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Long-Range Deuterium Isotope Effects on ^{13}C Chemical Shifts of Intramolecularly Hydrogen-Bonded N-Substituted 3-(Cycloamine)thiopropionamides or Amides: A Case of Electric Field Effects

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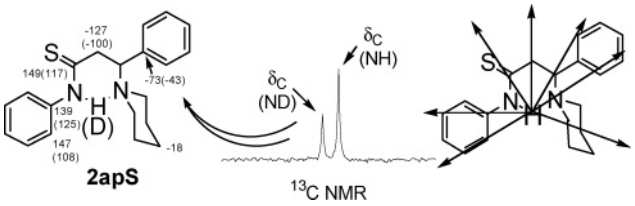

A series of intramolecularly hydrogen-bonded N-substituted 3-(piperidine, morpholine, *N*-methylpiperazine)thiopropionamides and some corresponding amides have been studied with special emphasis on hydrogen bonding. The compounds have been selected in order to vary and to minimize the N···N distance. Geometries, charge distributions, and chemical shifts of these compounds are obtained from DFT-type BP3LYP calculations. ^{1}H and ^{13}C 1D and 2D NMR experiments were performed to obtain H,H coupling constants, ^{13}C chemical shifts assignments, and deuterium isotope effects on^{13}C chemical shifts. Variable-temperature NMR studies and 2D exchange NMR spectra have been used to describe the rather complicated conformational behavior mainly governed by the ring flipping of the piperidine (morpholine) rings and intramolecular hydrogen bonding. Unusual long-range deuterium isotope effects on ^{13}C chemical shifts are observed over as far as eight bonds away from the site of deuteriation. The isotope effects are related to the N···N distances, thus being related to the hydrogen bonding and polarization of the N−H bond. Arguments are presented showing that the deuterium isotope effects on ^{13}C chemical shifts originate in electric field effects.

Introduction

Both inter- and intramolecularhydrogen bonding are very important structural motifs. Intramolecular hydrogen-bonded compounds can be subdivided into those with resonance assisted hydrogen bonding (RAHB) and those without.[1−3] RAHB is taken to mean that the donor (e.g., NH) and the acceptor (e.g., C═O) are linked with a double bond. The former group can effectively be studied by deuterium isotope effects on chemical shifts.[4−8] Recently proton sponges, a non-RAHB type with intramolecular hydrogen bonds, have been investigated.[9,10] Although the origin of deuterium isotope effects on chemical shifts is vibrational,[11,12] isotope effects on chemical shifts may occur in different ways. The normal scheme is the intrinsic

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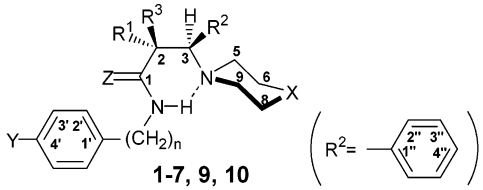
SCHEME 1. Investigated Compounds



Compounds[a]	R^1	R^2	R^3	X	Y	Z	n
1apS	H	H	H	CH_2	H	S	0
2apS	H	Ph	H	CH_2	H	S	0
2ap4"FS	H	4"-F	H	CH_2	H	S	0
2ap3"FS	H	3"-F	H	CH_2	H	S	0
2ap3"5"FFS	H	3",5"-diF	H	CH_2	H	S	0
2ap2"FS	H	2"-F	H	CH_2	H	S	0
2ap2"6"FFS	H	2",6"-diF	H	CH_2	H	S	0
2ap4"FO	H	4"-F	H	CH_2	H	O	0
2ap3"FO	H	3"-F	H	CH_2	H	O	0
2ap3"5"FFO	H	3",5"-diF	H	CH_2	H	O	0
2amS	H	Ph	H	O	H	S	0
2am4"FS	H	4"-F	H	O	H	S	0
2am4"FO	H	4"-F	H	O	H	O	0
2apmeS	H	Ph	H	$CHCH_3$	H	S	0
2am4´ClS	H	Ph	H	O	Cl	S	0
2am4´ClO	H	Ph	H	O	H	O	0
2anmpS	H	Ph	H	NCH_3	H	S	0
2annmp4"FS		4"-F	H	NCH_3	H	S	0
2annmp4"FO		4"-F	H	NCH_3	H	O	0
2ap4´NO_2S	H	Ph	H	CH_2	NO_2	S	0
2bepS	H	Ph	H	CH_2	H	S	1
2bemS	H	Ph	H	O	H	S	1
3apS	CH_3	H	H	CH_2	H	S	0
3amS	CH_3	H	H	O	H	S	0
4ap(t)S		-$(CH_2)_4$-	H	CH_2	H	S	0
4ap(t)O		-$(CH_2)_4$-	H	CH_2	H	O	0
4am(t)S		-$(CH_2)_4$-	H	O	H	S	0
4bep(t)S		-$(CH_2)_4$-	H	CH_2	H	S	1
4bep(c)S	H		-$(CH_2)_4$-	CH_2	H	S	1
5ap(t)S	CH_3	Ph	H	CH_2	H	S	0
5ap(c)S	H	Ph	CH_3	CH_2	H	S	0
5am(c)S	H	Ph	CH_3	O	H	S	0
6ap(t)S		-$(CH_2)_3$-	H	CH_2	H	S	0
6am(t)S		-$(CH_2)_3$-	H	O	H	S	0
6bep(t)S		-$(CH_2)_3$-	H	CH_2	H	S	1
6bem(t)S		-$(CH_2)_3$-	H	O	H	S	1
7apS	H	CH_3	H	CH_2	H	S	0
7bepS	H	CH_3	H	CH_2	H	S	1
7bemS	H	CH_3	H	O	H	S	1

[a] Symbols in acronyms of compounds mean the following: **a**, thioanilide or anilide; **be**, benzyl derivative; **p**, piperidine; **m**, morpholine; **nmp**, *N*-methylpiperazine; **pme**, 4-methylpiperidine; **(t)**, trans; **(c)**, cis; S, thioamide; O, amide.

effect.[11,12] Perturbation of an equilibrium caused by isotope substitution is also common,[13,14] as the type of equilibria can be many. One such example is the effect of deuteriation on conformational preferences as demonstrated for cyclohexanes.[15] The origin of isotope effects was at an early stage suggested by Gutowsky[16] to be due to different electric field effects from H or D caused by the different average bond lengths of the X−H and X−D bonds. This theory was shown not to be valid in general.[17] However, for strongly polarized hydrogen bonds this may hold true as suggested for proteins,[18] or for fluorinated N-substituted morpholino(piperidine)thiopropionamides.[19] The deuterium isotope effects on chemical shifts are defined as ${}^{n}\Delta X(\mathrm{YD}) = \delta X(\mathrm{H}) - \delta X(\mathrm{D})$.

Thioamides have shown interesting long-range isotope effects[19−22] and also the ability in special cases to take part in tautomeric equilibria.[21,22]

In the present study, thioamides [N-substituted 3-(piperidine, morpholine, or 4-*N*-methylpiperazine)thiopropionamides] and some corresponding amides (Scheme 1) are investigated by means of deuterium isotope effects on chemical shifts, chemical shifts, and coupling constants combined with theoretical predictions of structures. The derivatives, as indicated by the names, are divided into different types: (i) thioamides (marked by S) and amides (marked by O), where isotope effects of the latter are numerically smaller in line with a shorter NH bond in the latter, and (ii) piperidines (**p**), 4-methylpiperidine (**pme**), morpholines (**m**), and *N*-methylpiperazine (**nmp**). The molecules

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TABLE 1. NH Chemical Shifts, NN and NH Distances, and Deuterium Isotope Effects on ^{13}C Chemical Shifts (measured at 220 K unless State Otherwise)

compds	δ_{NH}	R_{NN}	R_{NH}	i.e. C-1	i.e. C-2	i.e. C-1′	i.e. C-2′	i.e. C-1″	i.e. C-4″
1apS	13.44	2.876	1.0302	159	−105	129	149		
2apS	13.77	2.854	1.0314	149	−127	139	147	−73	
2apmeS	13.70	2.854	1.0314	151	−122	143	140	−72	
2amS	12.94	2.876	1.0298	184	−95	119	140	−57	
2anmpS	13.35	2.872	1.0306					−57	
2ap4′NO$_2$S	14.30	2.846	1.0348	106	−160	168	196	−90	
2am4′ClS	13.06	2.866	1.0311						
2ap4″FS	13.72[a]	2.864	1.0311	165	−109	138	166	−65	17
2ap4″FO	11.49[a]	2.882	1.0251	85[a]	−32[a]	117[a]	97[a]	−45[a]	
2am4″FS	12.94[a]	2.876	1.0296	169[a]	−89[a]	125[a]	121[a]	−61[a]	
2am4″FO	10.68[a]	2.890	1.0240	91[a]	−21[a]	105[a]	97[a]	−44[a]	
2anmp4″FS	13.22[a]	2.874	1.0303	170[b]	−97[b]	129[b]	142[b]	−54[b]	12[b]
2anmp4″FO	11.09[a]	2.888	1.0244	93[a]	−29[a]	113[a]	102[a]	−52[a]	8[a]
2ap3″FS	13.69[a]	2.869	1.0308	158[b]	−109[b]	119[b]	142[b]	−70	
2ap3″FO	11.46[a]	2.885	1.0249	85[a]	−32[a]	117[a]	97[a]	−49	12
2ap3″5″FFS	13.39[a]	2.872	1.0303	165[b]	−101[b]	130[b]	142[b]	−61[a]	
2ap3″5″FFO	11.18[a]	2.888	1.0245	89[a]	−29[a]	113[a]	93[a]	−48[a]	12
2ap2″FS	13.61[a]	2.867	1.0311	146[b]	−113[b]	137[b]	146[b]	−50[b]	
2ap2″6″FFS	13.33[a]	2.884	1.0296	166[b]		121[b]	170[b]	−49[b]	20[b]
2bepS	12.01	2.8230	1.0285	53	−49	83	16	−59	
2bemS	11.28	2.8436	1.0270	92	−36	79	0	−55	
3apS	13.37	2.8568	1.0294	171	−96	156	141		
3amS	12.44	2.8667	1.0280	204	−68	131	143		
4ap(t)S	15.64	2.7994	1.0311	91	−250	261	106		
4ap(t)O	12.58	2.8008	1.0278	91	−29	135	109		
4bep(t)S	12.90	2.7586	1.0308		−114	117			
4bep(c)S	12.95	2.7715	1.0315	44	−82	107	22		
4amtS	14.16	2.8037	1.0289	132	−265	187	86		
5ap(t)S	13.72	2.8042	1.0310	129	−239	228	112	−106	
5am(c)S	11.04			213	−84[a]	138	105	−10[a]	
6ap(t)S	12.98	2.9274	1.0320	158	−75	130	147		
6am(t)S	12.33	2.9415	1.0269	191	−54	113	147		
6bep(t)S	11.36	2.8957	1.0268	52	−41	76	0		
6bem(t)S	10.68	2.9060	1.0256	87	−27	70	0		
7apS	13.86	2.8748	1.0307	130	−127	152	149		
7bemS	11.63	2.8556	1.0265	83	−29[a]	82	13[a]		

[a] Measured at 300 K; [b] Measured at 275 K

show an intriguing structural complexity: (i) inversion of the piperidine (morpholine) ring, (ii) rotation of the piperidine (morpholine) ring around the N−C-3 bond and ultimately the formation of a six-membered ring upon hydrogen bond formation, (iii) rotation of the phenyl groups at C-3 and at the thioamide nitrogen (if present), and (iv) rotation around the C-2,C-3 bond. The structure may be influenced by variations of the basicity of the heterocyclic nitrogen atom; variation of the acidity of the N−H bond through variation of substituents at Y (see Scheme 1), substituents at the 2- and 3-position, and variation of temperature and solvent.

The present compounds have some similarities to parts of the active site of enzymes for which hydrogen bonding is found to be extremely important.[23,24] DFT calculations have been used extensively to calculate structures, chemical shifts, and isotope effects, in the latter case based on both one- and two-dimensional hydrogen-bonding potentials.[25,26]

Results

Assignments. The assignment of the ^{13}C NMR spectra is only a problem for compounds **4** and **6** with many aliphatic carbons. The assignments are supported by COSY, DEPT, and HETCOR spectra. Furthermore, the assignments of carbons C-5,C-9 and C-6,C-8 are helped by the fact that they go from averaged to individual positions at low temperature. For the fluorinated compounds, C−F couplings help to assign the carbons of the substituted ring.

Chemical Shifts. The NH chemicals shifts are given in Table 1 and those of the ^{13}C chemical shifts not previously published[27]in Table 1S (Supporting Information) together with the H, H coupling constants. The NH chemical shifts are much larger than those for similar compounds without or with only weak hydrogen bonds.[22] The variation of the NH chemical shifts with temperature has been reported recently.[27] Variations of the ^{13}C chemical shifts with temperature are very moderate, <2 ppm for a change in temperature from ambient to 220 K.

Dynamic Behavior. Cooling influences the ring flipping of the piperidine or the morpholine rings as seen by the H-5_{ax}, H-5_{eq}, H-9_{ax}, and H-9_{eq} protons becoming nonequivalent. The reduced rate of ring flipping is monitored as mentioned through the chemical shift differences or by disappearance of exchange peaks in the NOESY spectra at low temperature. Figure 1Sa (Supporting Information) shows a spectrum in which the ring flipping is not yet stopped, whereas in Figure 1Sb (Supporting Information) no ring flipping occurs due to the methyl group at the piperidine ring. Cooling also influences the rotation around the N−C-3 bond (revealed as the C-5 and C-9 carbon resonances

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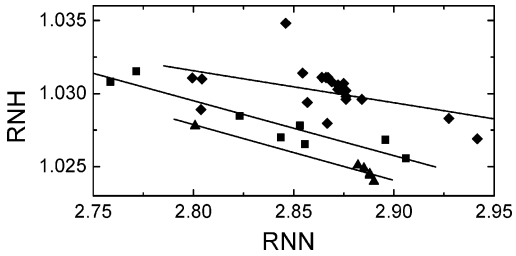


FIGURE 1. Plot of calculated NH bond lengths vs N···N distances: (◆) *N*-aryl derivatives (**aS**); (▲) *N*-benzyl derivatives (**beS**); and (■) oxygen derivatives (**O**).

or the C-6 and C-8 resonances becoming nonequivalent). Cooling can likewise influence the rotation around the C-3,C-1″ bond (revealed by nonequivalence of H-2″ and H-6″ resonances in the ^{1}H spectrum or by the corresponding carbon resonances in the ^{13}C spectrum, as for **5ap(t)S**[27] and for compound **2ap2″6″FFS** (Table 1Sb, Supporting Information)). In a similar way effects at H-2′,H-6′ or C-2′,C-6′ may be seen if rotation of the N−C-1′ bond is slowed down. This is a more general phenomenon and may influence the broadness of all resonances in the neighborhood of the slowly rotating benzene rings.

The behavior of the compounds is described briefly referring to the above features and **1apS.** The ^{1}H spectrum showed separation of the H-5$_{ax}$, H-5$_{eq}$ around 220 K, but no separation of the corresponding carbon resonances down to 210 K.

(a) 2apS, 2amS, and 4ap(t)S. The H-5,H-9 resonances are separated at 300 K, whereas the C-5,C-9 carbon resonances are broad at 300 K and showed coalescence at 270 K. The C-6 and C-8 resonances started broadening at this temperature. C-2″ broadened at 230 K and C-3″ at 220 K simultaneously with C-7.

For **2apS** a NOE spectrum showed exchange peaks at 220 K in $CDCl_3$ (Figure 1Sa, Supporting Information).

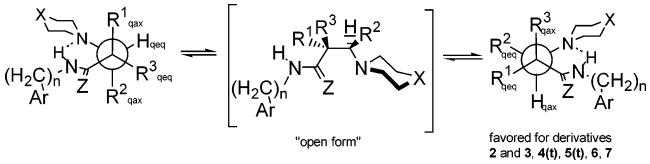
(b) 2apmeS. The 4-methyl group at the piperidine ring prevents ring flipping as seen by the absence of exchange peaks in the NOESY spectrum at 300 K in C_6D_6 (Figure 1Sb, Supporting Information). The behavior of C-5, C-9, and C-2″ is akin to that of **2apS**.

(c) 3apS. The ^{1}H and ^{13}C behavior of the piperidine ring is similar to that of **2apS**. The C-1′ and C-2′ resonances were broad at ambient temperature.

(d) 5ap(t)S. The greater steric encumbrance of this compound is seen by the broadness of all carbon resonances of the Ph″-ring even at ambient temperature. Furthermore, C-5 became narrow enough at 220 K to allow observation of an isotope effect (see the subsection Isotope Effects in the Discussion).

(e) 5am(c)S. Carbons C-5,C-9 showed broad resonances at 270 K and coalescence at 250 K. C-5,C-9 continued to be broad down to 220 K. C-6,C-8 showed likewise broad resonances in the temperature interval from 270 to 220 K and so did C-2″. The latter showed coalescence at 220 K. C-2 was broad in the range 230−220 K. At 180 K the NH resonance has disappeared completely to reappear as broad resonances at 13.96 and 10.13 ppm in the ratio 1:1.9. This shows clearly that at higher temperatures an equilibrium exists. Judging from the coupling constant, the form with a trans coupling dominates. The two forms can be assigned to the closed cis form (**5am(c)Sc**) (Scheme 3) with δ(NH) = 13.96 ppm and an open form (**5am(c)So**) (Scheme 3) with δ(NH) = 10.13 ppm.

SCHEME 2. Possible Conformations of Investigated Compounds[a]



[a] qax: quasiaxial. qeq: quasiequatorial. Presented for the single enantiomer.

(f) 5ap(c)S. This compound is not isolated, but only observed in a mixture with **5ap(t)S**. The behavior is very similar to that of **5am(c)S**, although the ratio between the two forms is closer to 1:1. The **5ap(c)S** has an NH chemical shift of 13.91 ppm in this case and the open form one of 10.88 ppm.

Calculations. (a) Structure Calculations. To understand better the isotope effects, DFT calculations of the B3LYP type of structures (Table 1) and chemical shifts have been performed.

The conformation of the various molecules seems to be determined by the substituents at C-2 and C-3 plus interactions between the piperidine (morpholine) and the H-2′,H-6′ protons plus the formation of the hydrogen bond. This is especially true for the N···N distance. For the *N*-benzyl derivatives (**be**) the N···N distance is generally shorter than that for the corresponding *N*-aryl (**a**) derivatives (Table 1). In **2apS**, **2apmeS**, **3apS**, **4ap(t)S**, **5ap(t)S**, and **6apS** the substituents are in an equatorial position of the six-membered ring forming the hydrogen bond (Scheme 2). This can be deduced from J_{HH} couplings (see the Supporting Information). The cis compound, **4bep(c)S**, may exist with the piperidine ring either equatorial or axial. The latter is energetically very unfavorable due to strong steric interactions. The cis compounds **5am(c)S** and **5ap(c)S** may similarly exist in two different conformations.

The NH bonds are found to be largely coplanar with the benzene ring. For some of the compounds the H−N−C═S dihedral angle is different from 180°.[27] The N−H bond lengths are calculated to be close to 1.03 Å illustrating the hydrogen bond formation but again with a difference between **a** and **be** derivatives (Table 1). A plot of NH bond length vs N···N distance illustrates this (Figure 1). The charge distribution shows the polarization of the N−H bond with some variations between **a** and **be** derivatives but also between piperidine (**p**) and morpholine (**m**) derivatives (see Figure 2). The derivatives with fluorines at the Ph″ ring show very similar geometries to those without as seen in Table 1.

(b) Calculated Chemical Shifts. All the calculated ^{13}C chemical shifts are compared with experimental results and a reasonable correlation is obtained: $\delta C_{Obs} = \sigma Cx - 1.0526 + 197.45$ ($R^2 = 0.9992$). Some of the calculated shifts are used to give estimates of chemical shift differences in cases where these shifts are not experimentally available. The C-5 and C-9 chemical shifts for **2apS**, **4ap(t)S**, **5ap(t)S**, and the 3-methyl and the 2,3-dimethyl derivative (only calculated not synthesized) are calculated 8.8 ppm apart with the former at the lower frequency. For **1apS** the difference is reduced to 5 ppm. For **4ap(c)S** the difference is only 2 ppm. For **5am(c)S** the difference between C-5 and C-9 is calculated to be very close to zero probably reflecting the different conformations of the phenyl rings. The calculated differences are in good agreement with the experimental findings.[27] C-5 is defined as the carbon closest to C-1″, when the hydrogen bond is present (Scheme 1). For C-6 and C-8 the nuclear shielding difference is only 0.4−0.8

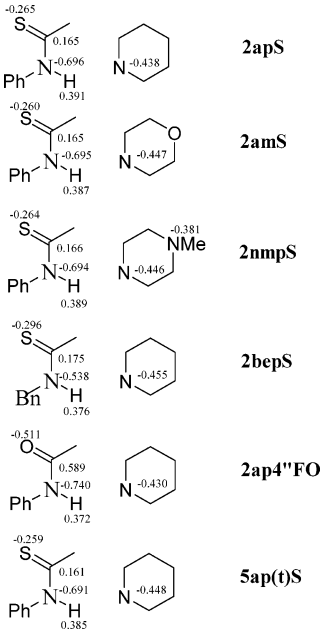


FIGURE 2. Charge distributions (taken from DFT calculations).

ppm, explaining the difference in behavior of C-5,C-9 and C-6,C-8 with temperature. The chemical shifts of the primed rings of the **a** derivatives are calculated less well than the remaining carbons. This is probably due to the stronger interlocking of the benzene ring with the piperidine ring due to the too short N···N distance. This may enforce the planarity with the thioamide moiety and lead to a conjugative effect larger than necessarily found in solution.

The nitrogen nuclear shieldings of the piperidine nitrogen are calculated in the following order: **1apS**, **2apS**, **2apNO$_2$S**, **5ap-(t)S** (200.17, 194.5, 194.0, 192.1). In other words, the ^{15}N chemical shifts are seen to reflect the stronger hydrogen bond as defined by a shorter N···N distance, although it should be taken into account that substituent effects due to the methyl and phenyl groups at C-2 and C-3 give contributions.

(c) Deuterium Isotope Effects on Chemical Shifts. Calculations of deuterium isotope effects on nuclear shieldings can be done according to the Jameson theory.[12] The change in the nuclear shielding upon deuteriation can be calculated just by varying the, e.g., N−H bond length. To calculate the change in the NH bond length upon deuteriation requires a potential scan, which is rather involved for the present, rather large compounds. However, a comparison of the calculated changes in nuclear shieldings with experimental values gives a good hint to the feasibility of predicting these small isotope effects.

We find the following isotope effects on chemical shifts in ppb for **2ap4′′FS** by changing the N−H bond length 0.01 Å (calculated values first): C-1 (−70, 165), C-2 (−120, −109), C-3 (40, 0), C-5,C-9(∼−30, n.m.), C-6,C-8(−40, n.m.), C-7 (−20, n.m.), C-1′ (70, 138), C-2′ (20, 166), C-3′ (−10, 0), C-4′ (−10, 0), C-1′′ (−40, -65), C-2′′ (10, 0), C-3′′ (10, 0), C-4′′ (100, 17), F (50, 35). Except for C-1 we find a very good agreement between predicted and observed signs. Previously, the sign of two-bond deuterium isotope effects on carbonyl carbons has likewise been calculated with the wrong sign.[25] For C-5,C-9 the isotope effects could not be measured due to averaging effects for **2ap4′′S**. However, for other compounds the isotope effects are observed and support the calculated findings of negative isotope effects (Schemes 3 and 4). Very promising is the calculation of a negative effect at C-2. This is three bonds away from the deuterium and in most compounds found to be positive.[7] Likewise, the very long-range effects at C-1′′,C-4′′ and F are predicted with the correct signs.

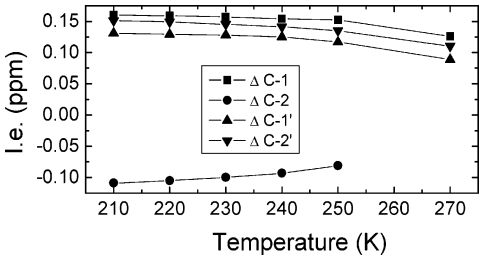


FIGURE 3. Isotope effects of **2apS** plotted vs temperature.

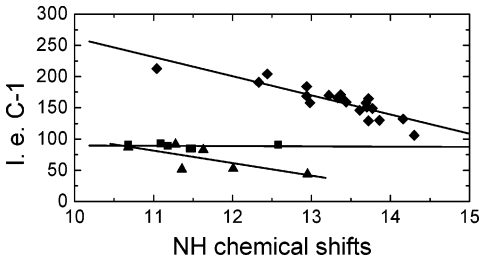


FIGURE 4. Plot of ΔC-1(ND) vs δNH: (◆) aniline derivatives (**aS**); (▲) benzyl derivatives (**beS**); and (■) oxygen derivatives (**O**).

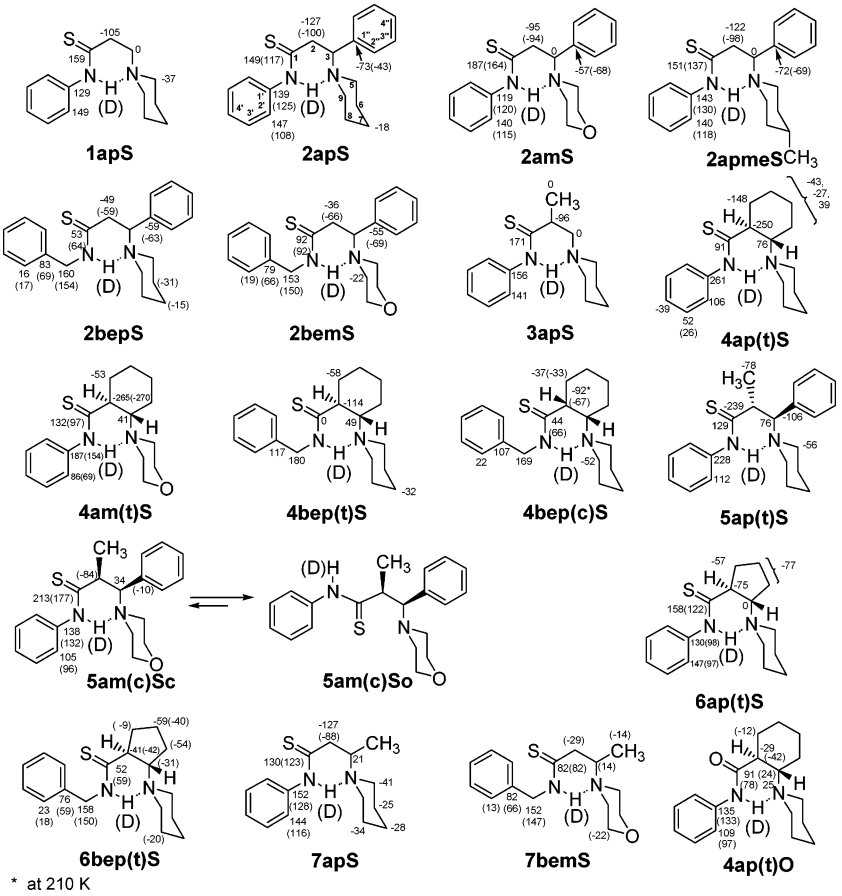
For **2ap3′′5′′FFS** we find the following: C-1 (−60, 165), C-2 (−92, −101), C-3 (7, 0), C-1′ (64, 130), C-2′ (51, 142), C-3′ (−5, 0), C-4′ (−16, 0), C-1′′ (−39, −61), C-2′′ (18, 0), C-3′′ (6, 0), C-4′′ (23, 0). The trends are largely similar to those found for **2ap4′′FS**, and for C-3′′ and C-5′′ the effects are seen to be very close to zero and for the fluorines the effects are likewise small.

***n*ΔC(ND).** Deuteriation at the NH position led to isotope effects at ^{13}C chemical shifts (Tables 1 and 1Sc; Schemes 3 and 4). In the cases **2apS**, **2amS**, **2apmeS**, **4ap(t)S**, and **5amS**, in the amides, and mostly in the **F**-series these isotope effects could be observed at ambient temperature. In other cases, isotope effects (observation of separate resonances) could only be observed at lower temperatures. This is so for **3apS** and **5ap-(t)S** for which all resonances were broad and for **1apS** no isotope effects were observed at ambient temperature. A distinct feature upon cooling is the large variation in the isotope effects (Table 1Sc, Supporting Information) observed in going from 300 to 270 K, whereas at lower temperatures the changes leveled off. This holds for all compounds except **2apS**, for which the isotope effects were largely invariant with temperature and **3apS** for which the changes were still significant from 240 to 230 K. The isotope effects for **2apS** are plotted vs temperature in Figure 3. Some rather unusual long-range isotope effects are observed at C-1′′ and in some case at the CH_3 group attached at C-2 (**3apS** and **5ap(t)S**, notice the distinct difference in isotope effects), as well as at the cyclohexane ring carbons of **4ap(t)S** derivatives or the cyclopentane ring of **6** derivatives.

The **5ap(t)S** showed a distinct negative effect at C-1′′, whereas the **5am(c)S** did not. The effect at C-1′′ of **5am(c)S** can be estimated to three times the measured isotope effect of −0.01 ppm based on the presence of only 33% of the closed *cis*-form in the equilibrium mixture.

Deuterium isotope effects on ^{13}C chemical shifts in amides and thioamides in which the NH bond is involved in hydrogen

SCHEME 3. Deuterium Isotope Effects on ^{13}C Chemical Shifts ($^{n}\Delta$C(ND)) at Low Temperature and at Ambient Temperature (in parentheses) of Selected Thioamides and Amides[a]



[a] For fluorinated compounds see Scheme 4. For a full list of data see Table 1 and the Supporting Information.

bonding are given in Schemes 3 and 4. The N···N distances are slightly shorter in the piperidines (**p**) derivatives than in the **m** and **nmp** derivatives (Table 1) and the isotope effects are numerically larger than in the corresponding **m** and **nmp** derivatives. As the geometry to a large extent is determined by the steric interactions between the azaheterocyclic base part and the substituents at the amide (thioamide) nitrogen the aniline and benzylamine (or N−Ph and N−Bn) types have quite different N···N distances and as the latter have much shorter NH bond lengths (Table 1) and charges at the N−H hydrogen a plot vs e.g. N···N distances will divide the **a** and **be** derivatives up into two groups as also seen in Figure 1.

The variations in the isotope effects are interesting. A plot of ΔC-1(ND) isotope effects vs δNH (Figure 4) indicates that hydrogen bonding and isotope effects are related (the data for the **be** derivatives fall outside the line most likely because the NH chemical shifts are not ring current shifted as is the case for the **a** derivatives). Plots of $R_{N\cdots N}$ from DFT calculations vs $^{2}\Delta$C-1(ND), $^{3}\Delta$C-2(ND), $^{2}\Delta$C-1′(ND), $^{3}\Delta$C-2′(ND), and $^{n}\Delta$C-1″(ND) showed different patterns (Figure 5). For C-1 it is difficult to see a clear pattern, but amides (O) and thioamides (S) are separate and so are anilides (**a**) and *N*-benzyl (**be**) derivatives. For C-2 a clear separation between **aS** and **beS** derivatives is found. For C-1′, C-2′, and C-1″ a rather similar pattern is seen and a pattern similar to those for C-2.

The dependence is continuous although not linear. The "slopes" are clearly largest for C-2 > C-1′ > C-2′ > C-1″. Generally, one can say that $^{n}\Delta$C-1″(ND) and $^{3}\Delta$C-2(ND) become more negative, $^{2}\Delta$C-1(ND) and $^{3}\Delta$C-2′(ND) decrease, and $^{2}\Delta$C-1′(ND) increases as the N···N distance decreases.

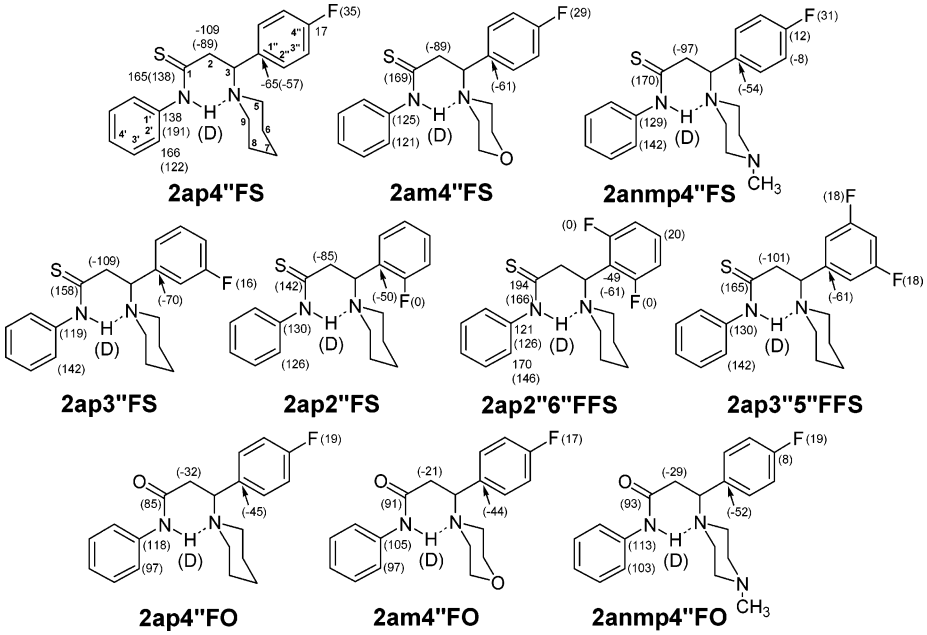
The isotope effects are slightly different for piperidine and morpholine derivatives. It is also interesting to notice that for most compounds no isotope effects are observed at C-3.

The effects observed in the amides are all numerically smaller than those for the corresponding thioamides.

Discussion

Conformations. The conformational scheme can be described as follows: Ring flipping of the piperidine or morpholine ring occurs and allows rotation around the N−C-3 bond at the same time and the hydrogen bond is maintained. The ring flipping is slowed down at lower temperatures, but is present even at 220 K judging from the NOE exchange peaks observed (see Figure 1Sa, Supporting Information). Taking into account the conformation of the piperidine ring, the geometry of the hydrogen-bonded system is such that the N···H bond is axial and the N−C-3 bond is equatorial (Scheme 2). This is the case for **2apS**, **2amS**, **2amClS**, **2apNO$_2$S**, **3apS**, **4ap(t)S**, **5am(c)S**, **5ap(t)S**, and **6apS**. For **2apmeS** the ring flipping is slow even at room temperature and only slow rotation around the N–C-3 bond occurs as the C-5 and C-9 carbons show separate although broad resonances at ambient temperature. The lack of substituents at the hydrogen-bonded six-membered ring for **1apS** makes the situation different. The observation of two three-bond couplings of the magnitude of 5−6 Hz suggests an equilibration between

SCHEME 4. Deuterium Isotope Effects on ^{13}C Chemical Shifts ($^{n}\Delta C(ND)$) and ^{19}F Chemical Shifts ($^{n}\Delta F(ND)$)[a] at Low Temperature and in Ambient Temperature (in parentheses) of Fluorinated Compounds



[a] Taken from ref 19.

two closed structures. The closed structure is supported by the finding of a rather large NH chemical shift. Additional evidence is the observation of equilibrium isotope effects at low temperature upon deuteriation at C-2, as the picture is akin to the effects of deuteriation at a cyclohexane ring (Figure 2Sb, Supporting Information).

For **5am(c)S** the calculations point toward a structure with the phenyl group at C-3 in the axial position and the methyl group at C-2 in the equatorial position with respect to the six-membered ring formed upon hydrogen bonding (Scheme 2 left). This finding is supported by the small chemical shifts difference between C-5 and C-9 (see previously) and the 2-CH_3 shift being clearly lower than that for the trans geometries.

Isotope Effects. The deuterium isotope effects on the ^{13}C chemical shifts at C-1, C-2, C-1′, and C-1″ of the present compounds are plotted vs the N···N distance in Figure 5. For C-2 the negative sign is unusual (see Figure 5b) and this isotope effect becomes more negative as the N···N distance decreases. The isotope effect at C-1″ is very unusual[19] not to speak of that of C-4″ of the 4″-fluorosubstituted derivatives **2ap4″FS**, **2anmp4″FS,** and **2ap4″FO**. Likewise, the isotope effects observed at the five- and six-membered rings of **4**- and **6**-type derivatives are very unusual. The effects at C-1″ are not intrinsic as isotope effects over five bonds (mainly saturated carbons) are normally very close to zero.[7,8] Very long range isotope effects on chemical shifts of negative signs could indicate a contribution from equilibrium isotope effects.[7] However, it is not related to a major conformational change as the **5am(c)S** is equilibrating between an open and a closed form and this compound does not show such long-range effects (see later and Scheme 3). Furthermore, the finding that the conformation is invariable upon deuterium substitution at N (according to ^{3}J(H−H) coupling constants) is also not supporting a conformational change. Isotope effects can also be transmitted through hydrogen bonds. The finding that the C-3 carbon in most cases only showed a small or no isotope effect is not supporting such a mechanism.

The charges at the CSNH group are quite distinct and a polarization of the N−H bond exists (see Figure 2). However, this polarization is much more pronounced for the aniline derivatives than for the benzyl derivatives (Figure 2). The finding that $^{n}\Delta$C-1″(ND), $^{2}\Delta$C-1(ND), $^{3}\Delta$C-2(ND), $^{2}\Delta$C-1′(ND), and $^{3}\Delta$C-2′(ND) all depend on the N···N distance and also that the larger slopes are found for the proximate $^{2}\Delta$C-1′(ND) and $_{3}\Delta$C-2(ND) combined with the above-mentioned polarization suggests that the isotope effects can be explained by assuming that an electric field effect[28] is at play. As the N−D bond on average is shorter than the N−H bond the electric fields will be different in those two cases. Furthermore, the lengthening of the ND bond will depend on the potential and follow the N···N distance (for IR data see ref 27). The charge distribution is also different for the thioamides and amides, in **a** and **be** derivatives and in **p**, **m**, and **nmp** derivatives (Figure 2).

From the study of deuterium isotope effects at the fluorine chemical shifts of the fluorosubstituted derivatives an electric field effect was also inferred.[19] As the effect of the electric field depends on the polarizability of the bond, the angle between the electric field, and the bond and the distance between the charge and the bond it is rather difficult to compare all long-range isotope effects. However, a comparison of the effect at C-1″[19] and C-4″ seemed appropriate as the direction is the same (Figure 6) and the aromatic bonds are comparable. The finding that the effect at C-1″ is negative and that at C-4″ is positive supports the idea of a polarization of the aromatic bonds. The numerical ratio between the two types of isotope effects is 4.7, 5.6, 4.5, and 5.5 for the four compounds, **2ap4F″S**, **2ap4F″O**, **2apnm4F″S**, and **2anmp4F″O**. For an electric field effect a $1/R^3$ is expected. Inserting the distances (R) from D to C-1″ and C-4″ a ratio of approximately 5 is calculated for **2ap4F″S**, assuming a point charge.

The many isotope effects observed at the ring carbon other than C-2 and C-3 of the five- and six-membered rings of **4**-

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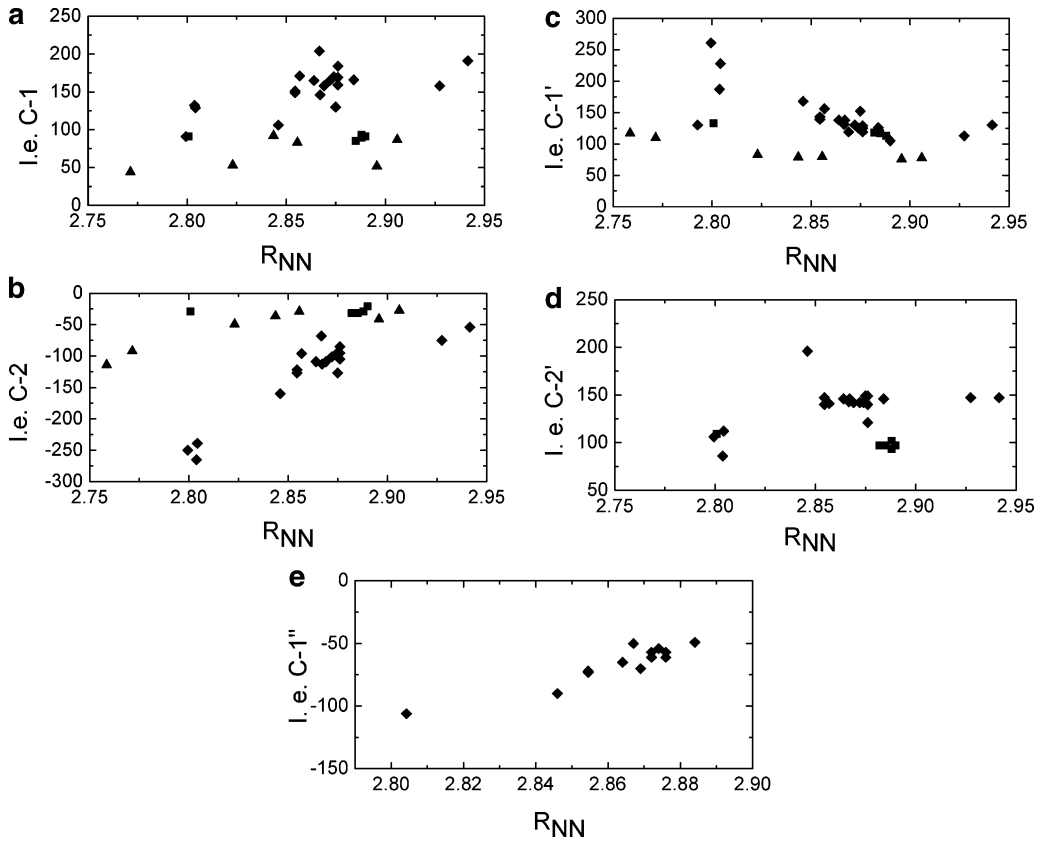

FIGURE 5. Plots of deuterium isotope effects on ^{13}C chemical shifts vs N···N distances: (◆) aniline derivatives (**aS**); (▲) benzyl derivatives (**beS**); and (■) oxygen derivatives (**O**). (a) Plot of ΔC-1(ND) vs $R_{N\cdots N}$; (b) plot of ΔC-2(ND) vs $R_{N\cdots N}$; (c) plot of ΔC-1′(ND) vs $R_{N\cdots N}$; (d) plot of ΔC-2′(ND) vs $R_{N\cdots N}$; and (e) plot of ΔC-1″(ND) vs $R_{N\cdots N}$.

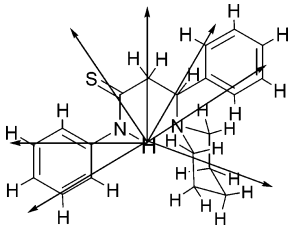

FIGURE 6. Figure showing the polarization of bonds due to electric fields. Directions are arbitrary and are chosen to help the eye.

and **6**-type derivatives are remarkable. First is their magnitudes considering the large number of bonds between the site of deuteriation and the carbon in question (four to six). The other unusual observation is that all these effects are large and negative. It is difficult to envisage that a conformational change would lead to only a change in chemical shifts in the same direction. It is not difficult to understand that as most C−H bonds have the same direction compared to the charge on N−H the polarization will be similar leading to negative isotope effects. Support for an electric field effect is seen in the fact that the **4** derivatives with short N···N distances show much larger effects at C-10 than the corresponding **2** derivatives (Scheme 3). For **5am(c)Sc** (the closed form) the estimated effect at C-1″ of ca. −0.03 ppm (see previously) is in line with a geometry in which the C-3,C-1″ bond is perpendicular to the NH, hence giving rise to a smaller electric field polarization of the aromatic system. All these observations are unified in Figure 6 in which arrows show the polarization of bonds due to electric field effects.

The temperature effects observed at isotope effects can be explained by noticing that the variations closely follow the variation in ring flipping of the piperidine or morpholine rings. For **2apmeS** for which no ring flipping occurs, the isotope effects are virtually invariant, whereas in other cases the variation of the isotope effects levels off when the piperidine ring flipping becomes slow. This coincides with maximal hydrogen bonding again linking the isotope effects to intramolecular hydrogen bonding and the N···N distance. Although the temperature effects level off, it can be seen for all piperidine derivatives that the proportionality found with $R_{N\cdots N}$ (Tables 1 and 1Sc) is also seen when decreasing the temperature except for C-1, which in most cases is invariant. For the morpholine and *N*-methylpiperazine derivatives, the trends are roughly opposite lending support to a common mechanism, the change of the electric field. With respect to conformation, this means that the piperidine derivatives contract at lower temperature as a consequence of the higher dielectric constant,[29] whereas the morpholine and *N*-methylpiperazine derivatives because of electrostatic repulsion end up in a conformation with a slightly longer N···N distance at lower temperature.

Conclusions

Isotope effects caused by deuteriation at the hydrogen of strongly polarized NH bonds can be explained by electric field effects caused by the average shorter ND than NH bond. Such

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effects are shown to be very long range and through space. Effects of this type are clearly not limited to the present compounds but may also be seen in proteins, nucleic acids, and other compounds with strongly polarized XH bonds. Furthermore, deuterium isotope effects can also be expected at other nuclei, especially ^{15}N and ^{19}F.[19] The prospects of using long-range isotope effects for assignment and structural studies seem very promising considering that the effects can be observed very strongly at ~4 Å and up to ~7 Å from the site of deuteriation.

Experimental Section

Compounds. The compounds are prepared as described in refs 19, 27, and 30.

Deuteriation. Deuteriation was achieved by dissolving the compounds in CH_3OD followed by evaporation under vacuum. Different levels of deuteriation were done.

NMR Measurements. ^1H, ^{13}C NMR spectroscopic measurements were performed on a 9.4 T NMR spectrometer equipped with an 5 mm ^1H/BB inverse probe head, operating at 400.13 and 100.62 MHz with a digital resolution of 0.12 and 0.97 Hz per point for ^1H and ^{13}C, respectively, or on a 7.05 T instrument operating at 300 and 75.44 MHz primarily with $CDCl_3$ as solvent except for the fluorinated compounds in which case CD_2Cl_2 was used.

TMS was used as internal reference. Two-dimensional spectra were acquired by using standard Bruker software.

Calculations. The molecular geometries were optimized by using the Gaussian98 suite of programs[31] and BPW91 Density Functional Theory (DFT) (Beckes exchange[32] and Perdew−Wang correlation term[33] and a mix of the built-in Gaussian-type basis sets). The 6-31G(d) basis set was used. The nuclear shieldings were calculated by using the GIAO approach.[34,35] Frequencies are calculated to check for negative ones.

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Supporting Information Available: Table 1S giving ^{13}C chemical shifts of fluorinated compounds, deuterium isotope effect on ^{13}C chemical shifts, and H,H coupling constants at variable temperatures, Figure 1S showing NOESY spectra of **2apS** and **2apmeS**, and Figure 2S showing the ^{13}C NMR spectrum of **1apS** partially deuteriated at N and C-2. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070285Z

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