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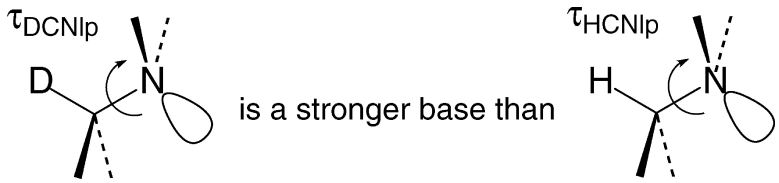

when lone pair is antiperiplanar or synperiplanar to C-D
($\tau = 180^{o}$ or 0^{o})

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Stereochemistry of β-Deuterium Isotope Effects on Amine Basicity

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Abstract: Secondary β-deuterium isotope effects on amine basicities are measured using a remarkably precise NMR titration method. Deuteration is found to increase the basicity of methylamine, dimethylamine, benzylamine, *N,N*-dimethylaniline, 2-methyl-2-azanorbornane, and pyrrolizidine. The increase in dimethylamine arises entirely from enthalpy, contrary to a previous report. The method permits a determination of intramolecular isotope effects in 1-benzyl-4-methylpiperidine and 2-benzyl-2-azanorbornane. It is found that deuteration has a larger isotope effect when either antiperiplanar or synperiplanar to a lone pair, but the synperiplanar effect is smaller, as confirmed by computations. The isotope effect is attributed to a lowered zero-point energy of a C−H bond adjacent to an amine nitrogen, arising from delocalization of either a syn or an anti lone pair, and with no detectable angle-independent inductive effect.

Introduction

Isotope effects (IEs) are characteristic features of rates and equilibria.[1] In contrast to primary IEs, secondary IEs arise when the bond to the isotope remains intact. They are further distinguished as α or β, depending on whether the isotope is separated by one or two bonds from the reaction center. They continue to provide mechanistic information regarding organic[2] and enzymatic reactions.[3] We now report definitive measurements of secondary deuterium IEs on amine basicities, and their dependence on temperature and stereochemistry, including the roles of both antiperiplanar and synperiplanar deuterium.

Alpha IEs usually arise from a change in hybridization, as in solvolyses,[4] where the reacting carbon changes from sp^3 to sp^2. This change is associated with a lowering of the C−H out-of-plane bending frequency ν, such that the zero-point energy ($= {}^1/_2 h\nu$) is reduced in the transition state. The reduction for C−D is less because zero-point energy is inversely proportional to the square root of mass. Consequently, the reduction for the protium substrate is greater, and it reacts faster than the deuterated one.

Beta IEs can be more problematic. In solvolyses they are generally attributed to hyperconjugation, whereby the electrons in the C−H bond are delocalized to stabilize the developing carbocation. In comparison, the C−D bond has a lower zero-point energy and is stronger, so delocalization becomes less effective. This cannot be a simple inductive effect, whereby protium is more electron-donating than deuterium, because the Born−Oppenheimer approximation guarantees the electronic wave function to be independent of nuclear mass.[5] Instead, it must derive from a change of vibrational frequencies, predominantly bending, and this requires orbital overlap.[6] Indeed, calculations indicate that the IE follows a $\cos^2$ dependence on the dihedral angle between the C−H or C−D bond and the vacant orbital of the developing carbocation.[7]

We here address β-deuterium IEs on amine basicity. These are equilibrium effects, not kinetic. Deuterium substitution consistently increases basicity, but the effects are small. For 2,4-dinitro-*N*-methylaniline-d_3 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 0.056 ± 0.001.[8] For benzylamine-α-d_2 the IE is 0.054 ± 0.001, but this was later revised to 0.032 ± 0.001. The error estimates are measures only of precision, and overoptimistic if there is systematic error due to an impurity in one of the samples, as the revision might suggest. Similarly, ΔpK_a is 0.056 for methylamine-d_3 and 0.12 for dimethylamine-d_6, but these are surprisingly temperature-independent.[9] The temperature independence was attributed to a fortuitous com-

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pensation of force constants, but it too would be consistent with systematic error from an impurity. Besides, temperature independence would require that the IE lie in the entropy. For trimethylamine-d_9 ΔpK_a is 0.185,[10] large enough to be beyond experimental error, but this could be due to steric repulsions,[11] which flatten trimethylamine-h_9, with its longer C−H bonds, owing to anharmonicity.

All of 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. Besides, the increase of basicity is opposite to deuterium's reduced electron-donating power in solvolyses. The IE in benzylamine was therefore attributed to an electrostatic interaction between the positive charge on the protonated nitrogen and the dipole moment of the C−H or C−D bond.[12] Because dipole moment is the product of charge separation and bond length, and because the C−H bond is longer than C−D, owing to anharmonicity, deuterium could show an electron-donating capability. Such an inductive effect, arising from monopole−dipole interaction, is consistent with the Born−Oppenheimer approximation. It seems to have been accepted as the source of these IEs,[13] even though the dipole moments involved are exceedingly small.

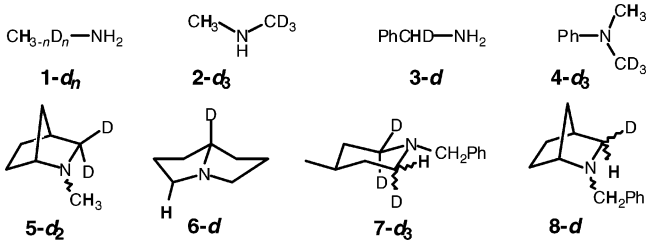
This inductive contribution can be estimated (if the dipole−dipole interaction between the lone pair and the bond is ignored relative to monopole−dipole). Anharmonicity leads to a $d_{CH} - d_{CD}$ of 0.34 pm. From infrared intensities of methane, the derivative of dipole moment with respect to C−H distance is $0.016e$.[14] The field effect on pK due to a dipole moment of 0.35D, as in propene, can be estimated as 0.95, the ΔpK between allylamine and methylamine. These combine to a ΔpK on deuteration of 0.0007, which is much smaller than the claimed IE.

Because we needed to be certain about such IEs before embarking on a study to assess the symmetry of NHN hydrogen bonds in tetramethylnaphthalenediamines,[15] we have reinvestigated them. A new NMR titration method makes it possible to measure relative basicities with great precision.[16] The procedure involves successive additions of small aliquots of acid to a mixture of bases. Acid will preferentially protonate the one that is more basic. Its chemical shift will then move ahead of that of the less basic one, which lags behind. Alternatively, it may be more convenient to add aliquots of base to a mixture of acids. Regardless, 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, as measured at the beginning or end of the titration. Therefore a plot of the quantity on the left versus $(\delta_1 - \delta_1^\circ)(\delta_2^+ - \delta_2)$ should be linear with zero intercept and with a slope equal to the ratio of acidity constants.

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

This method is capable of exquisite precision, because it is based only on chemical-shift measurements, not on pH or volume or molarity as in the usual pH titrations. The method is comparative. If there is no difference in basicities, there is no lag of one chemical shift behind the other. Therefore minute imbalances of basicities can be detected. Moreover, because the titration is performed on a mixture of the two bases, under conditions guaranteed identical for both, it avoids systematic error due to impurities. Further advantages are that it is applicable to a mixture of closely related substances, without the necessity of separating them, and that it can be applied in any solvent, even those where a pH electrode would be inoperative. Variants on this method have been developed for measuring IEs, using ^{19}F and ^{13}C NMR,[17] but without the advantage of data analysis by linear least squares.

IEs are now measured for deuterated methylamine (**1-$d_{0,1,2,3}$**), dimethylamine (**2-d_3**), benzylamine (**3-*d***), *N*,*N*-dimethylaniline (**4-d_3**), 2-methyl-2-azabicyclo[2.2.1]heptane (**5-d_2**), and pyrrolizidine (**6-*d***). Mixing any of these with the corresponding unlabeled material produces a ^1H NMR spectrum that shows resolvable isotope shifts[18] from the different isotopologues (isotopic homologues). The relevant reporter nuclei are depicted in boldface in the molecular structures. The acidity constant ratios for the isotopomers (isotopic stereoisomers) of 1-benzyl-4-methylpiperidine-d_3 (**7-d_3**) and 2-benzyl-2-azabicyclo[2.2.1]-heptane (**8-*d***) are also determined. Some of these results have been presented in a brief report.[19]



Experimental Section

NMR Spectroscopy. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 or Unity 500 spectrometer. Chemical shifts in aqueous solutions are relative to *tert*-butyl alcohol (δ 1.23) or dioxan (δ 3.75) as internal standard. The ^1H NMR signals of deuterated **1**−**6** were easily distinguished from those of undeuterated by using samples of known stoichiometry.

Syntheses. Benzylamine, *N*,*N*-dimethylaniline, dimethylamine·HCl, dimethyl-1,1,1-d_3-amine·HCl, and other reagents were commercially available and used without purification. Deuterated amines were obtained by reduction of a suitable precursor (trimethylsilyl isothiocyanate, benzaldehyde oxime, *N*-methyl-*N*-phenylcarbamic acid methyl ester, *N*-benzyl-3-methylglutarimide, $\Delta^{4(8)}$-dehydropyrrolizidinium perchlorate, or 2-benzyl-2-azabicyclo[2.2.1]heptan-3-one) with $LiAlD_4$ or a $LiAlD_4$−$LiAlH_4$ mixture. The ratio of $LiAlD_4$ to $LiAlH_4$ was adjusted empirically so as to produce ^1H NMR spectra in which the reporter peaks for all isotopologues are nearly equal in height, so that small

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chemical-shift differences can be resolved. For 2-benzyl-2-azabicyclo-[2.2.1]heptane-*d* and 1-benzyl-4-methylpiperidine-d_3 equality of peak heights is not necessary, because $H3_{exo}$ and $H3_{endo}$ or $H2_{ax}$ and $H2_{eq}$ are well separated, but these are necessarily produced in equal proportions as a consequence of the synthetic method. For these two cases the ratio of $LiAlD_4$ to $LiAlH_4$ was adjusted empirically so as to minimize interference from CH_2 signals without unduly reducing the intensity of the C−H signals. For **5-*d*$_2$** the source of deuterium was formaldehyde-d_2. Details of the syntheses are available in the Supporting Information, along with spectral characterizations.

^{1}H NMR Titrations. All samples, as well as stock solutions of DCl and NaOD, were prepared in D_2O or D_2O-CD_3OD, with care to prevent medium changes in aqueous methanol due to a varying solvent ratio. Dimethylamine·HCl and dimethyl-d_3-amine·HCl were simply mixed in a 1:2 ratio. Pyrrolizidine and pyrrolizidine-8-*d* were mixed in a 1:1 ratio. Aqueous methylamine·HCl and dimethylamine·HCl samples were back-titrated with a small quantity of DCl to ensure complete protonation and then titrated with 5−20-μL aliquots of 40% NaOD in D_2O. In DMSO-d_6 KOtBu was used as base. To catalyze proton-transfer equilibration between 2-methyl-2-azabicyclo[2.2.1]heptane isotopologues, a few drops of aqueous NH_3 was added. Benzylamine, *N*,*N*-dimethylaniline, 1-benzyl-4-methylpiperidine, and 2-benzyl-2-azabicyclo-[2.2.1]heptane samples in methanol-d_4:D_2O (1:1, 8:3, 4:1, and 5:1, respectively) were back-titrated with 5 μL of stock base and then titrated with aliquots (∼10 μL each) of acid. NMR spectra were recorded after each addition. At least 10 aliquots were used for each titration. Titrations were assumed to be complete when no peak movement was observed upon further additions of titrant.

Chemical shifts of appropriate reporter nuclei were extracted from the spectrum after adding each aliquot, and the data were fit to eq 1. The data for **7** showed poor linearity, because of insufficiently rapid proton exchange just before the end of the titration, so the endpoint chemical shifts δ^+ were taken from the sample with the most downfield δ_{eq}. At the end of the titration of **5** the methyl signals separate as exo and endo, and these chemical shifts were averaged. The intrinsic isotope shifts of $H3_{endo}$ in **6** and of the benzyl protons in **8** were not resolvable, so they were set equal to 1 ppb per D, as observed in **2** and **5**. This served to fix $\delta_D°$ and $\delta_D{}^+$.

Variable-Temperature Experiments. To probe the temperature dependence of the IE in dimethylamine-d_3, variable-temperature (VT) NMR experiments were performed using two different methodologies. For the first the VT controller was set to the desired temperature and NMR titrations were performed by adding titrant via a continual addition apparatus,[20] which avoids the need to eject the sample. Thus NMR spectra could be taken soon after addition of each aliquot, without a long wait for the sample to return to the probe temperature. Next, (K_a^H/K_a^D) was obtained from the measured chemical shifts, according to eq 1, and $\Delta\Delta H°$ and $\Delta\Delta S°$ could be determined from a plot of $\ln(K_a^H/K_a^D)$ versus $1/T$. It is thus possible to perform such titrations, but the procedure becomes tedious as the number of different temperatures increases.

Therefore an alternative method is rapid-pulse VT NMR "at constant probe temperature".[21] A 50%-deprotonated 1:2 sample of **2**·HCl and **2-*d*$_3$**·HCl in D_2O in an NMR tube with a concentric insert containing methanol was cooled to near freezing and placed into the probe, whose temperature had been set to 50 °C. Spectra were recorded every 5 s for a few minutes, until the sample attained the probe temperature. In each spectrum the peak separation Δ between the labeled and unlabeled dimethylamines was measured, and the temperature was monitored from the chemical shifts of the methanol. Control experiments with methanol in both compartments had shown that there is no appreciable temperature gradient across the tube. The chemical shift of either isotopologue of **2** is the weighted average of the chemical shifts of its protonated and neutral forms. At 50% neutralization the difference between these two chemical shifts can be simplified to eq 2, which relates the observed Δ to K_a^H/K_a^D, where Δ_o is the intrinsic separation in fully protonated or fully deprotonated amine and *D* is the difference, $\delta^+ - \delta^o$, between the limiting chemical shifts. Both Δ_o and *D* could be determined from previous titrations of dimethylamine. Because $K_a^H/K_a^D \approx 1$, eq 2 can be approximated by eq 3, so that a plot of Δ versus $1/T$ has slope equal to $-D\Delta\Delta H°/4R$ and intercept equal to $\Delta_o + D\Delta\Delta S°/4R$.

$$\Delta = \Delta_o + \frac{K_a^H/K_a^D - 1}{2(K_a^H/K_a^D + 1)}D \quad (2)$$

$$\Delta = \Delta_o + \frac{\ln(K_a^H/K_a^D)}{4}D \quad (3)$$

Computations. Ab initio density-functional calculations were performed on methylamine at the B3LYP/6-31G(d,p) level using Gaussian 98, revision A.7.[22] This level gives an HNH angle of 105.8°, properly less than tetrahedral, whereas it is 113.4° with HF/6-31G. The geometry was optimized with one HNCH dihedral angle constrained to a succession of values. From each such structure three C−H distances and three dihedral angles between C−H bonds and the lone pair were obtained. Also, in every structure each C−H was replaced sequentially by C−D and the C−D stretching frequency was calculated. This isotopic replacement serves to isolate a single stretch, uncoupled to others and without Fermi resonance.

Results

Assignment of Stereoisomers of 5·H$^+$. In DCl/D_2O exo/endo equilibration is slow, and a 1.6:1 ratio of stereoisomers is observed. The most downfield signals, at δ 2.72 (major) and 2.80 (minor), are readily assigned to H1. Saturating the major H1 enhances the major NCH_3 singlet at δ 1.61 by 2%, whereas saturating the minor H1 enhances the minor δ 1.62 singlet by only 1%. Because the relevant HH distances are estimated from MM2 modeling (ChemBats3DPro v.4.0) to be 2.46 Å for exo and 2.63 Å for endo, the major stereoisomer, with the larger NOE, is unquestionably the exo. An HMQC spectrum then correlates the δ 1.61 and 1.62 signals to the ^{13}C signals at δ 41.5 and 35.9, respectively. The latter must be the minor endo methyl, and this assignment is consistent with an upfield shift due to steric compression.

This agrees with the assignment of the major product from kinetic protonation of the amine as the exo,[23] but it is opposite from the assignment of the major form of the amine as endo.[24] Both of these previous assignments seem to be indisputable. Yet the major product from kinetic protonation must be the major form of the amine. The only way we perceive to reconcile this discrepancy is if equilibration occurred under conditions thought to achieve kinetic protonation. If so, then the major form of the amine is endo, but the more stable protonated form is the exo. This then requires that the exo be less acidic than the endo, even though these two structures are so similar.

Isotope Effects on Amine Basicity. Samples were subjected to 2−10 independent ^1H NMR titrations in D_2O or D_2O-CD_3OD and analyzed according to eq 1. Table S1 lists chemical shifts and isotope shifts ($\delta_D - \delta_H$) of each amine and ammonium ion. The isotopomers of **7-*d*$_3$** and **8-*d*** are specified by the

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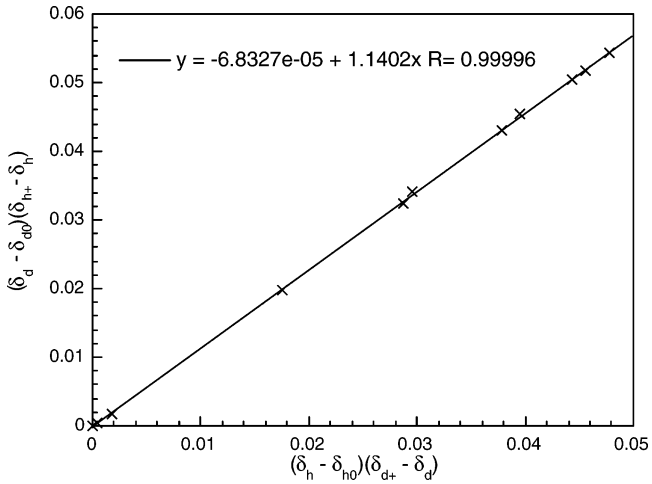


Figure 1. Linearized plot (eq 1) for titration of dimethylamine plus dimethylamine-d_3.

Table 1. β-Deuterium Isotope Effects on Amine Basicities

amine	K_H/K_D	ΔpK_a	$\Delta\Delta G°$ (cal/mol), per D
1	1.040 ± 0.006	0.017 ± 0.003	23.2 ± 3.4
1[a]	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
2[b]	1.174 ± 0.007	0.070 ± 0.002	31.6 ± 1.1
3	1.0419 ± 0.0009	0.0178 ± 0.0004	24.3 ± 0.5
4	1.1051 ± 0.0018	0.0434 ± 0.0007	19.8 ± 0.3
5[a]	1.092 ± 0.004	0.038 ± 0.002	26.1 ± 1.1
6[a]	1.029 ± 0.002	0.013 ± 0.001	16.9 ± 1.15
6[a]	1.037 ± 0.002[c]	0.016 ± 0.001	21.5 ± 1.1
7	1.060 ± 0.006[d]	0.0253 ± 0.0025	34 ± 3
8	1.039 ± 0.005	0.017 ± 0.002	23 ± 3
8[a]	1.074 ± 0.005	0.031 ± 0.002	21.1 ± 1.4
8	1.045 ± 0.004[c]	0.019 ± 0.002	26.1 ± 2.3
8[a]	1.086 ± 0.007[c]	0.038 ± 0.003	24.4 ± 1.9
8	1.003 ± 0.007[e]	0.001 ± 0.003	1.8 ± 4.1

[a] -d_2. [b] In DMSO-d_6. [c] Including estimated intrinsic isotope shifts. [d] K_{eq}/K_{ax}. [e] K_{exo}/K_{endo}.

orientation of deuterium, even though protium is the reporter nucleus. In particular, K_{eq} is for **7-*d*$_{eq}$**, which shows a 12-Hz doublet due to H_{ax}, whereas **7-*d*$_{ax}$** shows an H_{eq} multiplet further downfield. Likewise, K_{exo} and K_{endo} are for **8-*d*$_{exo}$** and **8-*d*$_{endo}$**, monitored by $H3_{endo}$ and $H3_{exo}$, respectively. This mixture of isotopomers was titrated using not only $H3_{endo}$ and $H3_{exo}$ as reporter nuclei but also the benzyl protons. The former provides K_{exo}/K_{endo}, and the latter provides K_H/K_D, which is also provided by **5**.

Excellent linearity was achieved for fits of NMR titration data to eq 1, with correlation coefficients typically >0.999. A typical titration of dimethylamine·HCl is shown as Figure 1. Individual titrations produced smaller errors than the variability among titrations, which were therefore averaged. Reported errors are the standard deviation of a set of titrations. Table 1 lists the IEs derived from such plots, expressed as K_H/K_D or K_{eq}/K_{ax} or K_{exo}/K_{endo}, along with ΔpK_a and $\Delta\Delta G°$ per D. For both **1** and **8** it was possible to measure the IEs separately for both single and double deuteration (but not for triple deuteration in **1**, because CD_3NH_2 is invisible by ^1H NMR). Data for **6** and **8** are presented both without and with correction for unresolvable intrinsic isotope shifts.

VT Experiments. Dimethylamine·HCl was titrated using two different NMR techniques to test the temperature dependence of the secondary β-deuterium IE. Figure 2 shows the results of

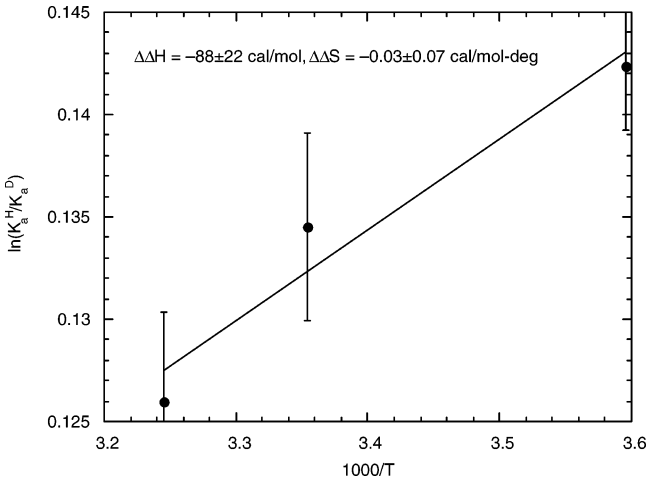


Figure 2. Variable-temperature data for relative basicities of dimethylamine and dimethylamine-d_3.

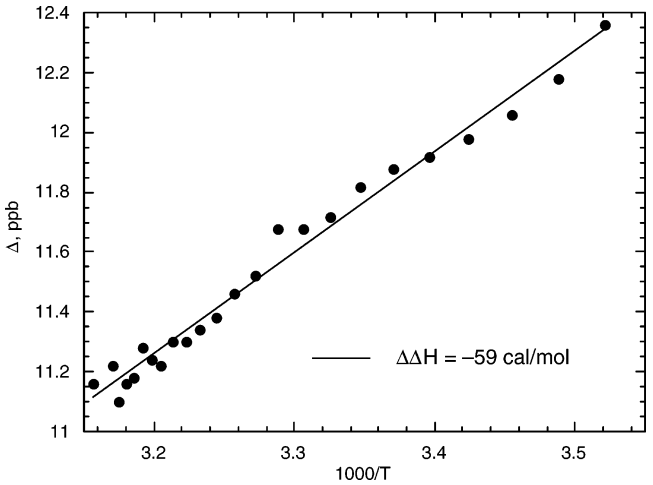
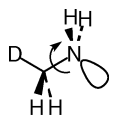


Figure 3. Temperature dependence of isotope shift in a half-neutralized mixture of **2** and **2-*d*$_3$**, by VT-NMR "at constant probe temperature".

separate NMR titrations run at 5, 25, and 35 °C. The IE is seen to be temperature-dependent, although the variation is hardly beyond the error bars. From the slope and intercept $\Delta\Delta H° = -88 \pm 21$ cal/mol and $\Delta\Delta S° = -0.034 \pm 0.072$ cal/mol·K. This $\Delta\Delta S°$ is not significantly different from zero.

An alternative methodology was utilized to acquire VT data at many more temperatures and across a wider range. The isotope shift was measured during the heating of a half-neutralized mixture of dimethylamine·HCl and dimethylamine-d_3·HCl from near freezing to ~50 °C. Figure 3 shows that this isotope shift is temperature-dependent, thus confirming the result in Figure 2. From the slope and intercept eq 3 leads to $\Delta\Delta H° = -58.7 \pm 1.7$ cal/mol and $\Delta\Delta S° = 0.060 \pm 0.006$ cal/mol·K.

Computations. Figure 4 shows the dependence of the C−H bond length in methylamine on the dihedral angle between the bond and the nitrogen lone pair, as well as the dependence of the C−D stretching frequency in DCH_2NH_2 (**1-*d***) on that dihedral angle. The solid curves are the best four-term Fourier



1-*d*

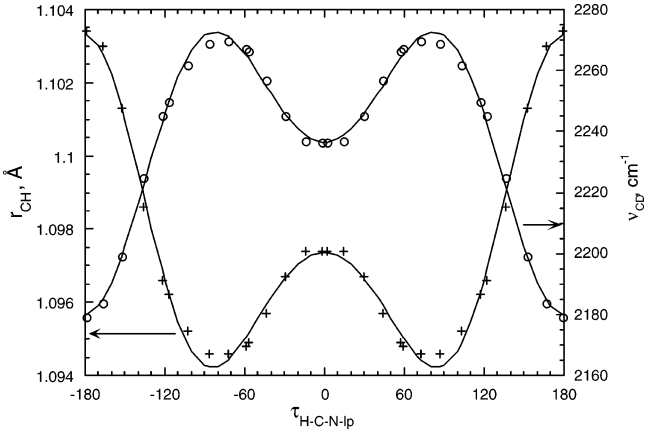


Figure 4. Relations among B3LYP/6-31G(d,p) C−H bond length in CH_3NH_2, C−D stretching frequency in DCH_2NH_2, and dihedral angle between the bond and the nitrogen lone pair.

fits. There is an almost linear relation between the frequency and the bond length (figure not shown), which reflects their contrary but nonlinear variations in Figure 4.

Discussion

Isotope Effects on Amine Basicity. The IEs in Table 1 are small, but they are highly accurate. For **1** the ΔpK_a's are proportional to the number of deuteriums, and for **1**−**3** and **8** the ΔpK_a per D or the $\Delta\Delta G°$ per D is nearly constant.

The key result is that there are secondary deuterium IEs on amine basicities. The linear least-squares method, combined with the ability to measure NMR chemical shifts accurately, improves the precision by an order of magnitude and confirms the previous reports.[8,9] The ΔpK_a data in Table 1, converted to a per-deuterium basis, agree with the (revised) value of 0.016 for **3** and 0.02 for **2**, but our 0.014 for **4** is significantly lower than the 0.019 for 2,4-dinitro-*N*-methylaniline,[8] which we conclude is erroneous, inasmuch as the IE should be lower for aromatic and nitroaromatic amines, whose nitrogen lone pairs are delocalized.

Origin of the Isotope Effects. Above we rejected the possibility that these IEs are due to an inductive effect. Instead, we attribute them to changes in vibrational frequencies, even without rehybridization at C or N upon protonating the nitrogen. IR spectra of amines show characteristic bands, known as Bohlmann bands, around 2700−2800 cm^{-1},[25] lower than the 2900 cm^{-1} of a typical C−H stretch. Upon *N*-protonation these seem to disappear, because they revert to typical frequencies and are lost among other C−H modes. Therefore the zero-point energy increases on protonation, but the increase is less for C−D than for C−H. Indeed, a frequency change of 100 cm^{-1} corresponds to a ΔpK_a of 0.03, comparable to the observed IEs. This good agreement supports the involvement of stretching modes, rather than the bending modes proposed for the kinetic IE in methylation of *N*,*N*-dimethylaniline-d_6.[26]

The reduction of frequency is associated with a C−H bond antiperiplanar to the nitrogen lone pair.[27] It is generally attributed to negative hyperconjugation, or delocalization of the lone pair into the vacant σ^*_{CH} orbital.[28] Isotope effects on gas-phase basicities of methylamine, dimethylamine, and trimethylamine can be reproduced by ab initio force constants for C−H stretching, which increase on *N*-protonation.[29] Negative hyperconjugation is also supported by calculations on carbanions and alcohols,[7,30] and by the ΔpK_a of 0.056 in trifluoroethanol-d_2.[31] These IEs are smaller than in solvolyses, because filled−filled orbital interactions are weaker than filled−vacant ones. They are also smaller than IEs calculated from (planar) $DCH_2CH_2^-$,[7] because the orbital energy of the lone pair on a nitrogen or oxygen is lower than that in the carbanion, thus reducing the interaction with the σ^* orbital.

Nonlinearity of Isotope Effects. In principle the IE of successive deuteriums is nonlinear, because of isotopic perturbation of conformational equilibrium, which increases the population of the rotamer with protium anti to the lone pair.[32] However, it can be estimated that $\Delta\Delta G°$ per D would increase by <1 cal/mol from CH_2D to CD_3. The errors in Table 1 show that this is too small a nonlinearity to be detected reliably, in contrast to 2,3-dimethyl-2-butyl cation and some iridium tri- and tetrahydrides.[33]

Solvent Dependence. For dimethylamine-d_3 the IE in DMSO is significantly greater than that in water. This is consistent with an IE that originates in n-σ^* delocalization. A protic solvent hydrogen bonds to that lone pair and reduces the delocalization, whereas in DMSO the lone pair is delocalized fully, allowing for a maximum IE.

Temperature Dependence. Figures 2 and 3 show that the IE in dimethylamine is definitely temperature dependent, contrary to a previous report.[9] Therefore there is no need to propose a fortuitous compensation of force constants. However, the variation is small, <2% change in K_H/K_D over a 30° range. The previous inability to detect so small a temperature dependence, by conductance measurements on dimethylamine and dimethylamine-d_6, is thus understandable.

The two methods give slightly different $\Delta\Delta H°$ or $\Delta\Delta S°$. However, the differences are not statistically significant, because of uncertainties in Δ_o and D (eq 3) and of the larger error in the first method. This error is due not only to the limited number of data points, but also to the large standard deviation of the individual points, as illustrated by the error bars in Figure 2. Besides, there may be systematic error in Figure 3 due to a slight initial temperature gradient between the amine sample and the methanol monitor, which is more insulated. This can account for why $\Delta\Delta H°$ appears less negative than in the first method. Despite the large error and the difference between the two methods, it is clear that the IE is definitely temperature dependent, in contrast to the previous report.[9] Moreover, this temperature dependence, along with a zero $\Delta\Delta S°$ (from the first method), shows that the IE lies entirely in the enthalpy. An IE that is manifested in the enthalpy is consistent with an origin in zero-point energy, as presented above.

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Stereochemical Dependence. If the IE is due to n_N-σ^*_{CH} delocalization, this requires overlap between the lone-pair and CH-bond orbitals. We have tested this with 1-benzyl-4-methylpiperidine-2,2,6-d_3 (**7**-d_3). According to the data in Table 1, the two isotopomers show a ΔpK_a of 0.0253 ± 0.0025, and the one with deuterium trans to the methyl group is the more basic. The accuracy here is not as high as in the other amines, because the signals are not sharp singlets, but it is adequate to demonstrate that the isotopomer with deuterium axial, and therefore antiplanar to the nitrogen lone pair, is the more basic, exactly as required.

It is remarkable that the basicities of cis and trans **7**-d_3 can be distinguished. These are isotopomers, or stereoisomers that differ only in the position of an isotope, so they are exceedingly similar. This is the first report (other than our earlier brief communication)[19] of a stereochemical dependence of β-deuterium IEs on amine basicity. Such effects are small and beyond most methods of measurement.

It should be acknowledged that a stereochemical dependence of these IEs could have been predicted from the preference for equatorial deuterium in 1,3,5,5-tetramethylhexahydropyrimidine-2-*d* and cis-*N*-methylpiperidine-2,6-d_2.[34] This preference too was attributed to n-σ^* delocalization, which weakens and lengthens a C−H bond that is anti to a lone electron pair. Subsequently this stereoelectronic interaction was used to induce diastereotopicity in the protons of an N−CH_2D group on a chiral piperidine.[35]

Calculations indicate a $\cos^2$ dependence of β-deuterium IEs on amine basicity, just as in solvolyses.[7] Indeed, the IEs can be fit to a $\cos^2$ dependence on the dihedral angle τ between the C−D bond and the nitrogen lone pair. The observed IE in **7** is the difference between IEs at 180° and 60° (if the inconsequential contributions from conformers with axial methyl or benzyl are ignored). The IE in **1** or **2** is the 2:1 sum of contributions at 60° and 180°. It should be noted that the same value is obtained for **3**, consistent with experimental and theoretical evidence that the phenyl group here exhibits no conformational preference.[36] Fitting the difference from **7** and the average from **1** and **2** then leads to eq 4. This fit shows that the IE is of stereoelectronic origin, with a maximum at 180°, when the C−D bond is antiperiplanar to the nitrogen lone pair. That maximum is 46 cal/mol, representing the IE of an antiperiplanar deuterium, relative to a protium.

$$\Delta\Delta G^\circ \text{ (cal/mol)} = (45.7 \pm 4.5)\cos^2\tau + (1.8 \pm 2.6) \quad (4)$$

It should be noted that this value is different from the 34 cal/mol in **7**, which is the difference between IEs of antiperiplanar ($\tau = 180°$) and synclinal ($\tau = 60°$) deuteriums. It is also different from the 24 cal/mol per D for **1**−**3**, which is the average IE of antiperiplanar and synclinal deuteriums. The $\cos^2$ dependence means that the IE of a synclinal deuterium is only $^1/_4$ that of an antiperiplanar one.

Moreover, the angle-independent term in eq 4 is zero, within an exceedingly small experimental error of <3 cal/mol. This is the term that would represent an electrostatic interaction between a positive charge and the C−H or C−D bond dipole.[12] We therefore confirm the above estimate that an inductive effect is too small to contribute to the observed IE.

Deuterium Syn to Lone Pair. Equation 4 is imperfect, insofar as it does not distinguish antiperiplanar ($\tau = 180°$) from synperiplanar ($\tau = 0°$). To probe IEs more broadly, it is necessary to generate amines with deuterium substitution at other dihedral angles, preferably with a C−D bond synperiplanar to the nitrogen lone pair.

For **5**, **6**, and **8** the data in Table 1 attest to an increased basicity due to synperiplanar deuterium. The correction for intrinsic isotope shifts in **6** and **8** provides closer agreement with **5**, where no correction is necessary. The average IE due to synperiplanar deuterium is 24 cal/mol, only half as large as the 46 cal/mol of an antiperiplanar deuterium. This is consistent with a lesser delocalization of a syn lone pair. It also parallels the delocalization that is responsible for reducing the one-bond coupling constant in the bridgehead C−H of a tricyclic orthoamide from 184 Hz when the C−H is synperiplanar to the three nitrogen lone pairs to 141 Hz when it is anti.[37]

Computational Comparison of Syn and Anti. Figure 4 shows the dependences on dihedral angle τ of the C−H bond length and of the C−D stretching frequency in methylamine or methylamine-*d*. The bond length is maximum when the dihedral angle between the bond and the nitrogen lone pair is 180°, but there is a secondary maximum at 0°. The minimum is near 90°. The stretching frequency varies in opposite fashion.

The longer bond and the reduction of frequency are due to delocalization of the lone pair into the C−H antibonding orbital. The maximum delocalization is when τ is 180°, and the minimum is near 90°, when the lone pair is orthogonal to the C−H. The secondary maximum at 0° is slightly less than one-half as large as the one at 180°. This agrees with the experimental observation that the IE due to synperiplanar deuterium is only one-half that of an antiperiplanar deuterium, and it supports the interpretation of IEs in terms of zero-point energies that are reduced when the C−H or C−D is antiperiplanar to the nitrogen lone pair. This also agrees qualitatively with the absence of distinctive Bohlmann bands in amines where the nitrogen lone pair is syn to the C−H.[38]

Isotopomers of 8-*d*. The behavior of **8** might appear to be contradictory. According to the benzyl protons as reporter nuclei, deuteration produces an IE of 1.045 (and 1.086 for dideuteration, very close to the 1.092 in **5**-d_2). Yet according to $H3_{exo}$ and $H3_{endo}$ as reporter nuclei in **8**-*d*, K_{ex}/K_{en} is not significantly different from unity. Thus it seems that the IE is independent of dihedral angle, contrary to the fit to eq 4. However, K_{ex}/K_{en} is an average over two stereoisomers, one with the benzyl exo and the other with it endo. If these stereoisomers were equally populated, the IE from an endo deuterium syn to the lone pair in the exo stereoisomer (actually, at a 10° dihedral angle, according to MM2 simulations) would balance the IE from an exo deuterium syn to the lone pair in the exo stereoisomer. Moreover, any IEs from anticlinal deuterium (at 131°, not 120°) would also be balanced. As a result, there would be no net intramolecular IE different from unity. Although the observed 1.6:1 ratio in **5**·H^+ differs from equal populations, it is close

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enough that the average K_{ex}/K_{en} is not significantly different from unity.

Comparison with $^1J_{CH}$ and $^1J_{CC}$. In Figure 4 ν_{CD} is fit by $1.097-0.0025\cos(\tau) + 0.0030\cos(2\tau) - 0.0005\cos(3\tau)$, with the coefficient of $\cos(2\tau)$ slightly greater than that of $\cos(\tau)$, and of opposite sign. The $\cos(2\tau)$ term represents the delocalization of the nitrogen lone pair, whether syn or anti to the C−D, and the $\cos(\tau)$ term distinguishes anti as more effective than syn. These results can be compared with one-bond coupling constants, $^1J_{CH}$ and $^1J_{CC}$, in some ethers, where the $\cos(\tau)$ term was found to be dominant,[39] showing that lone-pair delocalization is not primarily responsible, in contrast to these IEs.

Summary and Conclusions

Secondary β-deuterium IEs on amine basicities of amines **1**−**8** were measured using a precise NMR titration method. In all cases deuterium increases the basicity. For 1-benzyl-4-methylpiperidine-d_3 the isotopomer with axial deuterium is more basic. For **1**−**3** and **7** the IEs follow a $\cos^2$ dependence on dihedral angle, with no detectable angle-independent inductive effect. The IE is attributed to a lowered zero-point energy of a C−H bond adjacent to an amine nitrogen.

Amines **5**, **6**, and **8** show an IE due to synperiplanar deuterium, but this is only one-half as large as that of antiperiplanar deuterium. This is consistent with a lesser delocalization of a syn lone pair. It is also consistent with the conformational dependences of the calculated C−H bond length and C−D frequency in methylamine or methylamine-*d*.

It is remarkable that such small IEs can be measured. Even the relative basicities of cis and trans **7**-d_3 or of **8**-d_{exo} and **8**-d_{endo} can be measured. These are true isotopomers, or stereoisomers that differ only in the position of an isotope. Thus it is possible to document the stereochemical dependence of deuterium IEs on amine basicity.

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Supporting Information Available: Synthesis and spectral characterizations. Table S1 of chemical shifts and isotope shifts of reporter nuclei in free and protonated amines. Complete ref 22. Cartesian coordinates and B3LYP/6-31G(d,p) energies of methylamine conformations with one HNCH dihedral angle constrained to 180°, 165°, 150°, 135°, and 120°. This material is available free of charge via the Internet at http://pubs.acs.org.

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