Torsional Barriers in Substituted *NN*-Dimethylcarbamates. A Probe for Perturbational Molecular Orbital Analyses of Amide Rotation[1]

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Free energies of activation for torsion about the N–CO bond in four aryl *NN*-dimethylcarbamates, *p*-$YC_6H_4X{\cdot}CO{\cdot}NMe_2$ (1)—(4), were measured using dynamic n.m.r. spectroscopy, and utilizing a lanthanide shift reagent to increase resolution between the diastereotopic *N*-methyl groups. Barriers were: (1; X = O, Y = H) 16.5 kcal/mol) (69.0 kJ/mol); (2; X = O, Y = NO_2) 17.1 kcal/mol (71.5 kJ/mol); (3; X = S, Y = H) 14.9 kcal/mol; (62.3 kJ/mol) and (4; X = S, Y = NO_2) 15.0 kcal/mol (62.8 kJ/mol). The results are discussed in terms of two recently proposed PMO analyses of amide rotation, one focusing on effects of the substituents at the torsional ground state and the other one on effects at the transition state. The higher barriers obtained for the *para*-nitro-substituted compounds relative to the unsubstituted ones is evidence for the dominance of ground-state effects in this system.

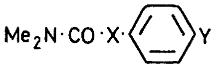
HINDERED rotation about the N–C bond in carbamates, $RO{\cdot}CO{\cdot}Nr_2'$, has been the subject of numerous studies.[2] However, many of these studies were of limited success, especially in cases where correlations were sought between structure and rotational barriers.[2e,h,i] The difficulties encountered while attempting to measure barriers in *N,N*-dimethylcarbamates are due mainly to the very small (and sometimes unresolvable) differences in chemical shifts ($\Delta\nu$) of the diastereotopic methyl groups. In addition, the situation is complicated by significant temperature and solvent dependencies of $\Delta\nu$. Thus, only the choice of a particular solvent, chlorobenzene, enabled dynamic n.m.r. measurements of all four barriers in the series $Me_2N{\cdot}CX{\cdot}YMe$ (X = O and S; Y = O and S), whereas in other solvents some members of the series showed accidental equivalence of the *N*-methyl signals.[2a] In some cases coalescence phenomena may be observed due to disappearance of the initially small $\Delta\nu$ values as a result of temperature changes alone, in the absence of fast exchange, leading inevitably to erroneous rate constants and barriers. Therefore, meaningful trends in the barriers of substituted carbamates can be obtained only under conditions of large enough signal separations.

Here we report on the measurement of activation free energies for rotation in *NN*-dimethyl-carbamates and -thiocarbamates utilizing lanthanide shift reagents (LSR), in order to overcome the difficulty of barely resolvable *N*-methyl signals. The aim of this study is to provide an experimental probe for two proposed perturbational molecular orbital (PMO) analyses of amide rotation, and to comment on them.

RESULTS

Activation free energies ($\Delta G^{\ddagger}$) for the degenerate *syn–anti* interconversion of the *NN*-dimethylcarbamates (1)—(4) were measured in the presence of various amounts of LSR, as first developed by Gutowsky and Cheng[3] and used extensively by Kessler and co-workers[4] in the analysis of *N*-protected amino-acid derivatives.

At room temperature, in the absence of LSR, no splitting of the *N*-methyl signals could be observed in the n.m.r. spectrum of any of the compounds (1)—(4). Tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)-europium [Eu(fod)$_3$] was introduced into each sample until the *N*-methyl singlets were well resolved. The temperature-dependent n.m.r. spectra were then recorded, and the first-order rate constants at the coalescence temperatures calculated using the equation $k_c = \pi\Delta\nu_c/\sqrt{2}$.[5] Free energies of activation were calculated using Eyring's equation.



(1) X = O; Y = H
(2) X = O; Y = NO_2
(3) X = S; Y = H
(4) X = S; Y = NO_2

Studies by Kessler and Molter[4] and by Springer and his co-workers[6] showed that the rotational barriers in carbamates were independent of LSR concentration, up to a concentration ratio of *ca.* $\rho = 0.5$. In order to confirm this finding, we repeated the dynamic n.m.r. measurements for each compound in presence of different ratios of LSR to substrate concentrations (see Table).

If it is accepted that the barriers should be independent of ρ [a statement certainly justified for (3) and (4)], then the

Dynamic n.m.r. data

Compd.	ρ [a]	T_c/K [b]	$\Delta\nu_c$/Hz [c]	k_c [d]/s^{-1}	$\Delta G^{\ddagger}$/kcal mol^{-1}	$\Delta G^{\ddagger}_m$ [e,g]	$\Delta G^{\ddagger}_{ex}$ [f,g]
(1)	0.19	328	36.5	81.0	16.4	16.5	16.1
	0.24	332	41.0	91.0	16.5	±0.1	±0.2
	0.30	335	51.5	114.3	16.5		
	0.33	338	51.0	113.2	16.7		
(2)	0.085	325	15.0	33.3	16.8		
	0.15	335	23.5	52.7	17.0	17.1	16.8
	0.22	342	35.5	78.8	17.1	±0.2	±0.1
	0.31	347	58.0	127.7	17.1		
	0.39	351	75.0	165.4	17.1		
	0.49	357	72.5	161.0	17.4		
(3)	0.35	305	60.0	132.0	14.9	14.9	
	0.41	307.5	69.0	153.2	14.9	±0.0	
	0.50	309	80.0	176.5	14.9		
(4)	0.16	301	33.0	73.3	15.0	15.0	
	0.19	302	38.5	85.5	15.0	±0.4	
	0.23	305	47.0	104.3	15.0		
	0.26	305	44.5	98.8	15.1		

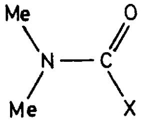
[a] ρ = [Eu(fod)$_3$]/[substrate]. [b] Coalescence temperature. [c] Taken as $\Delta\nu_c = W_{\frac{1}{2}}$ less intrinsic bandwidth (see text). [d] The coalescence rate constant calculated from $\Delta\nu_c$. [e] Arithmetic mean of $\Delta G^{\ddagger}$. [f] Obtained from linear extrapolation of $\Delta G^{\ddagger}$ values to $\rho = 0$. [g] Error ranges are standard deviations.

best results for the free energy barriers $\Delta G^{\ddagger}$ are the mean values of the different measurements. Alternatively, the free energies of activation in the absence of LSR can be extrapolated from plots of $\Delta G^{\ddagger}$ *vs.* ρ. Table 1 shows that *both* procedures lead to the following trends. (*a*) The thiocarbamates (3) and (4) exhibit rotational barriers *ca.* 1.5 and 2 kcal/mol, respectively, *lower* than the analogous carbamates (1) and (2). (*b*) The barriers for the *para*-nitro-substituted compounds (2) and (4) are slightly *higher* (*ca.* 0.5 and 0.1 kcal/mol, respectively) than those for the unsubstituted analogues (1) and (3).

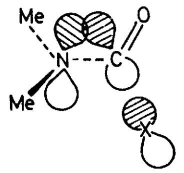
DISCUSSION

Arguments based on perturbational molecular orbital (PMO) theory have recently become most useful in analysing structures and conformational preferences of organic molecules.[7] In this method the molecule is conceptually dissected into two fragments, the molecular orbitals (MO's) of the fragments are calculated or estimated, and the interaction energies of MO's of one fragment with those of the other are evaluated as a function of some structural changes. Normally, the behaviour of the total energy (*i.e.* the behaviour of the molecule itself) is reflected in the variation in magnitude of one or two major interaction energies as a result of a certain structural change. Thus, utilizing PMO analysis, a structural phenomenon may be ' understood ' in terms of simple interactions between one or two pairs of fragment MO's. It has been postulated that the highest occupied MO (HOMO) is the one which most closely follows the behaviour of the total energy with respect to conformational changes.[8] Therefore one usually considers for a PMO analysis interactions between fragment orbitals (FO's) which, in the unfragmented molecule, make the greatest contribution to the HOMO.* However, one of the difficulties of the PMO treatment is that in many cases there are several important interactions to be considered, and the choice of suitable interactions for a meaningful analysis is not always obvious. Thus, sometimes the use of either stabilizing or destabilizing interactions † may lead to equally satisfying rationalizations of a chemical problem, as has been shown for the ' anomeric effect '.[10] In other cases, however, using different interactions may result in different or wrong interpretations of certain effects.

Structural effects on amide rotational barriers have been discussed recently in terms of two PMO approaches. Bingham,[11] in a discussion on lone-pair carbon–halogen bond hyperconjugation, attributed the differences in activation free energies for torsion in *NN*-dimethylcarbamoyl halides (5) to a stabilizing hyperconjugative interaction at the rotational transition state (6). The choice of this interaction, between the nitrogen long-pair and the unoccupied C–X antibonding orbital, could rationalize the experimental trend in the barriers (in order of decreasing barrier, X = F > Cl > Br).[12] Furthermore, the excellent correlations obtained between these rotational barriers and a few other observations connected with the C–X bond supported this analysis.[11]



(5)



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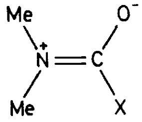

(7)

On the other hand, most of the classical discussions on electronic effects on amide barriers are based, in terms of valence bond theory, on the conjugation between the nitrogen lone-pair and the carbonyl π system *at the planar ground state* for rotation. Thus, any structural modification which acts to increase the contribution or stability of resonance hybrid (7) will result in an enhanced barrier. This view has been expressed recently using the language of PMO by Bernardi, Lunazzi, Zanirato, and Cerioni (BLZC).[13] The dominant interaction, according to these authors, is that of the nitrogen lone-pair orbital with the low-lying π^* orbital of the carbonyl fragment at the torsional ground state (Figure 1). To a first approximation, the stabilization energy of this type of interaction is inversely proportional to the energy gap (ΔE) between the levels.[7b] Any substitution which affects ΔE will result in a corresponding change in ground-state stability, and hence in the magnitude of the barrier.

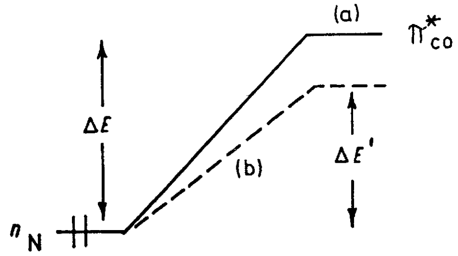

FIGURE 1 Schematic diagram of the major ground-state interaction, with different substituents on the carbonyl: (a) ΔE, phenyl; (b) $\Delta E'$, *p*-nitrophenyl

The aim of the present study has been to further test and to distinguish between the above mentioned PMO schemes. When the barriers for the oxygen compounds (1) and (2) are compared with those of their sulphur analogues (3) and (4), respectively, the same trend is found as in the halogen series (5). A change of substituent on the carbonyl carbon down a column of the periodic table results in a lower torsional barrier, in both the sixth and seventh columns. These results are thus in accord with Bingham's observation.‡

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* The exact contributions of various FO's to the HOMO are not always known. Recently a quantitative PMO method has been developed by Wolfe and his co-workers, which produces FO's and the MO's expressed in FO basis.[9]

† Interactions between doubly occupied and low lying vacant FO's, and between pairs of doubly occupied FO's, respectively.[7b]

‡ According to Bingham, the order of $\sigma^*_{\text{C-X}}$ orbital energies ($\sigma^*_{\text{C-F}} > \sigma^*_{\text{C-Cl}} > \sigma^*_{\text{C-Br}} > \sigma^*_{\text{C-I}}$) determines the order of transition-state stabilization of the corresponding carbamoyl halides, and hence the observed order of barriers. Since, in general, σ^* energies of C–Y bonds decrease when Y changes down a column of the periodic table,[7b] the analogy between the results in the halogens and O,S series seems to support Bingham's view.

Introduction of the *para*-nitro group in (2) and (4) has the effect of lowering the MO's in its vicinity, including the *p*-lone-pair on oxygen or sulphur, and the $\sigma^*_{\mathrm{CO-X}}$. According to Bingham's analysis, this should result in a larger hyperconjugative stabilization of the transition state, and hence in *lower* activation free energies for rotation. The results clearly show the opposite trend (Table). Thus, it is evident that in the present system the n_{N} to $\sigma^*_{\mathrm{C=O}}$ hyperconjugation at the torsional transition state is *not* the dominant interaction governing the variation of barrier with structure.

Examination of the results in light of the alternative BLZC theory yields a better agreement. In presence of the nitro group, the X atom in (2) and (4) acts as a more electronegative atom than in the unsubstituted compounds (1) and (3), respectively. The result (as stated earlier) is a decrease in various MO levels, including the carbonyl π^*. Consequently $\Delta E'$ (Figure 1) is smaller, the stabilization energy of the ground state greater and the barrier higher. The same result is obtained if one considers not the inductive (electronegative) effect of the substituent, but rather the mesomeric (conjugative) effect. The X atom (oxygen or sulphur) acts as a π-electron donor; its *p*-lone pair interacts with the carbonyl π^* orbital, resulting in an increase of the energy of the latter (relative to the parent formamide or acetamide). The stabilizing interaction between the nitrogen lone-pair and the π^* orbital at the ground state is therefore weaker, and the barrier to rotation lower. Since the X lone-pair energy level is lower in the nitro-compounds, its interaction with the $\pi^*_{\mathrm{C=O}}$ is weaker, resulting in a less increased π^* orbital energy than in the unsubstituted carbamates. As a result the rotational ground state in the nitro-compounds is more stabilized, and the barriers higher.

The difference in magnitude of the effects of *para*-substitution on the sulphur and oxygen compounds is readily understood in light of recent photoelectron spectroscopic studies:[14a] Bernardi *et al.*[14b] have shown that the energy level of the HOMO in *para*-substituted anisoles depends on the substituents to a much greater extent than that of the analogous thioanisoles. Hence the barriers, which depend on an interaction of that lone pair MO, will likewise show greater substituent dependence in the carbamates than in the thiocarbamates.

The observation that carbamates generally have lower barriers than analogous carbamides[15] suggests that the mesomeric influence of the oxygen as a π-donor is dominant over its inductive (σ-acceptor) effect. The even lower rotational barriers exhibited by the *thio*-carbamates (3) and (4), relative to (1) and (2) respectively, may seem to indicate that the sulphur is a better π-donor than oxygen in this system. It can, however, reflect the lower electronegativity of sulphur, combined with a certain π-donor ability.† The trend in the barriers of the carbamoyl halides can now be attributed to the electronegativity order of the halogens, in accord with BLZC. It is noteworthy that the results in the carbamoyl halide series may be rationalized also simply by invoking a steric effect of the halogen atom, which, of course increases in the order $\mathrm{F} < \mathrm{Cl} < \mathrm{Br} < \mathrm{I}$ and thus creates a destabilizing effect on the ground state. All three effects (the transition state hyperconjugation, the steric ground state destabilization, and the ground-state electronegativity effect) operate in the same direction, and may each contribute to some extent to the observed results in this series.

Finally, the superiority of the BLZC over the alternative approach might have been anticipated *a priori*: the interaction between the HOMO of one fragment (the nitrogen lone-pair) with the LUMO of the other (the $\pi^*_{\mathrm{C=O}}$ of the carbonyl fragment) is expected, due to the small separation ΔE, to be the strongest in the molecule, and therefore also dominant over the interaction (at the transition state) of the same HOMO with the higher lying $\sigma^*_{\mathrm{C-X}}$ orbital.

EXPERIMENTAL

NN-Dimethyl-carbamates and -thiocarbamates were synthesized by the addition of *NN*-dimethylcarbamoyl chloride to a pyridine solution of the appropriate phenol or thiophenol, followed by standard work-up and crystallization. *p*-Nitrothiophenol was prepared by the reduction of *p*-nitrophenyl disulphide with glucose.[19]

N.m.r. spectra were recorded on a Varian XL-100-15 spectrometer, equipped with a variable-temperature control unit, using tetramethylsilane as the internal lock signal. Temperatures were determined using ethylene glycol spectra as described in the Varian manual. Bromobenzene was used as solvent, and a few drops of cyclohexane were added to each sample as a homogeniety reference signal. Throughout the experiments the width ($W_{\frac{1}{2}}$) of the cyclohexane singlet never exceeded 1 Hz. Commercial $\mathrm{Eu(fod)_3}$ from a freshly opened ampoule was used without further treatment. The signal separation, $\Delta\nu_c$, was taken as the width at half height ($W_{\frac{1}{2}}$) of the coalescence spectrum,[20] less the width of the non-exchanging signals. The latter was estimated from a plot of $W_{\frac{1}{2}}$ against temperature (Figure 2), which gave an upper limit for each case.‡ The band widths estimated in this way never exceeded 2.5 Hz, and in each case the signal of the methyl *cis* to the carbonyl oxygen

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† The question whether oxygen or sulphur is a better π-electron donor is not a simple one: comparison of Hammett substituent constants σ_p (or, preferably, σ_R) for the methoxy- and methylthio-substituents indicates that O acts as a better donor when attached to a phenyl ring. *Ab initio* calculations have shown that sulphur has a greater π-donor ability when adjacent to a carbenium ion centre.[16] This apparent conflict has been rationalized recently using PMO arguments, concluding that whenever the acceptor MO (LUMO) has a relatively low energy (carbenium ion), S will act as the better donor, whereas a higher lying LUMO (such as vinyl or phenyl groups) will result in better π-donor ability for oxygen.[17] However, a recent dynamic n.m.r. study has shown *sulphur* to be the better π-donor in the system $\mathrm{CH{:}CH{\cdot}X{\cdot}CH{:}CH{\cdot}C{=}CRR'}$ ($\mathrm{X = O, S}$).[18] In our system, the $\pi^*_{\mathrm{C=O}}$ is probably intermediate between the LUMO levels of a vinyl (or phenyl) and a carbenium ion, so that the analysis fails to predict the order of π-donor ability in this case. The present evidence does not answer this question.

‡ Kessler and Molter,[4] used similar graphs and showed that above 300 K the line broadening due to LSR was no more than 3 Hz.

was more strongly broadened due to the proximity to the LSR molecule.[6]

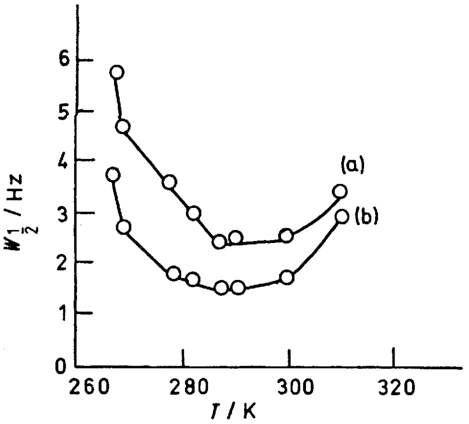

FIGURE 2 Variation of width at half height of the methyl signals in (2) with temperature, at $p = 0.39$; (a) methyl *cis*, and (b) *trans* to the carbonyl oxygen

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