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ROTATIONAL BARRIERS IN N,N-DIETHYLBENZAMIDES: SUBSTITUENT AND SOLVENT EFFECTS

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Abstract: The barrier to rotation about the C-N bond in a series of substituted N,N-diethylbenzamides has been calculated via total bandshape analysis of the exchanging alkyl carbons in the ^{13}C-NMR spectra in four solvents: C_6D_6, $CDCl_3$, CD_3CN and CF_3CH_2OD. A linear free energy relationship between the Hammett substituent parameters and the overall activation barrier is apparent for the p-substituted compounds. Resonance effects contribute more heavily than inductive effects and show increasing importance as solvent coordination ability increases. Substituents in the meta-position show a reduced effect. Solvents have a pronounced effect on the barrier. The free energy of activation for any given compound increases in the order: $C_6D_6 < CDCl_3 \approx CD_3CN < CF_3CH_2OD$. This trend is discussed in terms of the electrophilic character of the solvent.

Introduction: Certain N,N-diethylbenzamides are known neuroactive agents. For example, N,N-diethyl-m-toluamide and related compounds are currently being studied as effective topical mosquito repellants,[1] evidently acting on the insect's central nervous system (CNS). N,N-diethyl-4-hydroxy-3-methoxybenzamide (ethamivan) was once used as a temporary measure to correct acute respiratory insufficiency in patients with chronic obstructive pulmonary disease.[2] The N,N-diethylbenzamides are believed to function by interacting with membrane protein receptors. Electrostatic and hydrogen bonding interactions are suspected to play a major role in drug-protein interactions.[3] Solvent is also believed to play an important role. An understanding of the relationship between internal motions in these compounds as well as solute:solvent interactions, which will dictate the "effective solution structure" of such compounds, is critical to our understanding of how these molecules interact specifically with their protein receptors. The objective of the current study is to examine the degrees of rotational freedom about the amide bond in a wide range of substituted N,N-diethylbenzamides in several solvents. As all of the compounds examined in this study are structurally related to known neuroactive molecules, this study may provide information which will ultimately help us understand the manner in which this class of molecules interact with nervous system proteins.

Initial work in our laboratories on the measurement of barriers to rotation about the amide bond in neuro-active molecules focused on nikethamide (N,N-diethylnicotinamide), another CNS stimulant.[4] Using a set of nicotinamide analogues (N,N-dimethyl, -dipropyl and -piperidinyl), the effect of alkyl substitution on rotational energy barriers was determined in a number of solvents. The basic conclusions were the following:

(1) alkyl substitutions had only a modest effect on free energy of activation and the effects were not regular in a particular solvent, and

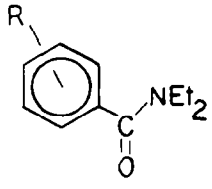
(2) the free energy of activation consistently increased for all compounds examined as the solvent polarity and propensity for hydrogen bonding increased.

The solvents used in the nikethamide study were (in order of decreasing polarity, based on dielectric constants) D_2O, CH_3OD, CH_3CH_2OD and $CDCl_3$. When rotational barriers in ethamivan were measured[5] and compared with the barriers in nikethamide in several solvents, it became obvious that the nature of the aromatic ring attached to the amide bond played a critical role in determining the free-energy of activation barrier. That is, the free-energy of activation for ethamivan was less than that for nikethamide in all of the above solvents, by about 1.0 kcal/mol. Jackman and co-workers[6] reported the results of an extensive study on substituted dimethylbenzamides in acetonitrile solution. Their findings showed substantial correlation between the ring substituents and the C-N rotational barrier. In addition, they indicated that the barrier to rotation in benzamide itself was solvent dependent, although no conclusions were drawn regarding the relative importance of the solvents polarity compared to its hydrogen bonding ability. Sattler and Schunack[7] have also found that the nature of the aromatic ring plays an important role in dictating the height of thermodynamic activation energy barriers. They found that methylation of the pyridyl ring of nikethamide (at C-2 and C-4) increases $\Delta G^{\ddagger}$, relative to unsubstituted nikethamide, by about 2 kcal/mol. The results of these studies, as well as our own nikethamide/ethamivan comparative study, provided the stimulus for the current work in which rotational barriers are measured on a series of N,N-diethylbenzamides (closer to the biologically active compounds than the previously studied dimethyl analogues). The nature and position of substituents on the aromatic ring have been systematically varied and all compounds have been studied in the four solvents used. The objective is to understand more completely the relative contributions of resonance and inductive effects in determining the thermodynamic activation parameters for rotation about the amide bond and to more firmly establish the cause of the observed solvent dependancy of the barrier.

RESULTS AND DISCUSSION

^{13}C-NMR {H} spectra were obtained for N,N-diethylbenzamide and its m- and p-F, -Me, -Cl, -C≡N and -NO_2 derivatives in four solvents; C_6D_6, $CD_3C{\equiv}N$, $CDCl_3$ and CF_3CH_2OD. No ortho-substituted compounds were included in this study so as to eliminate interference from steric and intra-molecular hydrogen bonding effects. Spectra were obtained from the low temperature limit to the high temperature limit within the working liquid range of the solvents. Usually the low temperature limits were not attained in d_6-benzene and the high temperature limits were not obtained in CF_3CH_2OD. For those compounds where the low temperature limiting resonant frequencies for the alkyl carbons could not be measured directly, an iterative process was used. The band shapes of the lowest temperature spectrum available were simulated using the resonance frequencies of that spectrum as input data. Once a satisfactory fit

Compound	R
1	H
2a	m-F
2b	p-F
3a	m-Me
3b	p-Me
4a	m-Cl
4b	p-Cl
5a	m-C≡N
5b	p-C≡N
6a	m-NO_2
6b	p-NO_2



was obtained, the differences between the input frequencies and the calculated peak maxima were determined and the input frequencies modified accordingly. The rotational rate was then adjusted to match the desired peak shape and the process repeated until a self-consistent approximation was obtained. Rotational frequencies at each temperature were determined by the Complete Bandshape Analysis method[8] for both the methyl and methylene carbons, thus providing an internal check.

Standard Eyring plots of 1/T vs. ln k/T for each series of spectra yielded $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. The resulting calculated values for $\Delta G^{\ddagger}$ at 298 K are given in Table I along with the correlation coefficients for the Eyring plots from which they were derived. Only those spectra near the coalescence temperature were used. As has been previously noted,[9] non-linearity was observed at very low and very high rotational rates. In addition, at very low and high rotational rates the errors in comparing the simulated and experimental spectra become significant. At very low rates (<20-30 Hz), changes of 20% or more produce no visible change in the spectrum. The same is true at high rotational rates (above ≈2000 Hz). For this reason also, only rotational frequencies obtained from spectra near the coalescence temperatures for the methyl or methylene signals were used. In a few instances (in 2,2,2-trifluoroethanol solution) the activation energies were high enough that only three or four data points were obtained near coalescence and below the boiling point of the solvent. A comparison of some of our results to literature values is given in Table II.

Two patterns emerge from the data presented in Table I. One is the relationship between the substituents and the rotational barrier within a given solvent. The second is the change in the rotational barrier for a single compound in different solvents.

Table I

Calculated Free Energies of Activation for Rotation About the C-N Bond of Substituted N,N-Diethylbenzamides in Four Solvents[a]

Compound	C_6D_6	$CDCl_3$	CD_3CN	CF_3CH_2OD
1 (H)	13.5 (0.999)	14.9 (0.999)	14.5 (0.990)	16.6 (0.988)
2a (m-F)	13.9 (0.989)	14.4 (0.953)	14.7 (0.995)	16.1 (0.996)
3a (m-Me)	13.9 (0.999)	14.9 (0.999)	14.5 (0.989)	15.9 (0.999)
4a (m-Cl)	13.9 (0.983)	14.6 (0.982)	14.9 (0.986)	16.0 (0.993)
5a (m-C≡N)	14.2 (0.991)	15.1 (0.989)	15.1 (0.990)	16.2 (0.979)
6a (m-NO_2)	14.1 (0.988)	14.9 (0.999)	14.8 (0.999)	16.8 (0.988)
2b (p-F)	13.4 (0.974)	14.0 (0.977)	14.2 (0.987)	15.8 (0.986)
3b (p-Me)	13.5 (0.983)	14.5 (0.999)	14.3 (0.985)	16.3 (0.987)
4b (p-Cl)	13.8 (0.980)	14.1 (0.954)	14.6 (0.993)	16.2 (0.979)
5b (p-C≡N)	14.4 (0.990)	15.7 (0.993)	15.4 (0.970)	16.1 (0.970)
6b (p-NO_2)	14.8 (0.966)	15.3 (0.999)	15.4 (0.988)	16.7 (0.984)

a) all values in kcal/mol; correlation coefficients of Eyring plots corresponding to each value are given in parentheses.

Table II

Comparison of Rotational Barriers[a] to Literature Values[b]

Compound	Lit. Value (T°K)	This Work
1	15.0 (291)	14.5
2b	14.7 (285)	14.3
3b	14.8 (285)	14.1
4b	15.1 (292)	14.5
6b	16.0 (311)	15.5

a) all in CD_3CN soln; kcal/mol
b) Gryff-Keller,A.; Terpinski,J.; Zajaczkowska-Terpinski,E. Pol. J. Chem. 1980, 54, 1465.

Table III

Correlation of Rotational Barrier vs. σ with varying inductive and resonance contributions for p-substituents

%		correlation coefficient			
σ_R	σ_I	C_6D_6	CD_3CN	$CDCl_3$	CF_3CH_2OD
100	0	0.749	0.864	0.928	0.996
95	5			0.930	0.990
90	10			0.923	
80	20	0.954	0.975	0.883	
75	25		0.982		
70	30	0.982	0.980		
65	35	0.982			
60	40	0.974			

Substituent Effects

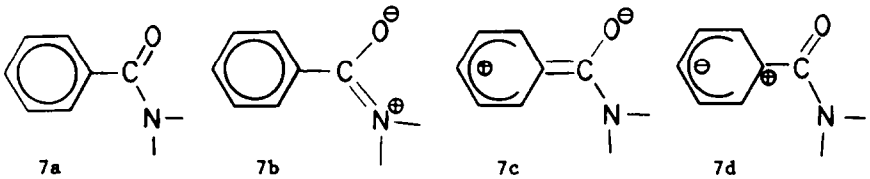
A linear free energy relationship is apparent between the electronic character of the para-substituents and the barrier to rotation within a given solvent. The rotational barriers for the p-substituted compounds were correlated with the Hammett-type substituent contribution, σ. The dual-substituent parameter system of Brownlee and co-workers[10] was used to determine σ with various percentage weights given to the individual inductive and resonance contributions. Sigma values were obtained using the formula:

$$\sigma = a\sigma_I + b\sigma_R$$

where σ_I and σ_R are the inductive and resonance substituent contributions, respectively,[11] and a and b are the weighting factors, normalized such that a + b = 1.00. The relative contributions of the inductive and resonance components for the para-substituents were varied in increments of 5.0% until optimum fits were obtained. The results are presented in Table III.

The maximum correlation between the substituent's electronic contribution and the rotational barrier was obtained at different weighting values for the inductive and resonance components in each solvent. In all cases, the resonance character of the substituent was the greater contributing factor at maximum correlation. For the four solvents C_6D_6, CD_3CN, $CDCl_3$ and CF_3CH_2OD, optimum correlation was reached at 65≈70%, 75%, 95% and 100% resonance contribution respectively. It is apparent from the free energy barriers in Table II that increasing electron releasing ability by the p-substituents causes a reduction in the barrier to rotation about the C-N bond. This is not surprising when one considers the relative contributions of the four resonance forms for the ground state of 7 (see figure 7a, 7b, 7c and 7d). The ground state C-N double bond character results primarily from the contribution of 7b. Factors which increase the partial positive charge at the carbonyl carbon (i.e. the electrophilicity) will increase the N→C π-donation and hence the contribution of 7b. The increased N-C double bond character is reflected in

an increased barrier height. As the contribution from 7c (favored by electron donating substituents) increases, it decreases the electrophilicity of the carbonyl carbon and diminishes the contribution of form 7b, thus reducing the barrier. Conversely, electron withdrawing substituents favor form 7d over 7c, increasing the electrophilicity of the carbonyl carbon. Thus, the contribution by 7b increases and the barrier is correspondingly greater.



7a 7b 7c 7d

We interpret the changing contributions of the inductive and resonance effects of the substituents in the various solvents as reflecting the coordination of the solvent to the carbonyl oxygen. In solvents with poorer proton donor character, the contribution from both resonance forms 7b and 7c is smaller due to reduced stabilization of the formal oxyanion; the inductive contribution of the substituent becomes accordingly more important. Solvents which stabilize forms 7b and 7c through hydrogen bonding increase the resonance contribution of the substituent, to the apparent complete exclusion of inductive effects for CF_3CH_2OD. This will be discussed further in the solvent effects section.

In contrast with the correlation observed for the p-substituted compounds, no correlation was found between the electronic character of the substituents in the m-substituted compounds and free energy barriers to rotation. All attempts to demonstrate a linear free energy relationship using a variety of σ values failed. This further illustrates the importance of resonance effects on the barrier, because the meta substituents are not in direct resonance with the amide carbonyl. Hence, their principle contribution must be an inductive one. Not only is there no apparent correlation of substituent effects in the m-substituted compounds, but the effect of substituents in general is also reduced. In a single solvent, the rotational barriers for para compounds vary by 1.0 to 1.7 kcal/mol. By contrast, the range of barriers observed for the meta compounds is only 0.5 to 1.1 kcal/mol.

Solvent Effects

In all cases, the barrier to rotation for a given compound increases in the order: $C_6D_6 < CDCl_3 \approx CD_3CN < CF_3CH_2OD$. We foresaw two possible explanations for this trend. The first is based upon solvent coordination to the amides, most likely through the carbonyl oxygen. Gutman[12] has proposed a system for measuring the electrophilic association character of solvents (Acceptor Number, AN) to compliment similar systems devised by him[13] and Drago[14] that indicate the Lewis basicity of solvents (Donor Number). The barrier to rotation for each amide was plotted versus the Acceptor Number for the solvents and very

good correlations were obtained. The Acceptor Numbers and correlation coefficients for the plots are shown in Table IV. From previous studies in our laboratories[15] we had data available for compounds 1, 2a and 6a in CH_3OD solution. The result of including these data points are also presented in Table IV. Although these additional points reduce the linearity somewhat, it is still clear that there is strong correlation between the electrophilic character of the solvent and the barrier to rotation in the diethylbenzamides studied. We believe that the increasing barrier to rotation with increasing solvent coordination can be explained in terms of steric hindrance. Binding of solvent to the carbonyl oxygen provides increased resistance to the rotational process. Steric hindrance to rotation has been previously observed in compounds with ortho-substituents where the barriers are substantially higher (2-4 kcal/mol) than their meta- or para-counterparts and seem to correlate with the size of the substituent.[16] As the acceptor character of the solvent increases, it binds more tightly to the carbonyl oxygen and increases the steric hindrance to rotation. This may also explain the observation of negative entropies of activation. Steric strain around the carbonyl should be reduced in the transition state where the N-ethyl groups are not in the plane of the carbonyl. This could allow either more solvent molecules to coordinate to the oxygen, or for those present to bind more tightly. Either should produce the observed negative entropy change. Unfortunately, the scatter observed in the $\Delta S^{\ddagger}$ values precludes formation of any general statement.

Table V

Correlation of Free Energy vs. Solvent Acceptor Number[a]

Compound	r	With MeOH
1	0.99	0.96
2a	0.98	0.98
2b	0.99	
3a	0.98	
3b	0.98	
4a	0.98	
4b	0.96	
5a	0.97	
5b	0.90	
6a	0.99	0.93
6b	0.99	

a. Values taken from U. Mayer Stud. Phys. Theo. Chem. 1983, 27, 219. C_6H_6, 8.2; CH_3CN, 18.9; $CHCl_3$, 25.1; CH_3OH, 41.5; CF_3CH_2OH, 53.3.

We also considered a simple polarity argument to explain the solvent dependency of the rotational barrier. Polar solvents should solvate the dipolar resonance form 7b much better than non-polar solvents. This would stabilize 7b and increase its contribution to the ground-state. The resulting increase in the C-N double bond character would lower the energy of the ground-state. Loss of conjugation in the transition state removes this resonance contributor; the transition state is less polar overall when compared to the ground state. Increased solvent polarity should therefore not stabilize the transition state correspondingly and the overall effect would be an increase in the rotational barrier. This explanation is not in agreement with our results. Dielectric constants for the four solvents increase in the order C_6H_6 (2.8) < $CHCl_3$ (4.8) < CF_3CH_2OH (26) < CH_3CN (38), not in correlation with the observed barrier to rotation.

Conclusions

It is clear that both the nature and position of substituents (on the aromatic ring of

the N,N-diethylbenzamide) and solvent electrophilicity play a significant role in determining the thermodynamic activation barriers associated with rotation about the amide bond in these molecules. The lowest barriers to rotation, in a particular solvent, occur when the parent N,N-diethylbenzamide is substituted with electron releasing substituents at the para-position. Since the N,N-diethylbenzamides are structurally related to known CNS stimulants (such as nikethamide and ethamivan), it is probable that some of the N,N-diethylbenzamide derivatives examined in the current study also have biological activity.

In the ground state (at physiological temperature, 37 C), the N,N-diethylbenzamides are expected to exist principally in a conformation in which the carbonyl carbon, the amide nitrogen and the two methylene carbons attached to that nitrogen are all in a plane. While complete knowledge is not available on the precise manner in which the CNS-active molecules interact with neurotransmitter receptor proteins, it is highly likely from what we know about the manner in which acetylcholine interacts with its receptor that the carbonyl group functions as a hydrogen bond acceptor to a hydrogen bond donor site on the protein. The ground state steric crowding caused by the close proximity of the carbonyl oxygen to the cis-methylene group in N,N-diethylbenzamides may present difficulties in forming complexes between these molecules and receptor binding sites. While free rotation may not be required for and in fact may be detrimental to N,N-diethylbenzamide-receptor complexation, perhaps a lower barrier may translate into an increased probability for librational motion about the amide bond (i.e., a slight twisting, back-and-forth, of perhaps 10° to 15°), which might facilitate N,N-diethylbenzamide-receptor contact. Our results also clearly indicate that the "sensitivity" of the height of the rotational barriers to solvent electrophilicity is pronounced for the series of N,N-diethylbenzamides studied. It would be important to characterize the binding of N,N-diethylbenzamide derivatives to neurotransmitter receptors known to bind structurally related CNS-stimulants. As more information becomes available on the constellation of residues that form the binding sites in the receptor proteins, correlations linking the nature of substituent groups to active site electrophilicity may become possible.

Summary

The barrier to rotation about the amide bond in a series of m- and p-substituted diethylbenzamides has been measured in four solvents. There does not appear to be any direct correlation between the electronic effects of the m-substituents and the observed barriers. The effects of m-substitution are smaller than those for p-substituted compounds, as judged by the range of barriers measured. In the p-substituted compounds, a linear free energy relationship is observed between the electron donor/acceptor character of the substituent and the barrier to rotation. Both the inductive and resonance character of the substituents contribute, but the resonance factor is more important and becomes increasingly more so with increasing electrophilicity of solvent to the apparent exclusion of inductive effects in CF_3CH_2OD. In all cases, the barrier to rotation in a single compound increases in direct correlation with the electrophilic nature of the solvent as measured by the solvent's Acceptor Number. The possibility that this observation is due simply to solvent polarity has been excluded.

EXPERIMENTAL

Materials and Synthesis:

The amides were prepared by standard literature methods from the commercially available carboxylic acid or acid chloride (Aldrich). Compounds were purified by distillation or recrystallization as appropriate and characterized by mp, IR, ^{1}H- and ^{13}C-NMR spectroscopy. All have been previously reported except **5a** (procedure below). IR spectra were taken on a Perkin-Elmer 1330 Spectrophotometer and calibrated against polystyrene. ^{1}H- and ^{13}C-NMR spectra were taken on a Bruker AC-200 or WM-250 Spectrometer and calibrated against internal TMS (^{1}H) or solvent (^{13}C). CHN analysis was performed by MultiChem Laboratories, Inc. Lowell, MA 01851.

N,N-Diethyl-3-cyanobenzamide (**5a**): 3-Cyanobenzoyl chloride (2.48g, 15mmol) was dissolved in 50 mL of Et_2O and diethylamine (3.41mL, 2.41g, 33mmol) added dropwise with vigorous stirring. The resulting white slurry was stirred an additional 2 h. The mixture was filtered, the ppt washed with 2x10 mL of Et_2O and the solvent removed *in vacuo* from the combined filtrate and washes to give a pale yellow solid. Recrystallization from heptane gave a white solid, 2.75g (90%). mp, 53-5 C. ^{13}C NMR ($CDCl_3$/13 C) δ 168.3 (C=O) 137.9 (C-C=O) 132.2, 130.1, 129.5, 129.1 (other Ar C's) 117.6 (C≡N) 112.2 (C-C≡N) 42.9, 39.0 (CH_2's) 13.7, 12.4 (CH_3's). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.28; H, 7.05; N, 13.86.

Data Analysis Methods:

Dynamic Fourier transform ^{13}C-NMR {H} spectra were obtained for each compound over the practical liquid range of each solvent. In cases where the low temperature limiting spectrum could not be obtained for a given series, because of the freezing point of the solvent, the carbon frequencies were determined by successive approximation of frequency and rotational rate until a fit was obtained for the lowest temperature spectrum. The resonance frequencies thus obtained were used in fitting the rest of the series. Samples were prepared at a concentration of 5% (v/v). A test series was run on **2b** in $CDCl_3$ at concentrations of 0.1%, 1.0%, 5.0% and 10.0% to verify that solute-solute interactions were negligible at the concentrations used. The spectra were superimposible. Previous workers have noted some concentration dependency of $\Delta G^{\ddagger}$, but the effects are only significant above 10 mol%.[17] Probe temperatures were determined by calibration against the temperature--dependent chemical shifts of ethylene glycol (above room temperature) or methanol (below room temperature).

Magnetic resonance spectra were calculated by the "complete bandshape method".[6,18] The lineshape equation, implemented on an IBM-XT personal computer, was designed to simultaneously simulate two pairs of coalescing resonances. The spectra were thereby "normalized". In brief, calculated NMR spectra were obtained as follows: experimental

frequencies and linewidths, as well as a projected rate constant, were input into the program to yield a set of contracted Lorentzian line shape functions. The line shape functions were then multiplied over the experimental frequency range to yield a calculated spectrum whose rate constant and transverse relaxation times could be adjusted to obtain the best fit with the experimental spectrum as determined by eye. We estimate the error in the rotational frequencies of spectra used in the Eyring analysis to be 5% or less.

Activation parameters were obtained by standard Eyring analysis.[19] All free energies of activation were calculated at the arbitrary temperature of 298 K for comparative purposes. Where comparisons are made to literature values, the free energies have been adjusted to the reported temperatures.

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