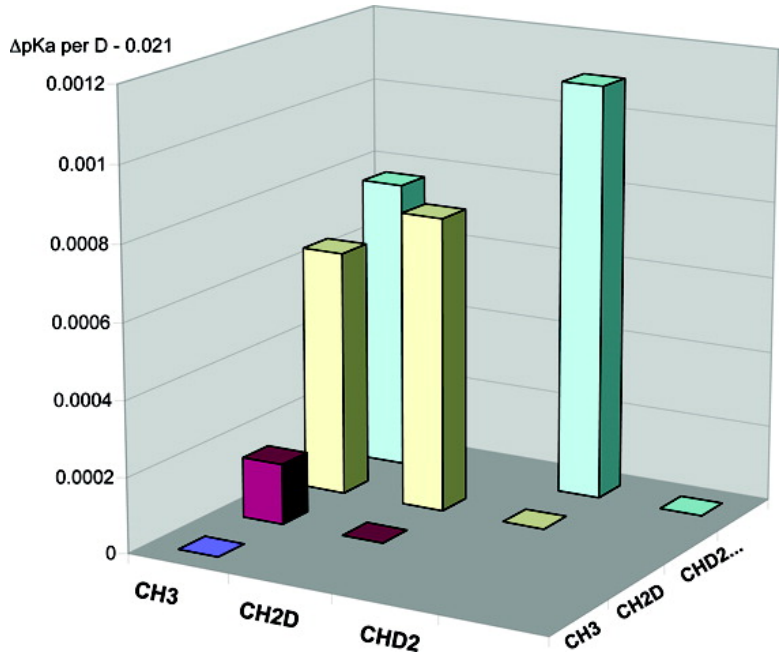
Article

Nonadditivity of Secondary Deuterium Isotope Effects on Basicity of Trimethylamine

Charles L. Perrin, and Yanmei Dong

J. Am. Chem. Soc., **2008**, 130 (33), 11143-11148 • DOI: 10.1021/ja803084w • Publication Date (Web): 29 July 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES

Published on Web 07/29/2008

Nonadditivity of Secondary Deuterium Isotope Effects on Basicity of Trimethylamine

Charles L. Perrin* and Yanmei Dong

Department of Chemistry 0358, University of California—San Diego, La Jolla, California 92093-0358

Received April 25, 2008; E-mail: cperrin@ucsd.edu

Abstract: Secondary deuterium isotope effects (IEs) on basicities of isotopologues of trimethylamine have been accurately measured by an NMR titration method applicable to a mixture. Deuteration definitely increases the basicity, by ~0.021 in the ΔpK per D. The IE is attributed to the lowering of the CH stretching frequency and zero-point energy by delocalization of the nitrogen lone pair into the C−H antibonding orbital. Because this depends on the dihedral angle between the lone pair and the C−H, a further consequence is a preference for conformations with H antiperiplanar to the lone pair and D gauche. This leads to a predicted nonadditivity of IEs, which is confirmed experimentally. It is found that the decrease in basicity, per deuterium, increases with the number of deuteriums. The nonadditivity of IEs is a violation of the widely assumed Rule of the Geometric Mean.

Introduction

A recent study reported secondary deuterium isotope effects (IEs) on amine basicity and verified that α-deuteration increases basicity.[1,2] The IE was attributed to a lowered zero-point energy (ZPE) of a CH bond when it is antiperiplanar or synperiplanar to a nitrogen lone pair, and the conformational dependence of IEs could be simulated computationally. We now report evidence for the nonadditivity of secondary deuterium IEs on amine basicity.

Conformational preference of an isotope can lead to nonadditivity of IEs on chemical shifts, as in benzylic carbocations,[3] 1-(*p*-fluorophenyl)cyclopentyl cation,[4] acetyl fluoride,[5] and 2,3-dimethyl-2-butyl cation.[6] In principle, the conformational isotope effect in 1,1,3,3-tetramethylcyclohexane, owing to the steric interaction between an axial CD_3 or CH_2D and an axial CH_3,[7] should show nonadditivity if two CD_3 or two CH_2D are compared. Nonadditivity of IEs on chemical shifts is also seen in some iridium tri- and tetrahydrides,[8] where it arises from a fluxional equilibrium between isotopomers (isomers that differ in the position of an isotope, as distinguished from isotopologues, which differ in the number of isotopic substitutions). The "simplest" cases of nonadditivity of IEs on NMR coupling constants and nuclear shielding are intrinsic, arising from interactions of vibrations, often bending modes.[9]

Conformational preference leads to nonadditivity of kinetic IEs in solvolysis of $(CH_3)_2CCl(CH_nD_{3-n})$ ($n = 0, 1, 2, 3$), where C−H trans to the leaving chloride provides more acceleration than C−D, but a second (and third) C−H provides a reduced acceleration.[10] We here seek the first example of nonadditivity of IEs on a chemical equilibrium, specifically amine basicities. This equilibrium represents a greater challenge than in solvolyses, where the filled−vacant hyperconjugative interaction of a C−H bond with the developing carbocation orbital is stronger than the filled−filled interaction ("negative hyperconjugation") of a C−H bond with the nitrogen lone pair.

If the IE on amine basicity arises from the conformational dependence of the ZPE of a CH bond, then in principle the IEs of successive deuteriums are nonadditive. However, this nonadditivity could not be detected with CH_3NH_2,[1] and it was estimated that $\Delta\Delta G°$ per D would increase by <1 cal/mol from CH_3 to CH_2D to CHD_2 to CD_3, which is too small to be detected reliably. To detect nonadditivity reliably, the IE must be magnified, as with three methyls. The isotopologues of trimethylamine are then the appropriate choice. Indeed, Northcutt and Robertson found that trimethylamine-d_9 is a stronger base than trimethylamine, with a substantial ΔpK, 0.206 at 0 °C.[11]

The nonadditivity of IEs on trimethylamine basicity depends on a greater stability for the rotamer with protium anti to the

(1) Perrin, C. L.; Ohta, B. K.; Kuperman, J. *J. Am. Chem. Soc.* **2003**, *125*, 15008.
(2) Perrin, C. L.; Ohta, B. K.; Kuperman, J.; Liberman, J.; Erdélyi, M. *J. Am. Chem. Soc.* **2005**, *127*, 9641.
(3) Forsyth, D. A.; Lucas, P.; Burk, R. M. *J. Am. Chem. Soc.* **1982**, *104*, 240.
(4) Forsyth, D. A.; Botkin, J. H. *J. Am. Chem. Soc.* **1984**, *106*, 4296.
(5) Hansen, P. E.; Nicolaisen, F. M.; Schaumburg, K. *J. Am. Chem. Soc.* **1986**, *108*, 625.
(6) Saunders, M.; Cline, G. W. *J. Am. Chem. Soc.* **1990**, *112*, 3955.
(7) Saunders, M.; Wolfsberg, M.; Anet, F. A. L.; Kronja, O. *J. Am. Chem. Soc.* **2007**, *129*, 10276.
(8) Heinekey, D. M.; Oldham, W. J., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 3137. Paneque, M.; Poveda, M. L.; Taboada, S. *J. Am. Chem. Soc.* **1994**, *116*, 4519. Webster, C. E.; Singleton, D. A.; Szymanski, M. J.; Hall, M. B.; Zhao, C.; Jia, G.; Lin, Z. *J. Am. Chem. Soc.* **2001**, *123*, 9822.
(9) Anet, F. A. L.; O'Leary, D. J. *Tetrahedron Lett.* **1989**, *30*, 2755. Sergeyev, N. M.; Sergeyeva, N. D.; Raynes, W. T. *Magn. Reson. Chem.* **1994**, *32*, 381. Sergeyev, N. M.; Sergeyeva, N. D.; Raynes, W. T. *Chem. Phys. Lett.* **1994**, *221*, 385. Wigglesworth, R. D.; Raynes, W. T.; Kirpekar, S.; Oddershede, J.; Sauer, S. P. A. *J. Chem. Phys.* **2000**, *112*, 736. Gee, C. H.; Raynes, W. T. *Chem. Phys. Lett.* **2000**, *330*, 595.
(10) Shiner, V. J., Jr.; Murr, B. L.; Heinemann, G. *J. Am. Chem. Soc.* **1963**, *85*, 2413.
(11) Northcott, D.; Robertson, R. E. *J. Phys. Chem.* **1969**, *73*, 1559.

lone pair. The first H on a methyl will thus take this position and lead to an increase in acidity of a CHD_2NH^+ over CD_3NH^+. An additional H, as in a CH_2D, cannot take that position, so that the increase in acidity will be less, and also less for CH_3. Thus, the IE per H will decrease as the number of H increases, or the IE per D will increase as the number of D increases. This is the direction of the nonadditivity that we have predicted and endeavored to test.

Success for this study can be anticipated from the preference for equatorial deuteriums in 1,3,5,5-tetramethylhexahydropyrimidine-2-*d* and 1-methylpiperidine-*cis*-2,6-d_2,[12] and from the elegant demonstration of diastereotopic H in 1,2-dimethylpiperidine-1-*d*, owing to perturbation of the rotameric equilibrium of the NCH_2D fragment.[13] Those are cases of isotopic perturbation of a conformational equilibrium, whereas this study involves a chemical reaction, with N−H bond-breaking or bond-making, and where the conformational equilibrium affects only one side of the equilibrium.

Nonadditivity is a powerful test for whether this IE might be of inductive origin. Although protium cannot simply be more electron-donating than deuterium,[14] an alternative is an electrostatic interaction between the N^+ and the dipole moment of the C−H bond, which is longer than C−D, owing to anharmonicity.[15] The dipole moments involved are exceedingly small, though. Besides, the interpretation in terms of ZPEs is consistent with the observation that the isotopomer of 1-benzyl-4-methylpiperidine-2,2,6-d_3 with deuterium trans to the methyl group is more basic.[1] Nevertheless, an inductive effect ought to be linear in the number of deuteriums, and nonadditivity would be strong evidence against an inductive origin for these IEs.

An NMR titration method makes it possible to measure IEs on basicities or acidities with great precision. The method depends on isotope shifts,[16] which lead to separate, resolvable, and assignable signals for isotopologues. The procedure involves successive additions of small aliquots of base to a mixture of acids. The stronger acid will be deprotonated first. Its chemical shift will then move ahead of that of the less acidic one, which lags behind. The acidity constants K_a and chemical shifts δ of both H and D acids can be related through eq 1,[17] where δ^+ or δ^0 is for the ammonium ion or amine, respectively, as measured at the beginning or end of the titration. Therefore, a plot of the quantity on the left vs $(\delta_H - \delta_H{}^0)(\delta_D{}^+ - \delta_D)$ should be linear, with zero intercept. The ratio of acidity constants, $K_a{}^h/K_a{}^d$, can then be evaluated as the least-squares slope of that plot.

$$(\delta_H{}^+ - \delta_H)(\delta_D - \delta_D{}^0) = (K_a{}^h/K_a{}^d)(\delta_H - \delta_H{}^0)(\delta_D{}^+ - \delta_D) \quad (1)$$

This method is capable of exquisite precision, because it is based only on chemical-shift measurements. It does not require accurate control of pH or volume or molarity or equivalents of base added, as is usual in pH titrations. The method is comparative. If there is no difference in acidities, there can be no lag of one chemical shift behind the other. As a result, minute imbalances of acidities are detectable. Moreover, because the titration is performed on a mixture of the two acids, under conditions guaranteed identical for both, it avoids systematic errors due to impurities that arise in the synthesis of one of the isotopologues but not the other. It has recently permitted measurement of secondary deuterium IEs in carboxylic acids and phenols.[18]

The titration can be performed on either the amine or the ammonium ion. We chose to titrate the amine hydrochloride with an anionic base, which has the advantage of maintaining constant ionic strength and reducing medium effects on chemical shifts. For solvents we chose DMSO-d_6, with KOtBu as base, and D_2O, with NaOD as base. The IE on the basicity of $(CH_3)_2NH$ had been found to be smaller in D_2O,[1] owing to hydrogen bonding to the lone pair, which reduces the n-σ^* delocalization that is responsible for the IE.[1,2,12] Consequently, DMSO offers the better prospect for detecting the nonadditivity, but it is also subject to random variations in its water content. Therefore, we measured IEs in both DMSO and D_2O.

The key comparison is between the IE on the basicity of $(CH_2D)_3N$ relative to $(CH_3)_3N$ and that on $(CHD_2)_3N$ relative to $(CH_2D)_3N$, each of these due to three additional deuteriums. To confirm these values, the composite of these two IEs can be measured from the comparison of $(CHD_2)_3N$ with $(CH_3)_3N$, due to six additional deuteriums. To be comprehensive, it is also possible to measure the IE of eight deuteriums by comparing trimethylamine with trimethylamine-d_8. All of these isotopologues are readily synthesized by standard procedures. We now report not only that deuteration decreases the acidity constant K_a of trimethylammonium ion (as had been known) but also that the IE is nonadditive, in that the decrease, per deuterium, increases with the number of deuteriums.

Experimental Section

NMR Spectroscopy. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 or Unity 500 spectrometer. All deuterium decoupling experiments were recorded on a Varian Mercury 400 spectrometer with a decoupling frequency calibrated from a ^2H NMR spectrum for amine C−D (not D_2O or DMSO-d_6). After each aliquot was added, the field homogeneity was shimmed on a ^1H NMR spectrum with deuterium lock, and then the cables were switched and a ^1H NMR spectrum was recorded with WALTZ decoupling through the lock channel. The spectral window was reduced to 700 Hz for ^1H NMR at 500 MHz or to 600 Hz for deuterium decoupling at 400 MHz, and the data were zero-filled to increase digital resolution. Proton chemical shifts in aqueous solutions are relative to acetonitrile (δ 2.05) as the internal standard, or to cyclohexane (δ 1.42) in DMSO-d_6. All chemical shifts were read as Hz, to avoid roundoff error in conversion to ppm. To help distinguish the peaks, an initial spectrum of a mixture of deuterated species and internal standard was obtained, and then the undeuterated or another deuterated compound was added.

Synthesis. After several unsuccessful attempts by various procedures that gave intolerably large contamination by $CH_3(CH_2D)_2N$, tri(methyl-*d*)amine hydrochloride [$(CH_2D)_3N\cdot HCl$] was obtained by reaction of tris(chloromethy1)amine[19] with $NaBD_4$. This procedure was adapted from the reaction with sodium methoxide in methanol,[20] but in D_2O to guard against H incorporation. Indeed, $CH_3(CH_2D)_2N$ did appear when D_2O was replaced by methanol or H_2O. The successful synthesis is remarkable in view of the extreme hygroscopicity and expected hydrolytic reactivity

(12) Anet, F. A. L.; Kopelevich, M. *Chem Commun.* **1987**, 595. Forsyth, D. A.; Hanley, J. A. *J. Am. Chem. Soc.* **1987**, *109*, 7930.
(13) Anet, F. A. L.; Kopelevich, M. *J. Am. Chem. Soc.* **1989**, *111*, 3429.
(14) Weston, R. E., Jr. *Tetrahedron* **1959**, *6*, 31.
(15) Halevi, E. A. *Prog. Phys. Org. Chem.* **1963**, *1*, 109.
(16) Batiz-Hernandez, H.; Bernheim, R. A. *Prog. Nucl. Magn. Reson. Spectrosc.* **1967**, *3*, 63. Jameson, C. J.; Osten, H. J. *Annu. Rep. NMR Spectrosc.* **1986**, *17*, 1. Hansen, P. E. *Prog. Nucl. Magn. Reson. Spectrosc.* **1988**, *20*, 207. Dziembowska, T.; Hansen, P. E.; Rozwadowski, Z. *Prog. Nucl. Magn. Reson. Spectrosc.* **2004**, *45*, 1.
(17) Perrin, C. L.; Fabian, M. A.; Armstrong, K. B. *J. Org. Chem.* **1994**, *59*, 5246. Perrin, C. L.; Fabian, M. A. *Anal. Chem.* **1996**, *68*, 2127.
(18) Perrin, C. L.; Dong, Y. *J. Am. Chem. Soc.* **2007**, *129*, 4490.
(19) Fluck, E.; Meiser, P. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 653.
(20) Fluck, E.; Meiser, P. *Chem. Ber.* **1973**, *106*, 69.

of $(ClCH_2)_3N$: ^1H NMR (D_2O) δ 2.72 (t, $J = 1.78$ Hz). Tri(methyl-d_2)amine hydrochloride [$(CHD_2)_3N\cdot HCl$] was readily obtained by an adaptation of a general procedure,[21] involving ammonium formate, formic acid, and formaldehyde-d_2: ^1H NMR (D_2O) δ 2.70 (qn, $J = 1.78$ Hz). A mixture of trimethylamine-d_8 hydrochloride, [$(CHD_2)(CD_3)_2N\cdot HCl$] and trimethylamine-$d_9$ hydrochloride [$(CD_3)_3N\cdot HCl$] was obtained similarly, from ammonium-d_x formate-d, formic-d_2 acid, anhydrous formic acid, and formaldehyde-d_2, with a total H content in the formates equal to 8 mol %: ^1H NMR (D_2O) δ 2.70 (quintet, $J = 1.78$ Hz), due to $(CD_3)_2(CHD_2)$-$N\cdot HCl$, without interference from $(CD_3)_3N\cdot HCl$, which is present in large amount but invisible. Nor can appreciable $CD_3(CHD_2)_2N$ be present, inasmuch as the deuterium-decoupled ^1H NMR spectrum shows no minor shoulder.

Each deuterated trimethylamine sample was extracted from aqueous NaOH into CH_2Cl_2 and then acidified with 6 M aqueous HCl and evaporated to dryness, to produce the hydrochloride salt as a white solid. Undeuterated trimethylamine hydrochloride was a commercial sample, used without purification.

NMR Titrations. The NMR sample prepared for each titration contained 0.5 mL of D_2O or organic solvent and appropriate concentrations of internal standard and a pair of isotopologues of the amine, adjusted to ensure nearly equal peak heights under conditions of deuterium decoupling, so that signal assignments could be maintained even if there is signal crossover during the titration.

Samples in DMSO-d_6 were first acidified with 2 μL of 0.1 M CF_3COOH to ensure complete protonation, and then 5-μL aliquots of KOtBu in DMSO-d_6 were used as the base. Aqueous samples were acidified with 5 μL of 0.1 M DCl and then titrated with as many as 20 5- or 10-μL aliquots of NaOD in D_2O.

NMR spectra were recorded after each addition. At least 10 aliquots were used for each titration. Titrations were assumed to be complete when there was no peak movement >0.002 ppm upon further addition of base. Small changes of chemical shifts past the end point were detected, owing to increasing ionic strength, but the IE values obtained were insensitive to the choice of end point. Chemical shifts of appropriate reporter nuclei were extracted from each spectrum, and the data were fit to eq 1.

Results

For trimethylamine, deuteration produces an upfield ^1H NMR shift, as is usual for isotope shifts.[16] Moreover, the signals of all trimethylammonium isotopologues move upfield on deprotonation. The ^1H NMR signals of protio and deuterio amines cross and recross during the titration. Because deuteration produces an upfield intrinsic isotope shift in both the amine and the ammonium ion, this is strong evidence that the protio ammonium ion is more acidic.

Figure 1 shows a plot of eq 1 from the NMR titration of a mixture of tri(methyl-d)ammonium and tri(methyl-d_2)ammonium hydrochlorides with NaOD in D_2O. The blank area in the middle is from spectra where signals crossed past each other and obscured the exact chemical shifts. The slope is 1.1618 ± 0.0004. The intercept is -0.0061 ± 0.0046, properly zero. The correlation coefficient is 0.999999.

All IEs were measured pairwise, from mixtures of trimethylamine and tri(methyl-d)amine, of tri(methyl-d)amine and tri(methyl-d_2)amine, of trimethylamine and tri(methyl-d_2)amine, or of trimethylamine and trimethylamine-d_8. Tables 1 and 2 list the various IEs, expressed (1) as the ratio of the acidity constant K_a of an ammonium ion to that of the corresponding ammonium ion with 3, 3, 6, 6, 8, or 2 additional deuteriums; (2) as $\Delta pK_a = \log_{10}(K_a/K_a^D)$; and (3) as ΔpK_a per additional deuterium.

(21) Icke, R. N.; Wisegarver, B. B.; Alles, G. A. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. 3, p 723. Lindeke, B.; Anderson, E.; Jenden, D. J. *Biomed. Mass Spectrom.* **1976**, *3*, 257.

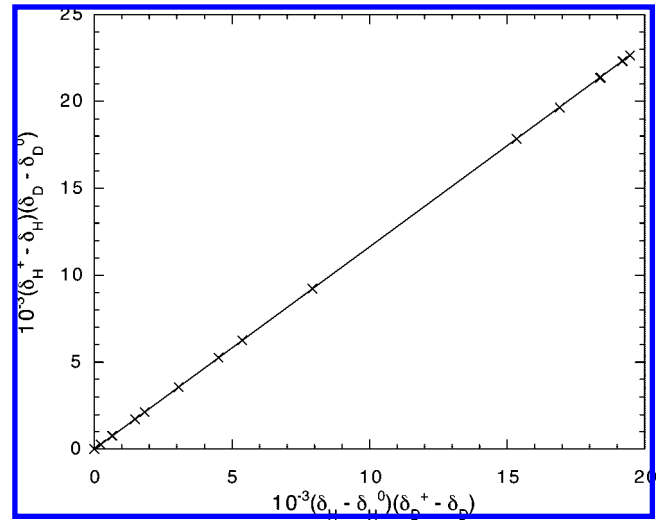


Figure 1. NMR titration (eq 1) of a mixture of $(CH_2D)_3NH^+$ and $(CH_2D)_3NH^+$.

Numbers in parentheses are errors in the last decimal place of the value reported. In all cases, K_a/K_a^D is greater than 1, corresponding to a deuterium IE that increases the basicity of trimethylamine. The positive ΔpK_a represents this same feature.

All titrations in D_2O were repeated, and values from separate titrations were averaged. The averages are reported in Table 3. Some of the data in Table 3 show larger errors between titrations than the errors in Table 2, which correspond to errors within a titration, but the data are very reproducible. It should be noted that the values of ΔpK_a per D in Table 3 correspond to values of $\Delta\Delta G°$ that range from 29.2 to 30.5 cal/mol. This reinforces the previous conclusion that the nonadditivity of the IE in methylamine would be <1 cal/mol.[1]

The ratio $K_a^{CH_3}/K_a^{CHD_2}$, evaluated directly from titration of a mixture of trimethylamine and tri(methyl-d_2)amine (third data column), agrees well with the product (fourth data column) of $K_a^{CH_3}/K_a^{CH_2D}$ and $K_a^{CH_2D}/K_a^{CHD_2}$. These ought to be identical, and the discrepancy between them is a measure of the systematic errors. This discrepancy is greater in DMSO, where it is intolerably large. We attribute the error to random variations in the water content of the DMSO-d_6. The data show that the IE is larger in DMSO, but the water content reduces the IE. Consequently, we place less reliance on the studies in DMSO, even though the larger IE ought to have made the nonadditivity easier to document.

The data in the tables are difficult to compare, because K_a/K_a^D and ΔpK_a correspond to the IEs from different numbers of deuteriums. Even ΔpK_a per D is difficult to comprehend, because the values are so small and so similar. To represent those values more clearly, ΔpK_a per D from Table 3 is displayed in Figure 2, showing pairwise comparisons of CH_3, CH_2D, and CHD_2 from left to right, against CH_3, CH_2D, CHD_2, and CD_3 (actually data for trimethylamine-d_8) from front to back. To exaggerate the variations, 0.021 has been subtracted from every value, so there are very tall columns below the "floor".

The key result is that $K_a^{CH_2D}/K_a^{CHD_2}$ (second column of data in Tables 1−3) is larger than $K_a^{CH_3}/K_a^{CH_2D}$ (first column of data) in both DMSO and D_2O. The difference between them is statistically significant. The ratio $K_a^{d_0}/K_a^{d_8}$ (last column) is still larger, because it is the IE of eight D, but on a per-deuterium basis it is intermediate between $K_a^{CH_3}/K_a^{CH_2D}$ and $K_a^{CH_2D}/K_a^{CHD_2}$ and closer to the latter. The ratio $K_a^{CH_3}/K_a^{CHD_2}$ (third or fourth

Table 1. Isotope Effects of $(CH_nD_{3-n})_3$ on Trimethylamine Basicities in DMSO-d_6

	CH_3/CH_2D	CH_2D/CHD_2	CH_3/CHD_2	CH_3/CHD_2[a]	d_0/d_8	d_6/d_8[b]
K_a/K_a^D	1.2008(10)	1.2042(8)	1.4358(11)	1.4460(15)	1.6374(19)	1.1404(16)
ΔpK_a	0.0795(4)	0.0807(3)	0.1571(3)	0.1602(5)	0.2142(5)	0.0571(6)
ΔpK_a per D	0.02649(12)	0.02690(9)	0.02618(5)	0.02670(8)	0.02677(6)	0.0285(3)

[a] Evaluated as the product of CH_3/CH_2D and CH_2D/CHD_2. [b] Evaluated as the ratio of d_0/d_8 to CH_3/CHD_2.

Table 2. Isotope Effects of $(CH_nD_{3-n})_3$ on Trimethylamine Basicities in D_2O

	CH_3/CH_2D	CH_2D/CHD_2	CH_3/CHD_2	CH_3/CHD_2[a]	d_0/d_8	d_6/d_8[b]
K_a/K_a^D	1.1573(7)	1.1618(4)	1.3509(7)	1.3446(9)	1.4939(6)	1.1058(7)
K_a/K_a^D, repeat	1.1574(6)	1.1628(7)	1.3465(6)	1.3458(11)	1.4929(8)	1.1087(8)
ΔpK_a	0.0635(2)	0.0651(1)	0.1306(2)	0.1286(3)	0.1743(2)	0.0437(3)
ΔpK_a, repeat	0.0635(2)	0.0655(3)	0.1292(2)	0.1290(3)	0.1740(2)	0.0448(3)
ΔpK_a per D	0.02115(8)	0.02171(5)	0.02177(4)	0.02143(5)	0.02179(2)	0.0218(1)
ΔpK_a per D, repeat	0.02116(7)	0.02184(9)	0.02154(3)	0.02150(6)	0.02176(3)	0.0224(2)

[a] Evaluated as the product of CH_3/CH_2D and CH_2D/CHD_2. [b] Evaluated as the ratio of d_0/d_8 to CH_3/CHD_2.

Table 3. Averaged Isotope Effects of $(CH_nD_{3-n})_3$ on Trimethylamine Basicities in D_2O

	CH_3/CH_2D	CH_2D/CHD_2	CH_3/CHD_2[a]	CH_3/CHD_2[b]	d_0/d_8	d_6/d_8[c]
K_a/K_a^D	1.15736(3)	1.1623(7)	1.3487(22)	1.3452(9)	1.4934(7)	1.1073(19)
ΔpK_a	0.06347(1)	0.0653(3)	0.1299(7)	0.1288(3)	0.1742(2)	0.0443(7)
ΔpK_a per D	0.02116(0)	0.02178(9)	0.02165(12)	0.02147(5)	0.02177(2)	0.0221(4)

[a] Includes data from a third titration. [b] Evaluated as the product of CH_3/CH_2D and CH_2D/CHD_2. [c] Evaluated as the ratio of d_0/d_8 to CH_3/CHD_2.

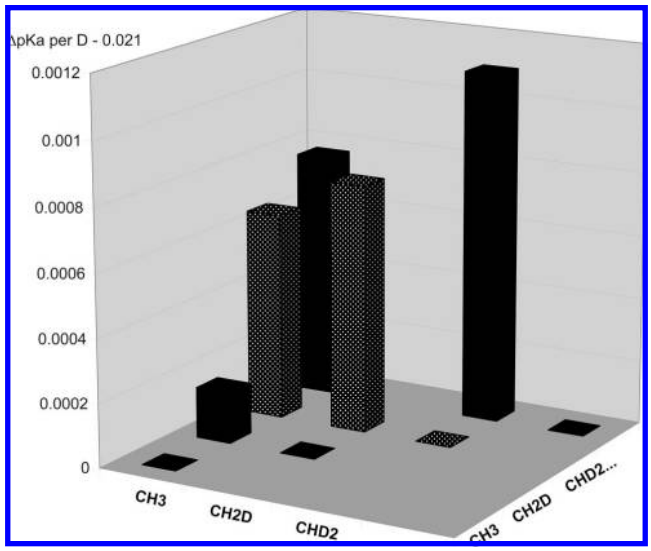


Figure 2. Nonlinearity of IEs on trimethylamine basicities in D_2O, comparing $(CH_nD_{3-n})_3$ ($n = 3, 2, 1$) to $(CH_nD_{3-n})_3$ ($n = 2, 1, 0$), displayed as ΔpK_a per D $-$ 0.021.

data column) is also larger than $K_a^{CH_2D}/K_a^{CHD_2}$ or $K_a^{CH_3}/K_a^{CH_2D}$, because it is the IE of six D, but on a per-deuterium basis it is intermediate between those two (except possibly in DMSO).

Another key result is that reported in the last column of the tables. This corresponds to the comparison between $(CD_3)_2(CHD_2)N$ and $(CHD_2)_3N$, obtained from the titrations of each vs $(CH_3)_3N$. It represents the IE of the two additional deuteriums in $(CD_3)_2(CHD_2)N$. Per deuterium, this IE is larger than any other. This is the tallest bar in Figure 2.

Discussion

Comments on Synthesis. Although tri(methyl-d_2)amine and tri(methyl-d_3)amine were readily prepared, without contamination by higher or lower isotopologues, the synthesis of tri(methyl-d)amine [$(CH_2D)_3N$] was plagued by formation of some $CH_3(CH_2D)_2N$. The amount was slight, but the presence of additional signals greatly complicates the NMR titration. The signals of the more acidic CH_3-containing material start downfield but move upfield more quickly on deprotonation. Consequently, those signals cross past that of the CH_2D-containing material. With so many extraneous signals, the crossovers obscure the exact chemical shifts. Therefore, it was necessary to eliminate the contamination.

The contamination undoubtedly arises from an impurity in the precursors. Impurities are especially problematic, because three deuteriums must be incorporated into $(CH_2D)_3N$. Yet it did not matter whether the source of the deuterium was DCOOH or $NaBD_4$ or whether the source of the CH_2 was CH_2O or paraformaldehyde or Na^+ $HOCH_2SO_3^-$ or $CH_2(OCH_3)_2$, any of which might enter into a chemical exchange reaction with the deuteride donor. Such exchange would be detrimental, inasmuch as H^- transfer would then be favored by a kinetic isotope effect, as is seen in the hydride transfer from formate to triarylmethyl cations.[22] Surprisingly, we could not find data on a kinetic isotope effect involving BD_4^-, but it is likely to be substantial. Yet the commercial $NaBD_4$ is claimed to be 98 atom % D, and we could not detect BHD_3^- by ^1H NMR. We suspect an exchange reaction, as has been observed between $(CH_3)_3NBH_3$ and D_2O.[23]

We found that isotopically pure tri(methyl-d)amine hydrochloride could be obtained by reaction of tris(chloromethy1)amine with $NaBD_4$ in D_2O. It may be that exchange was avoided, or that the kinetic isotope effect was smaller with a more reactive electrophile.

In contrast, heating a mixture of DCO_2NH_4, DCOOD, and CD_2O gave very pure $(CD_3)_3N\cdot HCl$, with no detectable ^1H NMR signal. This was unsuitable for NMR titration, because $(CD_3)_3N$ is invisible in ^1H NMR, and we needed $(CD_3)_2(CHD_2)N$ as an impurity. We therefore repeated the synthesis with a proportion of H^- donor that led to a mixture of

(22) Stewart, R.; Toone, T. W. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1243.
(23) Davis, R. E.; Brown, A. E.; Hopmann, R.; Kibby, C. L. *J. Am. Chem. Soc.* **1963**, *85*, 487.

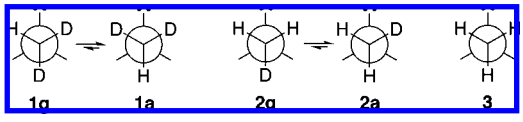
trimethylamine-d_8 and -d_9, without appreciable amounts of either isotopomer of trimethylamine-d_7.

Origin of Isotope Effect. Before considering the nonadditivity of IEs on amine basicity, it is necessary to recapitulate the origin of the IE itself.[1,2] The IR spectra of amines show characteristic bands (Bohlmann bands) around 2700−2800 cm^{-1},[24] lower than the 2900 cm^{-1} of a typical CH stretch. Upon *N*-protonation, these bands revert to a typical frequency. Therefore, the ZPE of the CH increases on protonation, but the increase is less for CD. Consequently, a CH amine resists *N*-protonation and is less basic.

The lowering of the CH stretching frequency in an amine, relative to the protonated amine, is attributed to delocalization of the nitrogen lone pair into the C−H antibonding orbital. This was shown to be of stereoelectronic origin, depending on the dihedral angle between the lone pair and the C−H.[1,2,12] It reaches a maximum when that dihedral angle is 180°, corresponding to a conformation with the lone pair antiperiplanar to the C−H.

Quantitative Origin of Nonadditivity. It is possible to express the acidity constants K_a of each of the isotopologues of trimethylammonium ion. For $(CD_3)_3NH^+$, which is a single conformer, this is simply $[H^+][(CD_3)_3N]/[(CD_3)_3NH^+]$, and analogously for $(CH_3)_3NH^+$. For the other two isotopologues, it is necessary to recognize that each acid and each base is a mixture of conformers. The acidity constant for $(CHD_2)_3NH^+$ is given by eq 2, where the sequence of *g*'s and *a*'s designates how many of the three methyl fragments have their single H gauche (**1g**) or anti (**1a**, more stable) to the lone pair. The acidity constant for $(CH_2D)_3NH^+$ is also given by eq 2, except that the sequence of *g*'s and *a*'s designates how many of the three methyl fragments have both H gauche to the lone pair (**2g**) or have one of the H's anti (**2a**, more stable). The denominators will simplify because all conformers of an acid have the same energy, but the denominators and the numerators have statistical factors 8, 12, 6, and 1 and 1, 6, 12, and 8 for *ggg*, *gga*, *aag*, and *aaa* of **1** and **2**, respectively.

$$K_a^{(CHD_2)_3NH^+} = [H^+]\frac{[ggg]+[gga]+[aag]+[aaa]}{[gggH^+]+[ggaH^+]+[aagH^+]+[aaaH^+]} = K_a^{(CH_2D)_3NH^+} \quad (2)$$



To simplify the numerators of eq 2, it is convenient to relate the concentrations of the various conformers to their molar ZPEs. Let the extra ZPE of a CHD_2NH^+ fragment, relative to that of CD_3NH^+, be designated as E_+, regardless of conformation. Then the extra ZPE of a protonated $CH_nD_{3-n}NH^+$ fragment, relative to CD_3NH^+, is simply nE_+, linear in *n*, the number of H. Further, let the extra ZPE of an unprotonated CH_3N fragment (**3**), relative to CD_3N, be $2E_g + E_a$, where separate E_g and E_a apply to H's that are gauche or anti to the N lone pair. Because the ZPE is lower for an H anti to the lone pair, $E_g > E_a$. Furthermore, the extra ZPEs of the conformers of $(CHD_2)_3N$, relative to $(CD_3)_3N$, are given by $n_gE_g + n_aE_a$, where n_g and n_a are the numbers of CHD_2N fragments with H gauche and anti to the lone pair, respectively (**1g** and **1a**). Likewise, the extra ZPEs of the conformers of $(CH_2D)_3N$, relative to $(CD_3)_3N$, are given by $2n_gE_g + n_a(E_a + E_g)$, where n_g is the number of CH_2DN fragments with both H gauche to the lone pair (**2g**) and n_a is the number of CH_2DN fragments with one H gauche to the lone pair and one H anti (**2a**).

For further simplification, all acidity constants can be compared to that of $(CD_3)_3NH^+$. The various concentrations in eq 2 can then be expressed in terms of Boltzmann factors governed by the ZPEs of the various conformations, along with their statistical factors, to obtain eqs 3 and 4. The third-power dependence is a confirmation of the magnification of the IEs by three methyls. For completeness, eq 5 gives the acidity constant for $(CH_3)_3NH^+$, which is a simpler expression because it and its conjugate base are single conformers.

$$\frac{K_a^{(CHD_2)_3NH^+}}{K_a^{(CD_3)_3NH^+}} = \frac{[2\exp(-E_g/RT)+\exp(-E_d/RT)]^3}{27\exp(-3E_+/RT)} \quad (3)$$

$$\frac{K_a^{(CH_2D)_3NH^+}}{K_a^{(CD_3)_3NH^+}} = \frac{[\exp(-2E_g/RT)+2\exp(-(E_a+E_g)/RT)]^3}{27\exp(-6E_+/RT)} \quad (4)$$

$$\frac{K_a^{(CH_3)_3NH^+}}{K_a^{(CD_3)_3NH^+}} = \frac{[3\exp(-(E_a+2E_g)/RT)]^3}{27\exp(-9E_+/RT)} \quad (5)$$

A further simplification results from setting $\varepsilon_g = E_+ - E_g$ and $\varepsilon_a = E_+ - E_a$, leading to eqs 6−8. These expressions are still sufficiently formidable that they verify the nonadditivity of the IE. Linearity would require the expression in eq 7 to be the square of that in eq 6, and would require the expression in eq 8 to be the product of those in eqs 6 and 7, and these requirements clearly do not hold. The nonadditivity can be traced to the preference for conformations with H anti to the lone pair, leading to the sums that appear in the numerators of these equations, with $\varepsilon_g < \varepsilon_a$. Notice further that the temperature dependence of the IE is quite complicated. Unfortunately, a separation into enthalpy and entropy is far beyond the accuracy of these measurements.

$$\frac{K_a^{(CHD_2)_3NH^+}}{K_a^{(CD_3)_3NH^+}} = \left[\frac{2}{3}\exp(\varepsilon_g/RT)+\frac{1}{3}\exp(\varepsilon_a/RT)\right]^3 \quad (6)$$

$$\frac{K_a^{(CH_2D)_3NH^+}}{K_a^{(CD_3)_3NH^+}} = \left[\frac{1}{3}\exp(2\varepsilon_g/RT)+\frac{2}{3}\exp((\varepsilon_a+\varepsilon_g)/RT)\right]^3 \quad (7)$$

$$\frac{K_a^{(CH_3)_3NH^+}}{K_a^{(CD_3)_3NH^+}} = [\exp((\varepsilon_a+2\varepsilon_g)/RT)]^3 \quad (8)$$

The IEs in Table 3 can be fit to eqs 6–8. From four independent IEs, the best values of ε_g and ε_a are 3 ± 1 and 24 ± 1 cm^{-1}, respectively, or 10 and 70 cal/mol. These values deviate slightly from a $\cos^2$ dependence of orbital overlap on dihedral angle, which would predict that the IE of a gauche deuterium is 25% that of an anti one. It should be noted that a dependence stronger than $\cos^2$ was also observed in solvolysis of $(CH_3)_2CCl(CH_nD_{3-n})$,[10] and in the calculated C−D stretching frequency in conformers of DCH_2NH_2. If the CH frequency of the trimethylammonium ion is taken as 2900 cm^{-1}, these values of ε_g and ε_a correspond to lower frequencies, 2880 and 2740

(24) Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157.

cm^{-1}, for CH gauche and anti, respectively, to the lone pair in trimethylamine. Such values are quite reasonable.

Significance of Nonadditivity. The nonadditivity is evidence for the origin of the IE in the ZPE of C−H vibrations. It is especially strong evidence that this IE is not of inductive origin, which ought to be linear in the number of deuteriums.

The nonadditivity of IEs is a violation of the widely assumed Rule of the Geometric Mean.[25] According to that rule, the equilibrium constants for the isotopic disproportionation equilibria of $(CH_2D)_3N$ and $(CHD_2)_3N$ (eqs 9 and 10) and of their conjugate acids (eqs 11 and 12) must be unity (because symmetry numbers cancel). It follows that the acidity constant of $(CH_2D)_3NH^+$ must be the geometric mean of the acidity constants of $(CH_3)_3NH^+$ and $(CHD_2)_3NH^+$ (eq 13), and likewise for $(CHD_2)_3NH^+$ (eq 14). Nevertheless, the nonadditivity that we have succeeded in detecting means that eqs 13 and 14 do not hold, although they are close approximations.

$$2(CH_2D)_3N \rightleftarrows (CH_3)_3N + (CHD_2)_3N \quad (9)$$

$$2(CHD_2)_3N \rightleftarrows (CH_2D)_3N + (CD_3)_3N \quad (10)$$

$$2(CH_2D)_3NH^+ \rightleftarrows (CH_3)_3NH^+ + (CHD_2)_3NH^+ \quad (11)$$

$$2(CHD_2)_3NH^+ \rightleftarrows (CH_2D)_3NH^+ + (CD_3)_3NH^+ \quad (12)$$

$$K_a^{(CH_2D)_3NH^+} = (K_a^{(CH_3)_3NH^+} K_a^{(CHD_2)_3NH^+})^{1/2} \quad (13)$$

$$K_a^{(CHD_2)_3NH^+} = (K_a^{(CH_2D)_3NH^+} K_a^{(CD_3)_3NH^+})^{1/2} \quad (14)$$

How general is the nonadditivity of IEs in a chemical reaction? It is quite common with kinetics in H_2O-D_2O mixtures, where proton inventory studies can show whether more than one hydrogen is transferred in the rate-limiting step.[26] Of course, it is much easier to detect nonadditivity in the cases of kinetic IEs, simply because they are larger than secondary equilibrium IEs. Indeed, this is perhaps the first example of nonadditive equilibrium IEs in a chemical reaction other than a conformational equilibrium.

It would be advantageous to compare these solution results with those obtained in the gas phase. Our data show that the IEs are larger in DMSO but less reliable. In water, hydrogen-bonding to the nitrogen lone pair reduces the delocalization of that lone pair into the C−H antibonding orbital and diminishes the IE. The IE can be expected to be larger in the gas phase, and the nonadditivity as well. It is not clear whether experimental techniques are sufficiently accurate to detect the nonadditivity of IEs in the gas phase.

Computation might be more successful. Indeed, it should be noted that the C−L bond lengths in $(CL_3)_nNH_{3-n}$ (n = 1, 2, 3) are calculated to decrease from L = H to D to T, along with an increased negative atomic charge at N, although the decreases in bond lengths are not greater for the longer antiperiplanar C−L, and no attempt was made to model the nonadditivity of IEs.[27]

Conclusions

Not only does deuteration decrease the acidity constant K_a of trimethylammonium ion, but also the IE can be shown experimentally to be nonadditive, in that the decrease, per deuterium, increases with the number of deuteriums. The IE is attributed to the lowering of the CH stretching frequency by delocalization of the nitrogen lone pair into the C−H antibonding orbital, which depends on the dihedral angle between the lone pair and the C−H. The nonadditivity can further be modeled in terms of the conformational dependence of the ZPEs of $CH_nD_{3-n}NH^+$ and $CH_nD_{3-n}N$ (n = 0, 1, 2, 3). The nonadditivity of IEs is a violation of the widely assumed Rule of the Geometric Mean.

Acknowledgment. This research was supported by NSF Grants CHE03-53091 and CHE07-42801. Purchase of the NMR spectrometers was made possible by grants from NIH and NSF. We are grateful to Martin Saunders for discussion and encouragement and to Vernon Anderson and Mark Ruszczycky for helpful suggestions regarding the analysis of nonadditivity.

Supporting Information Available: Details of synthesis and spectral characterization. This information is available free of charge via the Internet at http://pubs.acs.org.

JA803084W

(25) Bigeleisen, J. *J. Chem. Phys.* **1955**, *23*, 2264.
(26) Schowen, K. B.; Schowen, R. L. *Methods Enzymol.* **1982**, *87*, 551. Venkatasubban, K. S.; Schowen, R. L. *CRC Crit. Rev. Biochem.* **1984**, *17*, 1.
(27) Reyes, A.; Pak, M. V.; Hammes-Schiffer, S. *J. Chem. Phys.* **2005**, *123*, 064104.