comparison of the same compound pairs found no additional substructures. As an example, the structures of Figure 8 represent the ten best-matching compounds found (MF11.0) by STIRS for the mass spectrum of an unknown ketal. In comparing the 45 possible structure pairs, the program found 70 substructures common to both pair members; the largest (7 symbols) substructure found was $CH_3CHCH_2OCHCH_2CH_3$ common to 2-hydroxypropyl *sec*-butyl ether and 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane. Allowing the L and Y symbols to be equivalent gave 177 such substructures. Generation of these required 0.2-s calculation time per pair using a DEC PDP-11/45 computer.

Calculation requirements increase rapidly with structural complexity, especially with polycyclic fused-ring structures. Comparison (allowing no dot-plot equivalencies) of 28 pairs of steroids required an average of 100 s. For the example of Figure 9 the program found 19 substructures to be common to the pair; those substructures containing more than five carbons, or an oxygen, are shown. When the same problem was presented to chemists, most had difficulty in identifying all of those substructures. Thus the program in its present form appears to have substantial utility for detailed comparison of molecular structures in such problems as spectral interpretation (e.g., STIRS), structure/activity correlations, and synthesis design.

Possible Improvements. Reduction in the time requirements of the program would be of obvious benefit. For molecules such as fused-ring systems which can display complex symmetries, >99% of the computational time requirements are due to the multiplicity of possible paths introduced by each tertiary and quaternary carbon atom. A high proportion of these paths are redundant, and they necessitate extensive comparisons. These problems are similar to those encountered by Lederberg and co-workers[4,17] in development of the DENDRAL cyclic structure generator. Proper heuristics should minimize the path degeneracies; the vertex graph and pruning methods of DENDRAL should substantially reduce the number of nodes to be considered.

For most structural comparison applications it is advantageous that the system be flexible in its ability to introduce structural equivalencies. In the present system this can be done conveniently for dot-plot notations, such as setting "L" (methylene) and "Y" (methine) equivalent. A "ring perception" algorithm[4,17] which would allow a particular complex substructure such as a steroid skeleton to be recognized and treated as a single node would not only shorten calculation times but could also expedite comparisons. For example, the mass spectra of meta- and para-substituted aromatic compounds usually are closely similar; thus for the STIRS application it would be advantageous if the algorithm could treat such structures as equivalent. Work on such improvements is in progress.[18,19]

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Structure Elucidation with Lanthanide-Induced Shifts. 2. Conformational Analysis of Cyclohexanecarbonitrile

Douglas J. Raber,* Milton D. Johnston, Jr.,* and Michael A. Schwalke

Contribution from the Department of Chemistry, University of South Florida, Tampa, Florida 33620. *Received April 26, 1977*

Abstract: The molecular structure of cyclohexanecarbonitrile, a conformationally mobile molecule, has been examined in solution with the aid of a lanthanide shift reagent. Nonlinear regression analysis of the NMR data obtained in the presence of $Eu(fod)_3$ afforded the bound shifts of the LS complex. A priori calculation of the bound shifts for each of the two chair conformations using a parametrized form of the pseudocontact equation results in the conclusion that cyclohexanecarbonitrile exists in the conformation with an equatorial cyano group to the extent of 54%, in good agreement with previous work. Agreement between observed and calculated shifts for this distribution of conformers is excellent.

The rigorous determination of molecular structure is a problem of great significance in chemistry and is of particular importance for the case of conformationally flexible molecules in the liquid state. However, such structural information frequently has not been readily available. While NMR spectroscopy has proven to be the most powerful tool for confor-

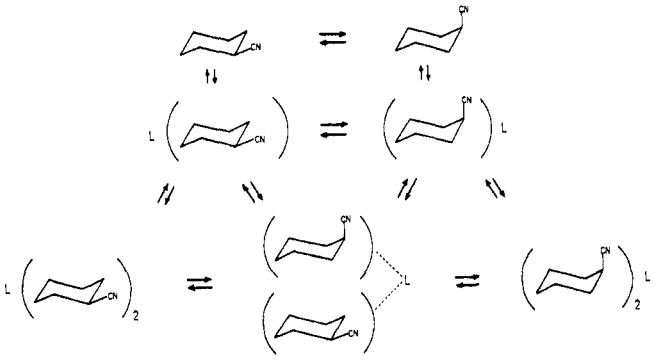

Figure 1. Conformational and complexational equilibria involving cyclohexanecarbonitrile and a lanthanide shift reagent (L).

Table I. Predicted and Experimental Bound Shifts for Cyclohexanecarbonitrile[a]

Hydrogen	Calcd[b] axial -CN	Calcd[b] equatorial -CN	Exptl[c]	Calcd[d,e] (54.5% eq -CN)
1			14.03	
Cis 2	8.25	8.25	8.47	8.25
Trans 2	5.64	8.25	7.11	7.06
Cis 3	9.40	3.17	6.09	6.00
Trans 3	3.58	4.13	3.90	3.88
Cis 4	2.52	3.40	3.03	3.00
Trans 4	3.55	2.54	3.03	3.00

[a] CCl_4 solution; shifts are in parts per million. [b] Equation 1. [c] By nonlinear regression analysis[8] of the NMR spectral data. [d] Equation 2. [e] The agreement factor for experimental vs. calculated shifts is 0.02; this corresponds to a mean deviation of 1.1%.

mational studies in solution, extrapolation of data obtained from model compounds has usually been necessary.[1,2] For example, while low-temperature NMR spectroscopy has been successful in some cases, the conformational preferences of cyclohexane derivatives typically have been derived from the chemical or spectroscopic behavior of the *tert*-butyl substituted compounds.[1-6] We report here the use of lanthanide-induced shifts to directly determine the solution structure of a conformationally mobile system, cyclohexanecarbonitrile. Not only have we been able to accurately assess the structures of the individual conformers, but we have also directly measured the position of the conformational equilibrium.

Results and Discussion

The interaction of a lanthanide shift reagent (LSR)[7] with cyclohexanecarbonitrile is not a simple one, and involves the series of equilibria illustrated in Figure 1. Since both the axial and equatorial conformers can each exist as free substrate (S), as the 1:1 complex (LS), or as the 2:1 complex (LS_2), the observed chemical shift of a given hydrogen will in fact be a weighted average of the individual shifts for all seven of the species shown in Figure 1. Consequently, the first step or our approach to this problem utilized nonlinear regression analysis[8] of the NMR spectra obtained over a series of concentrations of $Eu(fod)_3$ in CCl_4 in order to dissect observed chemical shifts into the components for S, LS, and LS_2. Since it is only the LS complex in which the metal ion has (or approximates) threefold symmetry,[9] it is that species which should be used to obtain structural information from the common form of the pseudocontact equation.

We have previously demonstrated that the bound shifts (Δ_1) of nitriles can be used for rigorous structure elucidation.[10] The dipolar form

$$\Delta_1 = \frac{k(3\cos^2\theta - 1)}{r^3} \qquad (1)$$

of the pseudocontact equation[11] was parametrized for a series of alkyl-substituted adamantanecarbonitriles with $Eu(fod)_3$ to yield a value of 760 for k and a Eu–N bond distance (R_{LN}) of 1.89 Å.[10] We are therefore now in a position to evaluate a proposed structure by a priori calculation of the bound shift for each hydrogen in the molecule (in the present case the weighted average of the bound shifts for each conformation must be considered). These calculated values may then be compared with the experimentally obtained bound shifts and statistical analysis may be used to evaluate the validity of the proposed structure.

A particularly important point must be considered when utilizing lanthanide shift reagents for the analysis of conformationally mobile systems:[2] does complexation perturb the conformational equilibrium? The bound shifts provide information about the conformational equilibrium of the LS complex, and the results can be extended to the free substrate only if the equilibrium constant is unaffected by complexation. We have evaluated this problem by careful observation of the coupling pattern exhibited by the hydrogen α to the cyano group. The observed pattern is intermediate between those observed for *cis*- and *trans*-4-*tert*-butylcyclohexanecarbonitrile,[12] indicating a mixture of the two chair conformations in which that hydrogen is equatorial and axial, respectively. If complexation with $Eu(fod)_3$ were to cause a substantial increase in the effective bulk of the cyano group, one would expect an increase in the conformer with an equatorial -CN (axial α-H) and a consequent increase in the width of the observed multiplet for that α hydrogen.[13]

Linear regression analysis of the width at half-height of the α-hydrogen resonance vs. LSR concentration clearly shows that no such change takes place: the slope of the best fit line is zero within experimental error. Consequently, the conformational equilibrium for free cyclohexanecarbonitrile must be essentially the same as that for the LS complex.[14] This is not surprising since the cyano group is known to have a very small steric requirement,[3] and location of the $Eu(fod)_3$ moiety further along the C–C≡N array should place it in a position which is unlikely to suffer significant nonbonded interaction with any other atom in the molecule.[15]

Calculation of the bound shifts for both conformations was carried out with eq 1 using $k = 760$ and $R_{LN} = 1.89$ Å as determined previously[10] and using geometries determined for standard bond lengths and bond angles.[16] These results, together with the experimental results, are reported in the first three columns of Table I.

The position of the conformational equilibrium was next determined by independent evaluation of each hydrogen for which the bound shifts of the two conformations differ by 1 ppm or more. Since the sum of the two mole fractions of the molecules with equatorial and axial cyano groups is unity, the equation

$$\Delta_{1[obsd]} = (n_{eq})\,\Delta_{1[eq]} + (1 - n_{eq})\,\Delta_{1[ax]} \qquad (2)$$

can be solved for the former. This procedure leads to the conclusion that in CCl_4 at 30 °C cyclohexanecarbonitrile exists in the conformation with an equatorial cyano group to the extent of 54.5 ± 3.1%. Evaluation of the available literature data[3,4] (based on low-temperature NMR work and on equilibration of the 4-*tert*-butylcyclohexanecarbonitriles) yields a value of 57.9 ± 1.7% for the equatorial conformer, and the two methods agree within experimental error.

Armed with the knowledge of the populations of the two conformers, we were able to utilize eq 2 for the prediction of the bound shifts for each[17] of the hydrogens in the molecule, and these are reported in the last column of Table I. Comparison of these predicted values with those obtained from

experiment leads to an agreement factor[18] of 0.02. This compares favorably with the agreement factors (≃0.01) we obtained previously[10] for conformationally restricted adamantane derivatives; other workers have reported agreement factors of 0.04–0.06 for nitriles.[18b] If one recalls that the present results are obtained from the parametrized form of the pseudocontact equation (eq 1) and do not involve a minimization process, the agreement factor of 0.02 for cyclohexanecarbonitrile becomes even more impressive.

The determination of bound shifts and the use of a parametrized form of the pseudocontact equation employing chemically reasonable bond lengths and angles has allowed us to overcome many of the obstacles and uncertainties encountered in previous efforts at utilizing lanthanide-induced shifts for conformational analysis.[5-7,19-21] Consequently, the results reported here further emphasize the value of lanthanide shift reagents for rigorous structure elucidation in the liquid state and demonstrate that structure determination of conformationally mobile systems can be accomplished with a high degree of accuracy.

Experimental Section

Cyclohexanecarbonitrile[22] was prepared by conversion of cyclohexanecarboxylic acid (Aldrich, no. 10,183-4) to the acid chloride and formation of the amide (concentrated aqueous ammonia) followed by dehydration ($POCl_3$). The sample used in this study was purified by preparative gas chromatography (Carbowax 20M).

Tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octadionato)-europium (Aldrich, Resolve-Al EnFOD, no. 16,093-8) was sublimed (160–165 °C, 0.05 Torr) and stored in a vacuum desiccator over P_2O_5 for at least 48 h prior to use.

Nuclear magnetic resonance spectra were obtained using Varian EM-360 and A-60 spectrometers. All spectra were recorded at either 600 (EM-360) or 500 Hz (A-60) sweep widths. Chemical shifts were measured relative to internal Me_4Si and sweep widths were calibrated with an external audio oscillator. When the widths of spectra exceeded the sweep widths, offset spectra were recorded and peak positions were measured relative to a Me_4Si audio sideband.

Shift reagent runs utilized the incremental dilution method[8] in which a CCl_4 solution containing both shift reagent (0.6 M) and the nitrile (0.2 M) was successively diluted with a 0.2 M CCl_4 solution of the nitrile. The precise relative concentrations of shift reagent and nitrile were determined gravimetrically, and spectra were recorded for a total of 25 different concentrations of shift reagent.

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Total Synthesis of (±)-Kadsurin

Miljenko Mervič and Eugene Ghera*

Contribution from the Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel. *Received March 4, 1977*

Abstract: The total synthesis of (±)-kadsurin has been achieved in 13 steps starting from 6-bromomyristicinaldehyde (**5**) and 3,4,5-trimethoxybenzyltriphenylphosphonium bromide (**6**). In the key step the 2,2′-bis(bromoacyl)-1,1′-biaryl **16** is cyclized intramolecularly to the diones **17** and **18.** Compound **17** was converted to kadsurin by a series of highly selective steps. Compound **18,** which has the unnatural biaryl configuration, could be also converted to kadsurin by the thermal isomerization of hydroxy ketone **23** to hydroxy ketone **19.**

Kadsurin (**1**) and kadsurarin (**2**) are the constituents of stem extracts from *Kadsura japonica,* used by the Taiwan population as a versatile therapeutic agent.[1] The dibenzocyclooctadiene skeletal structure and the gross substitution pattern classify these compounds as schizandrin-type lignans[2] which are usually characterized by an interesting biological activity related mainly to the central nervous system.[3] Several reports on their pharmacological evaluation are available.[4]