δ_b for each proton whose resonances are observable by this method.

In Figures 1 and 2 the values of δ at zero concentration of cholesterol are values of the chemical shifts observed in the absence of shift reagent. These values are identical with those for δ_m, as may be seen from eq 3 when $f = 0$. For certain protons, the values of δ_m can thus be obtained by observation. However, the values of δ_b cannot be obtained by direct measurement. Hence the total paramagnetic shift, $\Delta\delta = \delta_b - \delta_m$, is also unobtainable by direct measurement. A consequence of this latter statement is that attempts to evaluate contact and pseudocontact contributions to the total paramagnetic shift based upon observations at a single concentration of substrate[3] may be erroneous. Similarly, attempts to relate the paramagnetic induced shifts to the vector distance between the proton in question and the site of the complexation[1,3,9] may also be in error if the correct values of δ_m and δ_b are not used. The present method appears to offer a means of evaluating these parameters as well as obtaining equilibrium constants for the complexation process.[10]

(7) Such an equilibrium has been proposed by both Wahl[8a] and Briggs.[8b]

(8) (a) G. H. Wahl and M. R. Petersen, *Chem. Commun.*, 1167 (1970); (b) J. Briggs, F. A. Hart, and G. P. Moss, *ibid.*, 1506 (1970).

(9) P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, **92**, 5734 (1970).

(10) A referee has kindly pointed out that Armitage, *et al.*, have presented a method for determining K and $(\delta_b - \delta_m)$ for neopentyl alcohol and *n*-butylamine using Eu(dpm)$_3$ in experiments in which the concentration of substrate is much larger than that of shift reagent, without giving a derivation. I. Armitage, G. Dunsmore, L. D. Hall, and A. G. Marshall, *Chem. Commun.*, 128 (1971).

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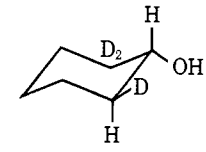
Stereochemistry of the Solvolysis of Cyclohexyl Tosylate[1]

Sir:

We wish to report that the solvolysis of cyclohexyl tosylate to give the substitution product cleanly partitions in a variety of solvents between two distinct pathways: (1) direct displacement of the leaving group to give exclusively the inverted product; (2) hydride shift to give ester at the adjacent position. No retention–racemization pathway is observed. In acetic acid[2] the reaction gives about 85% of unrearranged, inverted cyclohexyl ester, and 15% of hydride-shifted ester. In formic acid the split is about 60:40, and in trifluoroacetic acid the hydride-shift process provides at least 85% of the product.

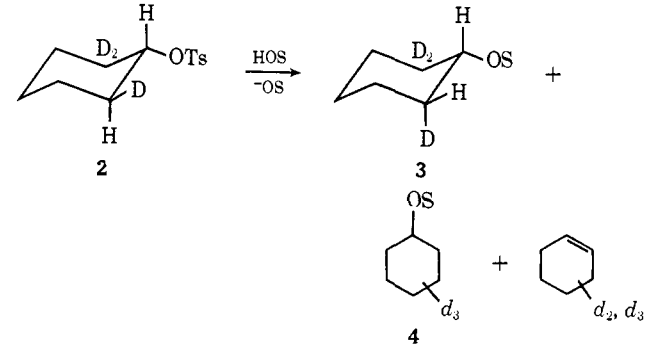
Previous stereochemical investigations of the cyclohexyl tosylate solvolysis have utilized a diastereomeric alkyl label. Thus, hydrolysis of *trans*-4-*tert*-butylcyclohexyl brosylate was found to occur with inversion, but the cis brosylate gave a mixture of retention and inversion.[3] Use of a *tert*-butyl label suffers from several serious limitations. Not only does the label distort the ground state, but, more importantly, it excludes certain transition-state geometries by steric strain. There is good evidence that the cis and trans 4-*tert*-butyl compounds solvolyze by quite different transition states.[4] Consequently, we have set out to determine the stereochemistry of the solvolysis of unsubstituted cyclohexyl tosylate,[5] since the system has no arbitrary limitations imposed on the transition state by substitution.[6]

The stereochemical label we used was a single proton vicinal to and of known relative orientation with respect to the leaving group, the remaining three vicinal protons having been replaced by deuterium (**1**). The labeling procedure was patterned after a report by Shiner and Jewett.[4] The relative orientation (trans) of the 1 and 6 protons in alcohol **1** was determined by



1

the synthetic procedure (hydroboration) and confirmed by the observed axial–axial coupling constant ($^3J_{1-6}$ = 9 Hz).[7] The alcohol was converted to the tosylate (**2**) with retention (^3J = 10.2 Hz), and this material was



2 **3**

4

solvolyzed in the various acids.[2] The ester and cyclohexene products were separated by preparative vpc.[2,8]

After acetolysis, the 1-proton resonance of the product ester was a doublet with ^3J = 3.6 Hz, corresponding to the product with inverted stereochemistry, **3**. No retained material was observed. Computer line-shape analysis showed that the amount of material with inversion corresponded to 80–85% of the product. The remainder appeared as a broadening at the base of the peaks. Inversion has been previously observed in acyclic systems,[9] but has not heretofore been documented in an unbiased, cyclic case.[6] After formolysis, the 3.6-Hz doublet (**3**) comprised 60–65% of the product, but in trifluoroacetolysis, little or no (<15%) unrearranged product was observed. If any unrearranged trifluoroacetate-*2,2,6-d*$_3$ is formed, its stereochemistry remains undetermined because it is insufficiently abundant to be analyzed by the present methods.

In each case, the remainder of the ester product consisted not of unrearranged, retained ester but of the hydride-shifted material **4**. The amount of hydride-shifted ester was directly and independently assessed by solvolysis of cyclohexyl-*1-d* tosylate and integration of the 1-proton resonance in the product ester. In this manner, we found the proportion of hydride-shifted product to be 15–20% in acetolysis, 35–40% in formolysis, and >75% in trifluoroacetolysis. These figures accurately complement those for the unrearranged, inverted product given above.

In summary, acetolysis of cyclohexyl tosylate to form the substitution product occurs almost entirely by an

(1) This work was supported by the National Science Foundation (Grant No. GP-22942) and by the Petroleum Research Fund, administered by the American Chemical Society (Grant No. 2970-AC4,5).

(2) The solvent was buffered with 1.1 equiv (with respect to the substrate) of the conjugate base. Cyclohexene is a major product in each solvent, but this report deals only with the substitution component of the reaction products. The elimination component will be discussed in the full paper.

(3) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, 77, 5562 (1955).

(4) V. J. Shiner and J. G. Jewett, *ibid.*, 87, 1382, 1383 (1965); N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc. B*, 355 (1968); M. Tichý, J. Hapala, and J. Sicher, *Tetrahedron Lett.*, 3739 (1969).

(5) W. H. Saunders, Jr., and K. T. Finley, *J. Amer. Chem. Soc.*, 87, 1384 (1965); J. L. Mateos, C. Percy, and H. Kwart, *Chem. Commun.*, 125 (1967); J. E. Nordlander, J. M. Blank, and S. P. Jindal, *Tetrahedron Lett.*, 3477 (1969).

(6) J. E. Nordlander and T. J. McCrary, Jr., have accomplished similar objectives by a different labeling procedure (*J. Amer. Chem. Soc.*, **94**, 5133 (1972)). We thank Professor Nordlander for making his results available to us prior to their publication.

(7) Measurements were made at −80° with deuterium decoupling and signal averaging on a Bruker HFX-10. At this temperature, ring reversal is slow and the resonance of the equatorial conformer can be observed separately from that of the axial conformer. We thank the National Science Foundation for an instrument grant that made possible the purchase of the signal-averaging equipment.

(8) Reaction conditions of time and temperature were chosen so that the cyclohexene was stable. Under more strenuous conditions, trifluoroacetic acid adds rapidly and formic acid slowly to the double bond, even with the buffer[2] present.

(9) H. Weiner and R. A. Sneen, *J. Amer. Chem. Soc.*, 87, 287 (1965); A. Streitwieser, Jr., T. D. Walsh, and J. R. Wolfe, *ibid.*, 87, 2682 (1965).