Structure Elucidation with Lanthanide-Induced Shifts. 3. Acyclic Aliphatic Nitriles[1]

Douglas J. Raber,* Milton D. Johnston, Jr.,* Joseph W. Perry, and George F. Jackson III[2]

Department of Chemistry, University of South Florida, Tampa, Florida 33620

Received May 20, 1977

The structures of a series of acyclic aliphatic nitriles have been studied with lanthanide-shift reagents. The experimental values of the bound shifts induced by Eu(fod)$_3$ are compared with the values obtained by a priori calculation for a proposed structure using a parameterized form of the pseudocontact equation. The agreement between predicted and experimental data allows assessment of the validity of the proposed structure. The method permits direct determination of conformer populations, as well as of gross molecular structure.

Knowledge of the structure of organic molecules is of considerable importance in terms of understanding chemical reactivity, particularly in the case of conformationally flexible molecules in solution. While diffraction techniques can afford accurate and detailed information about molecular structure, they are not applicable to the liquid state. The most powerful tool for organic chemists has been NMR spectroscopy,[3] although many difficulties are still encountered with this method. For example, conformational analysis frequently has relied on the interpretation of coupling constants, using empirical relationships to estimate the values of coupling constants of the individual conformers.[4] We report here the successful use of lanthanide-induced shifts (LIS) to evaluate the structures in solution of the series of aliphatic nitriles 1–7 (Table I).

Results and Discussion

We have previously shown[1,5] that the bound shifts[6] of nitriles are accurately correlated with molecular structure according to the dipolar form of the pseudocontact equation (eq 1). Parameterization of eq 1 for a series of substituted adamantanecarbonitriles with Eu(fod)$_3$ in CCl$_4$ afforded[5] a value of 760 for k and a nitrogen–carbon bond length (R_{LX}) of 1.89 Å. With these parameters in hand it is possible to evaluate a proposed structure by a priori prediction of the bound shifts (Δ_1) with eq 1 followed by comparison with the experimentally determined LIS. A point of particular importance here is that, unlike much of the previous work[7–9] in this area, we are not adjusting the parameters of eq 1 or structural parameters such as R_{LX} in order to obtain the best fit between relative induced shifts and the experimental data; rather, eq 1 is used to predict the absolute magnitudes of the LIS which can be directly compared with experimental values.

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

Bound shifts [with Eu(fod)$_3$ in CCl$_4$] for the series of nitriles 1–7 were calculated with eq 1 using $k = 760$, $R_{LX} = 1.89$ Å, and using standard bond lengths and angles.[10,11] The resulting bound shifts for hydrogens in each of the possible orientations corresponding to a stable conformation are illustrated in the composite molecular structure of Figure 1. For hydrogens in the β and γ positions, several nonequivalent locations (with respect to the cyano group) are possible, and the actual shift for a given hydrogen will be the weighted average of the shifts for each of the individual conformers. In cases (e.g., methyl-group rotation) where the conformers have the same energy, the weighting will be the same for each and the calculated Δ_1 will be the simple arithmetic mean of the individual values. This is the situation for the methyl groups (β-hydrogens) of 2–4; similarly, the calculated Δ_1 for the methyl groups (γ-hydrogens) of 7 is the average of the values for the nine possible orientations shown in Figure 1.

The situation is somewhat more complicated for butyronitrile (**5**) and isovaleronitrile (**6**) where the different conformations (Figure 2) are not equivalent. As shown in Figure 2, each of these compounds may exist in either conformation I (which possesses a plane of symmetry) or conformation II (which is actually a mixture of enantiomers IIa and IIb). Since the sum of the mole fractions of the conformers is unity and the mole fractions of enantiomers IIa and IIb must be equal in an achiral environment, the conformational equilibrium is related to the lanthanide-induced shift of a given hydrogen by eq 2.

$$\Delta_{1[\text{obsd}]} = (n_{\text{I}})(\Delta_{1[\text{I}]}) + \frac{1}{2}(1 - n_{\text{I}})(\Delta_{1[\text{IIa}]}) + \frac{1}{2}(1 - n_{\text{I}})(\Delta_{1[\text{IIb}]}) \qquad (2)$$

Using the experimental bound shifts for the γ (methyl) hydrogens[12] and the values for $\Delta_{1[\text{I}]}$, $\Delta_{1[\text{IIa}]}$, and $\Delta_{1[\text{IIb}]}$ calculated from eq 1 (i.e., the averages of the values shown for the three hydrogens of each methyl group in Figure 1), eq 2 yields direct determinations of the conformational equilibria of **5** and **6**. These are summarized in Table III together with estimates based on analysis of the H$_\alpha$–H$_\beta$ coupling constants. The results obtained from these two methods are in quite good agreement. A crucial point here is that we have measured the conformational equilibrium of the LS complexes and have extended the results to the free substrates; this requires that the conformational equilibrium I $\rightleftarrows$ II be unaffected by complexation. While there are literature reports indicating that complexation can alter the conformational equilibrium for some functional groups,[13] nitriles appear to be much less sensitive to such perturbations, since the lanthanide ion must be located on an extension of the linear C—C≡N array and is unlikely to suffer significant steric interaction with the remainder of the organic moiety.[1,14] In any event, the magnitudes of the H$_\alpha$–H$_\beta$ coupling constants for **5** and **6** are unaffected by complexation,[15] thus demonstrating that the relative populations of I and II are essentially the same for both the complexed and free substrate.

Having determined the relative conformer populations of nitriles **5** and **6**, it was possible to predict the bound shifts of each hydrogen in compounds **1–7**.[19] As discussed above, the weighting of different conformations was equal for **1–4** and **7**; for **5** and **6**, eq 2 was employed using the conformation populations determined from the LIS data for the γ-hydro-

Table I

RC≡N	RCH$_2$C≡N	R
1	**2**	CH$_3$
2	**5**	C$_2$H$_5$
3	**6**	*i*-C$_3$H$_7$
4	**7**	*t*-C$_4$H$_9$

0022-3263/78/1943-0229$01.00/0

Table II. Conformer Populations of Butyronitrile (5) and Isovaleronitrile (6)

	Δ_I, γ-Hydrogens[a]			$J_{\alpha\beta}$[b]		
	n_I	n_{II}	ΔG, kcal	n_I	n_{II}	ΔG, kcal
5	0.45	0.55	−0.12	0.54	0.46	0.10
6	0.24	0.76	−0.69	0.25	0.74	−0.65

[a] Populations calculated using eq 2 (see text). [b] *Coupling constants for the individual conformers were estimated from the* data of A. A. Bothner-By [*Adv. Magn. Reson.*, 1, 225–227 (1965)]; for **5**, J_{180} = 12.85, J_{60} = 4.0 Hz; for **6**, J_{180} = 12.0, J_{60} = 3.7 Hz.

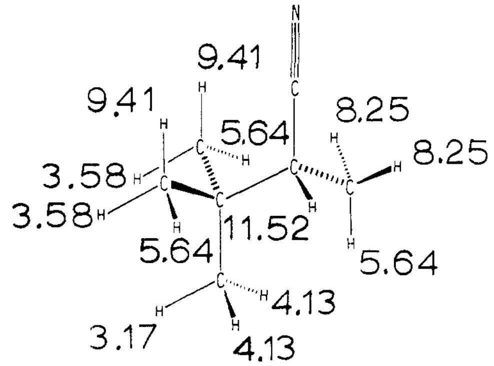

Figure 1. Composite structure illustrating the various possible stable orientations of hydrogen atoms in aliphatic nitriles with chain lengths of four or fewer carbons. The bound shifts shown are values predicted for each of the hydrogen atoms in a static conformation having standard bond lengths and angles.

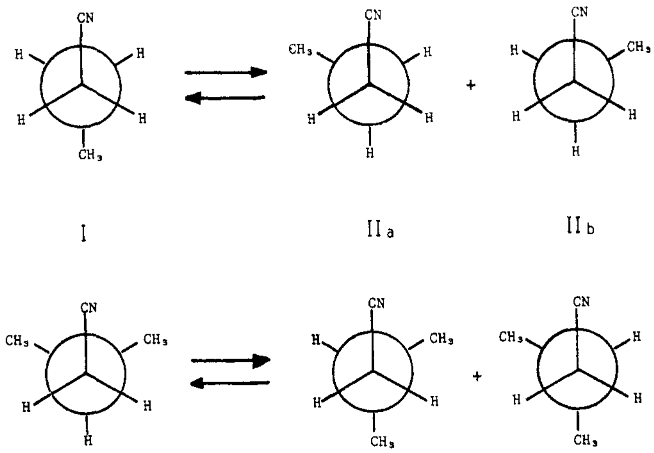

Figure 2. Conformational equilibria of butyronitrile (**5**) (top) and of isovaleronitrile (**6**) (bottom).

gens. The results of these calculations together with the experimental LIS data are presented in Table III.

Clearly, the agreement between observed and calculated values of bound shifts is quite good. The agreement factors are comparable to those reported by previous workers[8,9] who have treated k and R_{LX} as variable parameters in order to minimize disagreement between calculated and observed shifts. Even if the data for α-hydrogens (for which the calculation of Δ_I is not totally a priori because of the inclusion of a contact shift correction) are excluded, the mean relative error increases only from 0.039 to 0.056. The determination of conformer populations by this method offers an excellent alternative to other techniques based on vicinal coupling

Table III. Calculated and Experimentally Observed Values of Lanthanide-Induced Shifts (Δ_I) for Aliphatic Nitriles[a]

Substrate	Registry no.	Position	Calcd[b]	Exptl[c]	calcd − obsd[d] / obsd	Agreement[e] factor
1 $CH_3C{\equiv}N$	75-05-8	α	13.19	13.16 ± 0.33	0.002	0.002
2 $CH_3CH_2C{\equiv}N$	107-12-0	α	13.19	12.99 ± 0.04	0.015	0.053
		β	7.38	6.64 ± 0.01	0.113	
3 $CH_3\overset{CH_3}{\overset{\vert}{C}}HC{\equiv}N$	78-82-0	α	13.19	13.17	0.002	0.026
		β	7.38	7.00	0.054	
4 $CH_3\underset{\underset{CH_3}{\vert}}{\overset{\overset{CH_3}{\vert}}{C}}C{\equiv}N$	630-18-2	β	7.38	7.47 ± 0.18	0.012	0.012
5 $CH_3CH_2CH_2C{\equiv}N$	109-74-0	α	13.19	12.91	0.022	0.054
		β	7.53	6.75	0.116	
		γ	5.12	5.12	0.000	
6 $CH_3\overset{CH_3}{\overset{\vert}{C}}HCH_2C{\equiv}N$	625-28-5	α	13.19	13.16	0.002	0.036
		β	7.62	7.05	0.081	
		γ	5.30	5.30	0.000	
7 $CH_3\underset{\underset{CH_3}{\vert}}{\overset{\overset{CH_3}{\vert}}{C}}CH_2C{\equiv}N$	3302-16-7	α	13.19	14.02	0.059	0.061
		γ	5.41	5.82	0.070	

[a] Shifts are reported in ppm. [b] Calculated using eq 1. The shifts for the α-hydrogens also include a contact shift contribution of 1.67 ppm. [c] Errors reported are standard errors for multiple determinations. [d] Relative error. The mean relative error is 0.039 for all data; if the data for the α-hydrogens is excluded, the mean relative error is 0.056. [e] The mean agreement factor for all compounds is 0.035.

constants. While the approximations involving "standard" geometries and lack of conformational perturbation by the shift reagent undoubtedly place some limitations on the accuracy of the method, we believe these limitations are minor. For example we conclude from the data in Table II that the populations of the anti and gauche (I and II) conformations of butyronitrile are nearly equal; the agreement factor calculated for butyronitrile existing to the extent of 75% in the anti conformation is 0.090, a value substantially larger than any of those reported in Table III. Thus, the present work effectively demonstrates that the use of bound shifts together with a chemically reasonable parameterization of the pseudocontact equation allows lanthanide-induced shifts to be used for rigorous and accurate evaluation of the molecular structures of conformationally mobile molecules.

Experimental Section

Nitriles. Acetonitrile (**1**) was obtained from Fisher Scientific Co. (catalog no. A-21) and was dried over Linde 4-Å molecular sieves prior to use. Propionitrile (**2**) was obtained from Eastmen Organic Chemicals (catalog no. 528) and was dried over Linde 4-Å molecular sieves prior to use. Isobutyronitrile (**3**), trimethylacetonitrile (**4**), and butyronitrile (**5**) were all purchased from Aldrich Chemical Co. (catalog no. I-1,560-2, T-7200-1, and B-10,380-2, respectively) and were each dried over Linde 4-Å molecular sieves prior to use. Isovaleronitrile (**6**) was purchased form K &K Chemicals and was purified by preparative gas chromatography (Carbowax 20M). *tert*-Butylacetonitrile (**7**)[20] was prepared from the corresponding acid chloride (ALDRICH NO/ B-8,880-2) via conversion to the amide followed by dehydration with P_2O_5 according to the procedure of Kent and McElvain for isobutyronitrile.[21]

Tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium (Aldrich, Resolve-Al EuFOD™, no. 16,093-8) was sublimed (160–165 °C, 0.05 Torr) and stored in a vacuum dessicator 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 side band.

Shift reagent runs utilized the incremental dilution method[6] 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 concentrations of shift reagent and nitrile were determined gravimetrically for each sample, and spectra were recorded for a total of 25 different concentrations (including zero) of shift reagent.

Acknowledgments. This work was supported by a grant from the Research Corporation (to M.D.J.) and in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—Eu(fod)$_3$, 17631-68-4.

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(12) Use of the bound shifts for the β-hydrogens does not afford satisfactory results; for example, a negative mole fraction (−0.15) is calculated for conformation I of **5**. We believe that this is a result of deviation from the "standard" geometries[10] assumed for our calculations. Small distortions would result in the greatest errors when the hydrogen is relatively close to the lanthanide ion; such is the case for two of the three possible orientations of a β-hydrogen (cf. Figure 1).
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(15) For both **5** and **6**, plots of $J_{\alpha\beta}$ vs. [Eu]/[R–CN] are horizontal lines having slopes of zero within experimental error (linear-regression analysis).
(16) That butyronitrile (**5**) exists to the extent of approximately 50% in conformation II (which appears to have increased steric interactions relative to I) might initially seem surprising. However, it should be recalled that the steric requirements of a cyano group are small[17] and that for both **5** and **6** conformation II (a *d*, *1*-pair) is favored by an entropy term of *R* ln2.[18]
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