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Tetrahedron Letters 45 (2004) 2747–2749

Tetrahedron Letters

Substituent effects on the barrier to carbamate C–N rotation

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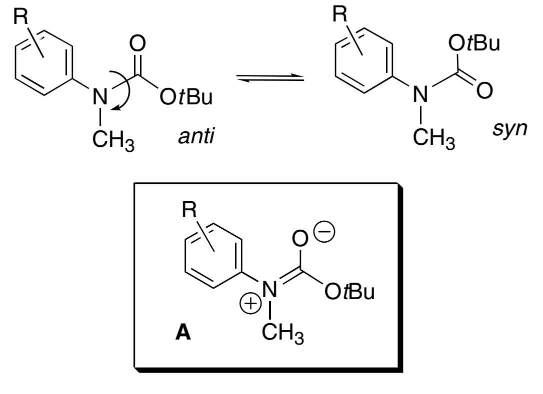
Received 30 January 2004; revised 6 February 2004; accepted 9 February 2004

Abstract—Seven aryl-substituted *t*-butyl *N*-methyl-*N*-aryl carbamates were prepared, and in each case, the barrier to C–N bond rotation, $\Delta G^{\ddagger}$, was determined in $CDCl_3$ solution using variable temperature NMR. A linear free energy relationship is observed between $\Delta G^{\ddagger}$ and the electronic stabilization effect of the substituent on the *N*-aryl ring. More specifically, electron donating groups increase $\Delta G^{\ddagger}$, whereas withdrawing groups decrease $\Delta G^{\ddagger}$. A plot against $\sigma-$ was more linear ($r^2 = 0.96$), than a plot against σ ($r^2 = 0.90$) or $\sigma+$ ($r^2 = 0.88$) and a value of $\rho = 1.76$ was obtained at 243 K. Thus, rotation about the carbamate C–N bond in weakly polar chloroform involves a decrease in positive charge on the nitrogen.

Hindered rotation about the C–N bond in amides,[1] carbamates,[2] and related systems is an on-going topic in conformational stereochemistry that has attracted the interest of many investigators.[3] The subject remains relevant because a very large number of biological molecules have amide bonds, and many pharmaceutical agents and polymeric materials have carbamate bonds. Thus, it is important to fully understand how structural and environmental factors control the associated kinetics and thermodynamics. In the case of amides it is well accepted that C–N bond rotation is slow because it involves disruption of a partial double bond.[3] Furthermore, the amide ground state is more polar than the transition state and the rotational barrier ($\Delta G^{\ddagger}$) is increased by structural and environmental factors that favor increased polarity. The mechanistic picture is not so straightforward in the case of carbamate C–N rotation, where it appears that, depending on the solvent, the transition state may be more or less polar than the ground state.[2a,b,e]

The literature contains a few isolated studies of substituent electronic effects on amide and carbamate rotation, but there has been no systematic attempt to develop 'Hammett-like' free energy relationships, due in part to the lack of suitably tractable systems.[1–3] The rotational barrier is often measured by dynamic NMR methods,[4] but this can be challenging in the case of secondary amide and carbamates, because the *syn*/*anti* equilibrium is often strongly biased to one side, which makes it difficult to accurately measure line shapes and relative populations. It is usually more convenient to employ molecular systems with trisubstituted nitrogens because they have rotamer equilibria that are closer to unity. For example, this present contribution concerns a series of substituted *t*-butyl *N*-methyl-*N*-aryl carbamates whose *syn* and *anti* rotamers are defined in Scheme 1. At low temperatures, NMR signals for the different rotamers can be observed, and the rotational barrier ($\Delta G^{\ddagger}$)

R = 4-CH_3, 4-OCH_3, 4-Br, 4-Cl, 4-H, 3-OCH_3, 4-CN



Scheme 1. *t*-Butyl *N*-methyl-*N*-aryl carbamates.

Keywords: Amide bond; Conformational isomer; Dynamic NMR spectroscopy; Hammett plot.

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doi:10.1016/j.tetlet.2004.02.037

Table 1. Dynamic ^{1}H NMR data and substituent constants[a] for carbamate C–N rotation

R	Δp	$\Delta \nu$ (Hz)	k (s^{-1})	τ_c (K)	$\Delta G^{\ddagger b}$	σ	$\sigma+$	$\sigma-$
4-CH$_3$	0.26	48	78	254	12.5	−0.17	−0.31	−0.17
4-OCH$_3$	0.20	56	93	268	13.2	−0.27	−0.76	−0.27
4-Br	0.17	49	85	246	12.1	0.23	0.15	0.23
4-H	0.18	53	90	250	12.3	0.00	0.00	0.00
4-Cl	0.17	51	86	247	12.3	0.23	0.11	0.23
3-OCH$_3$	0.21	43	71	239	11.8	0.12	0.05	—
4-CN	0.11	31	57	215	10.7	0.63	0.63	1.00

[a] Reference 9.

[b] ±0.2 kcal/mol.

can be easily measured at signal coalescence. Recently, we reported that an *N*-arylcarbamate has a smaller $\Delta G^{\ddagger}$ value than an analogous *N*-alkylcarbamate.[5] We attributed this observation to the electron withdrawing nature of the *N*-aryl group, which attenuates the dipolar character of the carbamate ground state and induces more C–N single bond character. In this present report, we investigate this effect in more detail. We compare the related carbamate compounds shown in Scheme 1 and observe a linear free energy relationship between $\Delta G^{\ddagger}$ and the electronic stabilization effect of the remote R group. Specifically, we find that electron donating R groups increase $\Delta G^{\ddagger}$, whereas withdrawing R groups decrease $\Delta G^{\ddagger}$.

The seven analogues shown in Scheme 1 were prepared by a previously reported synthetic method.[5] In each case, the rotational equilibrium in CDCl$_3$ solution was characterized by variable temperature ^{1}H NMR,[6] and the data treated as an exchange between two unequally populated sites.[7] The exchange was sufficiently slow at low temperatures that separate signals were observed for the *syn* and *anti* rotamers. The coalescence temperatures, τ_c, were determined and values for Δp (the rotamer population difference) and $\Delta \nu$ (the limiting chemical shift difference) were obtained from spectra acquired at temperatures well below coalescence. The rotational rate constants, k, were calculated and the Eyring equation was used to extract values for $\Delta G^{\ddagger}$, which are listed in Table 1.

Inspection of Table 1 shows that changing from 4-CN to 4-OCH$_3$ leads to an increase in $\Delta G^{\ddagger}$ of 2.5 ± 0.4 kcal/mol.[8] This corresponds to a 180-fold decrease in the rate of C–N bond rotation at 243 K. The data in Table 1 was treated and evaluated for free energy relationships. Thus, $\Delta G^{\ddagger}-\Delta G^{\ddagger}_{\mathrm{H}}$ was plotted against various substituent constants.[9] A plot against $\sigma-$ was more linear ($r^2 = 0.96$), than a plot against σ ($r^2 = 0.90$) or $\sigma+$ ($r^2 = 0.88$). The slope of the plot against $\sigma-$ was divided by 2.3RT to give a value of $\rho = +1.76$ at 243 K, which indicates that rotation about the C–N bond involves a decrease in positive charge on the nitrogen atom. This linear free energy relationship is consistent with a rotation process in weakly polar CDCl$_3$ that involves a relatively dipolar carbamate ground state (due to resonance contributor **A** in Scheme 1) and a less polar transition state. The mechanistic picture is in agreement with recent experimental and theoretical studies.[2a,b,e] The magnitude of ρ is much less than that reported for the deprotonation of substituted anilinium cations ($\rho = +3.53$ in ethanol),[9] an equilibration process that is electronically related. A likely contributing factor to the difference is steric hindrance in the carbamate system, which forces the *N*-aryl ring to rotate out of co-planarity with carbamate C–N bond.[5,10] This means that the *N*-aryl ring is not fully conjugated with the lone pairs on the attached nitrogen, and thus the substituent-induced resonance effects are attenuated.

In terms of equilibrium position, there seems to be a weak trend of Δp increasing as the *N*-aryl ring becomes more electron rich. Attempts to assign the resolved low temperature signals to *syn* or *anti* rotamers by NOE were unsuccessful. For example, irradiation of the *N*-methyl signals produced no enhancement of either of the *t*-butyl signals. However, in all cases the most upfield *t*-butyl peak is the most intense, and this peak increases as the *N*-aryl becomes more electron rich. Molecular models suggest that this upfield peak is due to the *syn* rotamer, which places the *t*-butyl group in a shielding region above the face of the *N*-aryl ring. Thus, the carbamate *syn*/*anti* equilibrium appears to be influenced by a repulsive interaction in the *anti* rotamer between the carbonyl oxygen and the face of the *N*-aryl ring.

In summary, this study shows how linear free energy relationships can be used to probe the mechanism of C–N rotation. The data indicates that carbamate C–N rotation in a weakly polar solvent involves a dipolar carbamate ground state and a relatively less polar transition state. It will be interesting to repeat this substituent study in a polar, protic solvent, where the mechanism may involve a transition state that is more polar than the carbamate ground state.[2a]

Acknowledgements

This work was supported by the National Science Foundation and the University of Notre Dame.

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