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β-Deuterium Isotope Effects on Amine Basicity, "Inductive" and Stereochemical

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Isotope effects (IEs) are characteristic features of rates and equilibria.[1] Primary IEs arise when a bond to the isotope is formed or cleaved. Secondary ones arise when that bond remains intact. Those due to an isotope one or two bonds distant from the reaction site are called α or β, respectively. They continue to provide mechanistic information regarding organic[2] and enzymatic reactions.[3] We now report definitive data regarding secondary deuterium IEs on amine basicities.

Alpha secondary IEs usually arise from a change in hybridization. Historic examples come from solvolyses,[4] where the reacting carbon changes from sp^3 to sp^2. Since the out-of-plane bending frequency ν of an sp^2 CH bond is unusually low, the zero-point energy ($=^1/_2h\nu$) is reduced in the transition state. The reduction is less for CD because zero-point energy is inversely proportional to square root of mass. Consequently, the protium substrate reacts faster than the deuterated one.

Beta effects are more subtle. In solvolyses they are generally associated with hyperconjugation, whereby the CH bond delocalizes its electrons to stabilize a developing carbocation. Delocalization from the stronger CD bond, of lower zero-point energy, is then less effective. This cannot be an inductive effect, whereby protium is simply more electron-donating than deuterium, since according to the Born−Oppenheimer Approximation, the electronic wave function is independent of nuclear mass.[5] Instead, it must be attributed to a change of vibrational frequencies.

Our interest is in β deuterium IEs on amine basicity. IEs involving filled orbitals are less common, and they are usually equilibrium effects. Deuteration consistently increases the basicity of amines, but the effects are small and opposite to deuterium's reduced electron-donating power in solvolyses. For benzylamine-α-d_2, the IE, expressed as ΔpK_a ($= -\log K_a^D + \log K_a^H$, where K_a is the acidity constant of the conjugate acid), is 0.054 ± 0.001, which was subsequently revised to 0.032, and 0.056 ± 0.001 for 2,4-dinitro-*N*-methylaniline-d_3.[6] The error estimates are only measures of precision, and they are overoptimistic if systematic error arises from an impurity in one of the samples.

Similarly, ΔpK_a is 0.056 for methylamine-d_3 and 0.12 for dimethylamine-d_6, but these are surprisingly temperature-independent,[7] as would be consistent with impurities. For trimethylamine-d_9, ΔpK_a is 0.185,[8] well beyond experimental error, but this could be due to steric repulsions, which flatten trimethylamine-h_9.

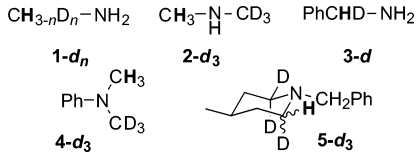
These cases differ from solvolyses in that there is no rehybridization, neither of the carbon bearing the isotope nor of the nitrogen, which remains nominally sp^3 on deprotonation. The IE was therefore attributed to an electrostatic interaction between the positive charge on the NH^+ and the dipole moment of the CH or CD bond.[9] Since dipole moment is charge times distance and since the average CH bond is longer than CD, because of anharmonicity, deuterium could be effectively electron-donating. This sort of inductive effect is consistent with the Born−Oppenheimer Approximation, and it seems to be accepted as the source of these IEs.[10] Yet both the charge separation in a nonpolar CH bond and the difference due to anharmonicity are small. Thus their product, the IE, ought to be vanishingly small. Since such IEs were crucial to assessing the symmetry of NHN hydrogen bonds,[11] we have reinvestigated them.

A new titration method permits precise measurement of relative basicities.[12] Successive aliquots of acid are added to a mixture of bases. Acid will preferentially protonate the more basic species, whose NMR chemical shift will move ahead of that of the less basic one. The acidity constants K_a and chemical shifts δ can be related through eq 1, where δ^+ or δ^0 is for the protonated or deprotonated form, measured at the beginning or end of the titration. Therefore, a plot of the quantity on the left vs $(\delta_1 - \delta_1^\circ)(\delta_2^+ - \delta_2)$ should be linear with the zero intercept and with a slope equal to the ratio of acidity constants.

$$(\delta_1^+ - \delta_1)(\delta_2 - \delta_2^0) = (K_a^1/K_a^2)(\delta_1 - \delta_1^0)(\delta_2^+ - \delta_2) \quad (1)$$

This method is capable of exquisite precision, since it is based only on chemical-shift measurements, not pH or volume or molarity. Since the titration is performed on a mixture of the two bases, under conditions guaranteed identical for both, it avoids systematic error due to possible impurities.

IEs are now measured for deuterated methylamine (**1-d_{0-3}**), dimethylamine (**2-d_3**), benzylamine (**3-*d***), and *N*,*N*-dimethylaniline (**4-d_3**).[13] Mixing each of these last three with unlabeled material produces a ^{1}H NMR spectrum with resolvable signals due to different isotopologs, from reporter nuclei that are depicted in boldface in the molecular structures. The ratio of acidity constants for the isotopomers of 1-benzyl-4-methylpiperidine-d_3 (**5-d_3**) is also determined.[14]



Samples were subjected to ^{1}H NMR titration in D_2O or D_2O−CD_3OD and analyzed according to eq 1. Signals of deuterated **1**−**4** were assigned from samples of known stoichiometry. The isotopomers of **5-d_3** are specified by the orientation of deuterium, so that K_{eq} is for **5-d_{eq}**, which shows a 12-Hz doublet due to H_{ax}, whereas **5-d_{ax}** shows an H_{eq} multiplet further downfield.

Excellent linearity was achieved, with correlation coefficients typically >0.999. A typical titration is shown in Figure 1. Individual titrations produced smaller errors than the variability among titrations, and they were therefore averaged. Table 1 lists the IEs.

The IEs are small but accurately measurable. This is because the method is comparative; therefore, any minute imbalance of basicities can be detected. For **1**, the IEs are linear in the number of deuteriums, and for **1**−**3** the IE per D is nearly constant.

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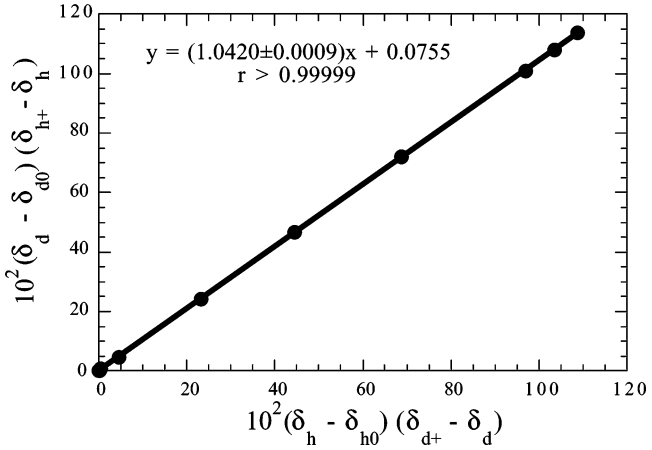

Figure 1. Plot (eq 1) from titration of **3** plus **3-*d***.

Table 1. Isotope Effects on Amine Basicities

amine	K_H/K_D	ΔpK_a	$\Delta\Delta G^0$ (cal/mol)[a]
1	1.040 ± 0.006	0.017 ± 0.003	23.2 ± 3.4
1[b]	1.081 ± 0.004	0.034 ± 0.002	23.1 ± 1.1
2	1.144 ± 0.005	0.058 ± 0.002	26.6 ± 0.9
3	1.0419 ± 0.0009	0.0178 ± 0.0004	24.4 ± 0.5
4	1.1051 ± 0.0018	0.0434 ± 0.0007	19.7 ± 0.3
5	1.060 ± 0.006[c]	0.0253 ± 0.0025	34 ± 3

[a] Per D. [b] **-*d*$_2$**. [c] K_{eq}/K_{ax} (K_{eq} is for isotopomer with equatorial D).

The key result is that deuterium increases the basicity. The ΔpK_a data in Table 1, converted to a per deuterium basis, confirm some previous reports on **2** and **3**,[6,7] and our value for **4** agrees with the ΔpK_a for *N*-methyl- and *N*,*N*-dimethyl-*p*-fluoroaniline, measured with a single-point version of eq 1.[15] However, these values are significantly lower than that reported for 2,4-dinitro-*N*-methylaniline,[6] which is likely to be erroneous because the IE ought to be lower for a nitroaromatic amine, where the lone pair is delocalized. Regardless, all these values are smaller than the K_H/K_D of ~1.2 per D observed in solvolysis, since filled−filled orbital interactions are weaker than filled−vacant ones.

It still seems very unlikely that these IEs are due to an inductive effect. Instead, we reconsider changes in vibrational frequencies, despite the lack of rehybridization on protonating the nitrogen. The IR spectra of amines show characteristic "Bohlmann bands" around 2700−2800 cm^{-1},[16] lower than the 2900 cm^{-1} of a typical CH stretch. Upon N-protonation, these bands revert to a typical frequency. Therefore, the zero-point energy of the CH increases on protonation, but the increase is less for CD. Indeed, a $\Delta\nu$ of 100 cm^{-1} would produce a ΔpK_a of 0.03, comparable to the IEs observed.

The reduction of frequency is generally attributed to negative hyperconjugation, or delocalization of the lone pair into the vacant σ^*_{CH} orbital.[17] This is supported by calculations on carbanions and alcohols,[18] by the ΔpK_a of 0.056 in trifluoroethanol-d_2,[19] and by the preference for equatorial deuteriums in 1,3,5,5-tetramethylhexahydropyrimidine-2-*d* and *cis*-*N*-methylpiperidine-2,6-d_2.[20] Indeed, the stereochemical dependence of the IE on basicity could have been inferred on the basis of these latter results.

The involvement of orbital interactions implies a stereochemical requirement. Only if there is overlap between lone-pair and CH-bond orbitals can the IE operate. We have tested this with 1-benzyl-4-methylpiperidine-2,2,6-d_3 (**5-*d*$_3$**), also listed in Table 1. The two isotopomers show a ΔpK_a of 0.025, and the one with deuterium trans to the methyl group, and therefore axial, is the more basic, exactly as required. It is remarkable that basicities of isotopomers can be distinguished. These are stereoisomers that differ only in the position of an isotope.

The secondary β deuterium IEs on amine basicity can be fit to a $\cos^2$ dependence on the dihedral angle between the CD and the lone pair. As in solvolyses, calculations indicate a $\cos^2$ dependence of such IEs on dihedral angle.[18] The average value from **1** and **2** is the 2:1 sum of contributions at 60° and 180°, and the value from **5** is the difference between these two. The resulting equation is $\Delta\Delta G°$ (cal/mol) = (45.7 ± 4.5) $\cos^2\theta$ + (1.8 ± 2.6). This equation is imperfect since it does not distinguish antiperiplanar from synperiplanar, and studies are underway to generate amines with deuterium at other dihedral angles. However, the fit shows that there is a stereochemical dependence of the IE on amine basicity. This is the first such report because basicity differences between isotopomers are small and beyond most measurements.

Moreover, there is no angle-independent term. Within an exceedingly small experimental error, <3 cal/mol, this is not significantly different from zero. This is the term that would arise from an electrostatic interaction between a positive charge and a bond dipole.[9] We therefore conclude that an inductive effect does not contribute to the observed IE.

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References

(1) (a) Melander, L.; Saunders, W. H. *Reaction Rates of Isotopic Molecules*; Wiley: New York, 1980. (b) Carroll, F. A. *Perspectives on Structure and Mechanism in Organic Chemistry*; Brooks/Cole: Pacific Grove, CA, 1998; pp 349−365.
(2) (a) Adcock, W.; Trout, N. A.; Vercoe, D.; Taylor, D. K.; Shiner, V. J.; Sorensen, T. S. *J. Org. Chem.* **2003**, *68*, 5399. (b) Gajewski, J. J.; Bocian, W.; Brichford, N. L.; Henderson, J. L. *J. Org. Chem.* **2002**, *67*, 4236. (c) Van Pham, T.; McClelland, R. A. *Can. J. Chem.* **2001**, *79*, 1887. (d) Smith, P. J.; Crowe, D. A. J.; Westaway, K. C. *Can. J. Chem.* **2001**, *79*, 1145.
(3) (a) Spies, M. A.; Toney, M. D. *Biochemistry* **2003**, *42*, 5099. (b) Mitchell, K. H.; Rogge, C. E.; Gierahn, T.; Fox, B. G. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 3784. (c) Rye, C. S.; Withers, S. G. *J. Am. Chem. Soc.* **2002**, *124*, 9756. (d) Frantom, P. A.; Pongdee, R.; Sulikowski, G. A.; Fitzpatrick, P. F. *J. Am. Chem. Soc.* **2002**, *124*, 4202.
(4) Streitwieser, A., Jr.; Jagow, R. H.; Fahey, R. C.; Suzuki, S. *J. Am. Chem. Soc.* **1958**, *80*, 2326.
(5) Weston, R. E., Jr. *Tetrahedron* **1959**, *6*. 31.
(6) (a) Halevi, E. A.; Nussim, M.; Ron, A. *J. Chem. Soc.* **1963**, 866. (b) Bary, Y.; Gilboa, H.; Halevi, E. A. *J. Chem. Soc., Perkin Trans. 2* **1979**, 938.
(7) Van der Linde, W.; Robertson, R. E. *J. Am. Chem. Soc.* **1964**, *86*, 4505.
(8) Northcott, D.; Robertson, R. E. *J. Phys. Chem.* **1969**, *73*, 1559.
(9) Halevi, E. A. *Prog. Phys. Org. Chem.* **1963**, *1*, 109.
(10) Toyota, S.; Oki, M. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2215.
(11) (a) Perrin, C. L.; Ohta, B. K. *J. Am. Chem. Soc.* **2001**, *123*, 6520. (b) Perrin, C. L.; Ohta, B. K. *J. Mol. Struct.* **2003**, *644*, 1.
(12) Perrin, C. L.; Fabian, M. A. *Anal. Chem.* **1996**, *68*, 2127.
(13) The mixture of methylamine (**1**) isotopologs was synthesized by reduction of trimethylsilyl isothiocyanate with $LiAlD_4$ + $LiAlH_4$. Deuterated **3** and **4** were synthesized by reduction of benzaldehyde oxime or *N*-methyl-*N*-phenylcarbamic acid methyl ester with $LiAlD_4$.
(14) Reduction of *N*-benzyl-3-methylglutarimide with 9:1 $LiAlD_4/LiAlH_4$ produced a sample with ^1H NMR signals α to the nitrogen due to a 1:1 mixture of isotopomers of **5-*d*$_3$**.
(15) Forsyth, D. A.; Yang, J.-R. *J. Am. Chem. Soc.* **1986**, *108*, 2157.
(16) Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157.
(17) Thomas, H. D.; Chen, K. H.; Allinger, N. L. *J. Am. Chem. Soc.* **1994**, *116*, 5887.
(18) (a) Sunko, D. E.; Hehre, W. J. *Prog. Phys. Org. Chem.* **1983**, *14*, 205. (b) Williams, I. H. *J. Mol. Struct. (THEOCHEM)* **1983**, *14*, 105.
(19) Gawlita, E.; Lantz, M.; Paneth, P.; Bell, A. F.; Tonge, P. J.; Anderson, V. E. *J. Am. Chem. Soc.* **2000**, *122*, 11660.
(20) (a) Anet, F. A. L.; Kopelevich, M. *Chem Commun.* **1987**, 595. (b) Forsyth, D. A.; Hanley, J. A. *J. Am. Chem. Soc.* **1987**, *109*, 7930.

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