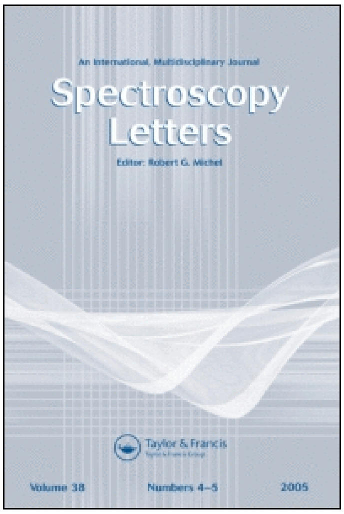

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Structure Elucidation with Lanthanide Induced Shifts. 14. Structural Effects on Equilibria between Nitriles and EU(fod)$_3$

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STRUCTURE ELUCIDATION WITH LANTHANIDE INDUCED SHIFTS. 14.
STRUCTURAL EFFECTS ON EQUILIBRIA BETWEEN NITRILES AND EU(FOD)$_3$.[1]

Key Words: Lanthanide Shift Reagents, NMR Spectra, Association Constants.

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INTRODUCTION

In recent years lanthanide shift reagents have become increasingly valuable as aids in the analysis of organic structures by nmr spectroscopy.[2] They can be used qualitatively in order to simplify nmr spectra, and the lanthanide induced shifts can also be used quantitatively for the mathamatical analysis of a proposed structure.[3-6] Whatever the particular case may demand, these reagents can be utilized most effectively when the equilibria between shift reagent and substrate are well understood. We have previously reported[7] the binding abilities of a variety of functional groups with Eu(fod)$_3$, and we have also discussed[8] the effects of structural variation on the corresponding equilibria of ketones. We now consider structural effects on the association equilibria for a variety of nitriles with Eu(fod)$_3$ in CCl$_4$.

RESULTS AND DISCUSSION

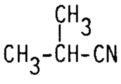
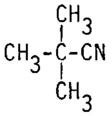
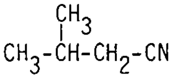
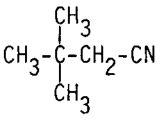
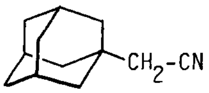
The lanthanide induced shifts for nitriles 1-32 with Eu(fod)$_3$ in CCl$_4$ were measured over a range of lanthanide:substrate ratios, and nonlinear regression analysis by the method of Shapiro and Johnston[9] afforded the equilibrium constants. Values of K_1, the association constant for the 1:1 complex, are reported in Tables 1-4.

Although nitriles 1-32 encompass a wide range of structural changes, the variation in the equilibrium constants is relatively small. The largest and smallest association constants (for 13 and 23, respectively) differ by a factor of 200, but if these two data points are excluded the range (bounded by the constants for 9 and 25) is decreased to a factor of only 22. Nearly all of the nitriles studied therefore exhibit free energies of association with Eu(fod)$_3$ in CCl$_4$ which fall in the range of -2.1 to -4.0 kcal/mol.

Our earlier studies[7,8] as well as those of Rackham[10-18] have indicated that both steric and electronic effects play important roles in determining the magnitude of the association constants. Steric effects were found to be particularly important with ketones when the position α to the carbonyl group is quaternary.[8] On the other hand, we previously observed that the coupling pattern exhibited by the proton α to the cyano group in cyclohexanecarbonitrile (15) is unchanged upon addition of Eu(fod)$_3$, and this indicated that complexation does not significantly perturb the conformational equilibrium.[19] This in turn suggested that

TABLE 1

Association Constants (K_1, M^{-1}) for Acyclic Nitriles with $Eu(fod)_3$ in CCl_4.

	Compound	Equilibrium Constant[a]	σ^{*}[b]
1	$CH_3\text{-}CN$	52 ± 3 (3)	0.00
2	$CH_3\text{-}CH_2\text{-}CN$	154 ± 57 (3)	-0.10
3	$CH_3\text{-}CH_2\text{-}CH_2\text{-}CN$	59	-0.12
4	 $CH_3\text{-}\overset{CH_3}{C}H\text{-}CN$	251	-0.20
5	 $CH_3\text{-}\overset{CH_3}{\underset{CH_3}{C}}\text{-}CN$	134 ± 34 (5)	-0.30
6	 $CH_3\text{-}\overset{CH_3}{C}H\text{-}CH_2\text{-}CN$	85	-0.14
7	 $CH_3\text{-}\overset{CH_3}{\underset{CH_3}{C}}\text{-}CH_2\text{-}CN$	155	-0.16
8		289	-0.19

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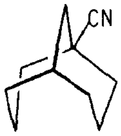
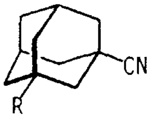
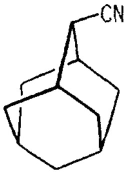
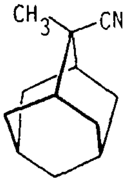
[a] Errors are standard errors for multiple determinations; the number of determinations is given in parentheses. [b] Values for σ^{*} constants were calculated using the following contributions: α-alkyl, -0.10; β-alkyl, -0.02; γ-alkyl, -0.01; α-phenyl, +0.20.

TABLE 2

Association Constants (K_1, M^{-1}) for Bridged Nitriles with Eu(fod)$_3$ in CCl$_4$.[a]

Compound		Equilibrium Constant	σ*
9		750	-0.40
10		484 ± 135 (7)	-0.42
11[b]		440 ± 120 (8)	-0.43
12		195	-0.32
13		3802	-0.42

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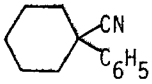
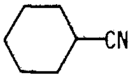
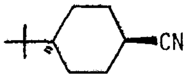
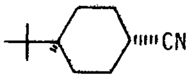
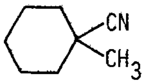
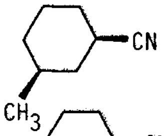
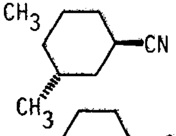
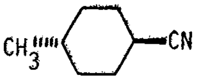
[a] See footnotes to Table 1. [b] See Ref. 3 for alkyl groups (R).

TABLE 3

Association Constants (K_1, M^{-1}) for Cyclohexanecarbonitriles with Eu(fod)$_3$ in CCl$_4$.[a]

Compound		Equilibrium Constant	σ^{*b}
14		38	-0.06
15		328	-0.26
16		115 ± 29 (3)	-0.26
17		97	-0.26
18		336 ± 190 (2)	-0.36
19		57	-0.27
20		174	-0.27
21		102	-0.26
22		41	-0.26

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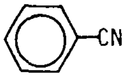
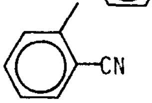
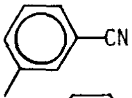
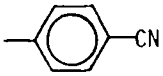
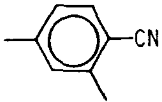
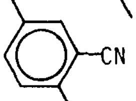
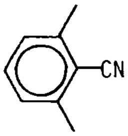
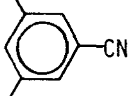
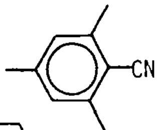
[a] See footnotes to Table 1.

TABLE 4

Association Constants (K_1, M^{-1}) for Aromatic Nitriles with Eu(fod)$_3$ in CCl_4.

Compound	Equilibrium Constant[a]	σ[b]
23 	19 ± 6 (3)	0.00
24 	51	-0.17
25 	34 ± 1 (2)	-0.07
26 	57 ± 3 (2)	-0.17
27 	120 ± 9 (2)	-0.34
28 	41	-0.24
29 	70	-0.34
30 	68	-0.14
31 	68	-0.51
32 	71	-0.20

[a] See footnote 1 of Table 1. [b] Values for σ constants were calculated using the following contributions: o, p methyl, -0.17; m methyl, -0.07; p tert-butyl, -0.20 (see ref. 20).

steric interactions between the $Eu(fod)_3$ moiety and the cyclohexane ring are small, even in the axial conformation. Steric effects therefore might well be less important for nitriles than for ketones. The C-C-N distance of a nitrile is larger than the analogous C-O distance of a ketone by about 1.4 Å, and the $Eu(fod)_3$ group would be located further from the substrate moiety by a corresponding distance.

If the preceding analysis is correct, than the variation in association constants observed for nitriles 1-32 must be a consequence primarily of electronic rather than steric effects. In order to test this idea we have plotted the logarithm of the association constants against the σ^* and σ substituent constants[20,21] for the aliphatic and aromatic nitriles, respectively (Figures 1 and 2). Although there is considerable scatter in the plots, it is nevertheless clear that there is a correlation between log K_1 and the appropriate substituent constant, σ^* or σ. These substituent constants are based on electronic rather than steric effects, and our results support the hypothesis that steric effects are relatively small for the association equilibria of nitriles with shift reagents. The experimental uncertainty in the equilibrium constants corresponds to about 0.2 log units,[7] and this compares favorably with the standard deviations of 0.3 and 0.2 in log K_1 calculated by by linear regression analysis of the data plotted in Figures 1 and 2, respectively.

The greatest deviations from the least squares lines of Figures 1 and 2 do not correspond to unfavorable steric interactions.

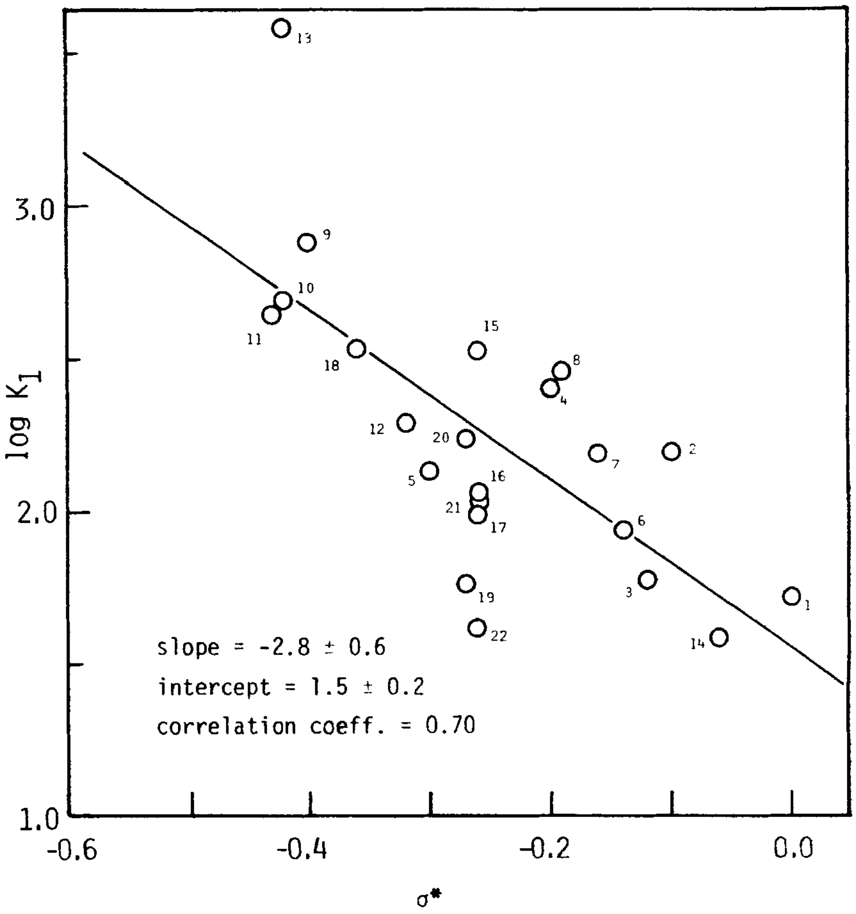


Figure 1. A Plot of log K_1 vs. σ* for Aromatic Nitriles with $Eu(fod)_3$ in CCl_4.

Thus the point for 13 in Figure 1 falls above the line, whereas steric interference resulting from methyl substitution (relative to 12) would have resulted in an equilibrium constant smaller than that corresponding to the least squares line. The point in Figure 2 for nitrile 31 lies below the line as would be expected for unfavorable steric interactions involving the two *ortho* methyl

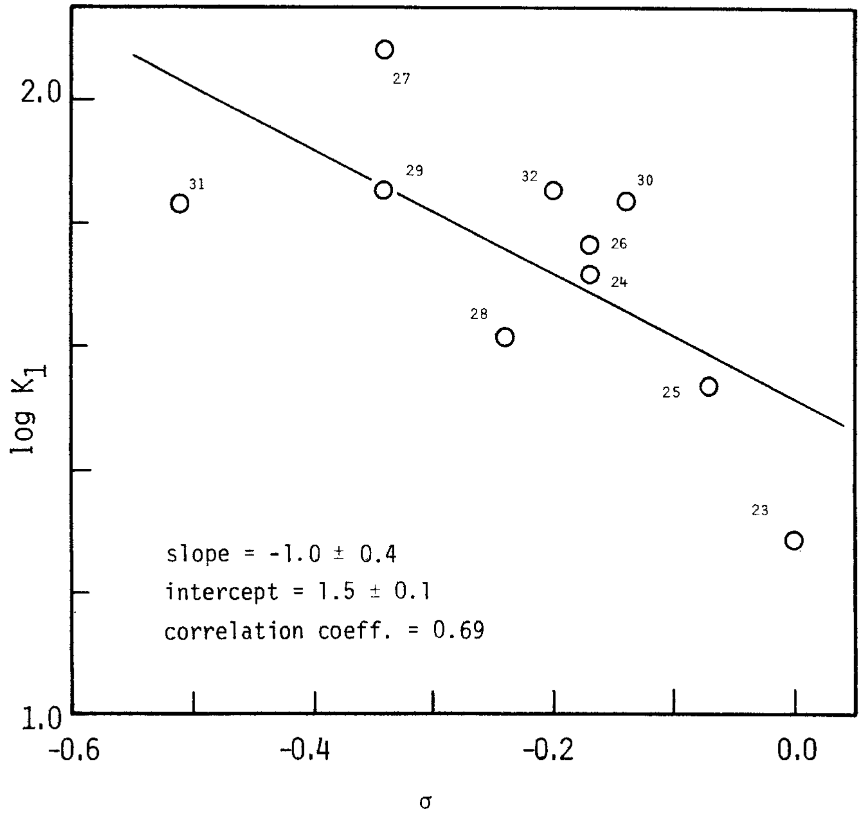
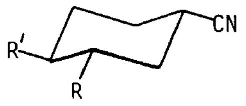
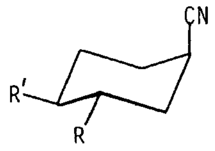


Figure 2. A Plot of log K_1 *vs.* σ for Aromatic Nitriles with $Eu(fod)_3$ in CCl_4.

groups. But this is clearly not the source of the deviation for **31**, since **29** (which has the identical substitution pattern at the *ortho* positions) falls precisely on the least squares line. Similarly, the points for **19** and **22** fall well below the line in Figure 1, but these compounds both exist preferentially in the conformation with the cyano group equatorial.[22] If steric repulsions between the shift reagent and substrate moieties were important, the points for **20** and **21** (axial CN) should have fallen below the line.





19 (R = CH_3 R' = H) **20**
22 (R = H R' = CH_3) **21**

We believe that the large deviations observed for cases such as **13**, **19**, **22** and **31** reflect a combination of experimental error in determination of the equilibrium constants[7] and the approximations used in calculating the substituent constants for these derivatives. Overall we find no evidence for unfavorable steric interactions on the complexation with $Eu(fod)_3$ with any of the nitriles studied, and we conclude that the variation in the association constants results almost entirely from electronic effects.

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21. The σ^* constants for nitriles 1-22 were calculated on the basis of the appropriate contributions from the alkyl groups on the α, β and γ carbons; cf. ref. 20, p. 601. The σ constants for the aromatic nitriles were calculated by considering the contributions from each alkyl group to be additive. Since the cyano group has axial symmetry, an ortho substituent is not expected to alter the interaction between the cyano group and the aromatic ring. Consequently the σ con-

stant for a _para_ methyl was used for both _ortho_ and _para_ substituents.

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