Steric Effects on Nitrogen-15 Chemical Shifts of 4-Aminooxanes (Tetrahydropyrans), 4-Aminothianes, and the Corresponding *N,N*-Dimethyl Derivatives. Use of Nitrogen-15 Shifts as an Aid in Stereochemical Analysis of These Heterocyclic Systems

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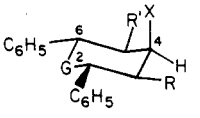
The ^{15}N NMR spectral chemical shifts of natural abundance in several 2,6-diaryl-substituted 4-aminooxanes (tetrahydropyrans), 4-aminothianes, and their corresponding *N,N*-dimethyl derivatives have been measured in $DCCl_3$ for the first time in this family of six-membered heterocyclic amines, and the observed chemical shifts are analyzed in terms of conformational properties. Steric interactions between the amino or dimethylamino group with axial H(2,6) protons and alkyl substituents have been shown to cause important chemical shift changes. Additivity parameters have been derived for the substituents. The ^{15}N spectral results indicate that *cis*-2,-*trans*-2-dimethyl-*trans*-6-phenyl-*r*-4-aminothiane (**3a**) and *cis*-2,*trans*-2-dimethyl-*trans*-6-phenyl-*r*-4-(dimethylamino)thiane (**3b**) appear to exist in nonchair conformations. The chemical shift differences for the ^{15}N signals between isomers appears to be of significance so that stereochemical assignments for the configuration at carbon can be made.

Natural-abundance ^{15}N NMR spectra of saturated aliphatic primary, secondary, and tertiary amines and their hydrochlorides have been measured.[1] The ^{15}N shifts of some secondary acetamides have also been reported by Westerman and Roberts.[2] Coxon and co-workers have used ^{15}N spectral data for elucidating the stereochemistry of amino sugars.[3] The dependance of ^{15}N chemical shifts on the nitrogen lone-pair orientation has been utilized in assigning the stereochemistry of alkaloids.[4] As a continuation of our work on the conformational analysis of 4-aminooxanes[5] and 4-aminothianes,[6] we report an analysis of the ^{15}N spectra of these heterocyclics with a view to glean information about the steric environment around the nitrogen atom. This is the first systematic study of the ^{15}N NMR chemical shifts of heterocyclic amines.

The ^{15}N chemical shifts of epimeric heterocyclic amines **1a–n**, **2a–n**, **3a,b**, and **4a,b** (Chart I) are listed in Table I. The configuration and conformation of these 4-aminooxanes[5] and 4-aminothianes[6] and their corresponding tertiary amines[7] have been established via stereospecific syntheses and ^1H NMR and ^{13}C NMR spectral analysis.[5,6]

An inspection of Table I reveals that the ^{15}N chemical shift in epimeric aminooxanes **1a–d** and **2a–d** and in 4-aminothianes **1e–g**, **2e–g**, **3a** and **4a** depends significantly upon the configuration of the amino group. For example,

Chart I



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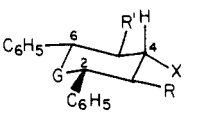
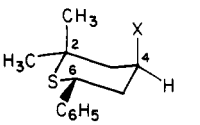
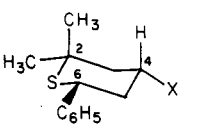


2

	G	R	R'	X
a	O	H	H	NH_2
b	O	CH_3	H	NH_2
c	O	C_2H_5	H	NH_2
d	O	CH_3	CH_3	NH_2
e	S	H	H	NH_2
f	S	CH_3	H	NH_2
g	S	C_2H_5	H	NH_2
h	O	H	H	$N(CH_3)_2$
i	O	CH_3	H	$N(CH_3)_2$
j	O	C_2H_5	H	$N(CH_3)_2$
k	O	CH_3	CH_3	$N(CH_3)_2$
l	S	H	H	$N(CH_3)_2$
m	S	CH_3	H	$N(CH_3)_2$
n	S	C_2H_5	H	$N(CH_3)_2$

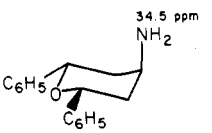


3a, X = NH_2
b, X = $N(CH_3)_2$

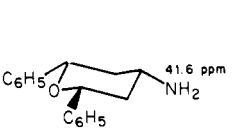


4a, X = NH_2
b, X = $N(CH_3)_2$

the nitrogen atom on an axial C–NH_2 bond is shielded by about 7 ppm for compounds **1a** and **2a**. Such a chemical



1a



2a

(1) (a) Duthaler, R. O.; Roberts, J. D. *J. Am. Chem. Soc.* **1978**, *100*, 3889. (b) Levy, G. C.; Lichter, R. L. "Nitrogen-15 Nuclear Magnetic Resonances Spectroscopy"; Wiley-Interscience: New York, 1979; Chapter 3.

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(7) Ramalingam, K.; Berlin, K. D., unpublished results.

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Table I. ^{15}N Shifts (ppm) of 4-Aminooxanes (Tetrahydropyrans), 4-Aminothianes, and the Corresponding *N,N*-Dimethyl Derivatives

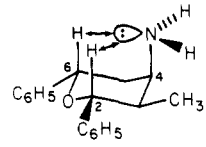
compd (axial)	δ[a]	compd (equatorial)	δ[a]
1a	34.5	2a	41.6
1b	24.7	2b	36.5
1c	23.3	2c	36.1
1d	15.4	2d	31.4
1e	33.6	2e	42.6[b]
1f	24.1	2f	38.9
1g	22.9	2g	38.0
1h	27.0	2h	31.7
1i	25.7	2i	20.1
1j	24.5	2j	19.0
1k		2k	13.5
1l	27.4	2l	30.2
1m	27.4	2m	21.2
1n	26.0	2n	20.0
3a	39.8	4a	42.7[b]
3b	29.3	4b	29.3

[a] For a 0.4 M solution in $DCCl_3$ unless otherwise stated. [b] In C_6D_6 (concentration <0.2 M). All ^{15}N chemical shifts were measured with respect to an external standard of 5 M $^{15}NH_4NO_3$ in 2 M HNO_3 taken in a capillary tube ($^{15}NH_4NO_3$ = 21.6 ppm relative to anhydrous ammonia).

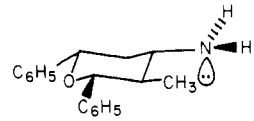
shift difference has been recently reported for eipimeric 4-*tert*-butylcyclohexylamines.[1] Hence, ^{15}N chemical shift differences can be employed for the successful assignment of the configuration of the amino group in these heterocycles.

Introduction of an equatorial methyl group at C(3) causes a large upfield shift on the nitrogen resonance compared to that in the nonmethyl-substituted amines. The nitrogen resonances in **1b** and **1f** are shifted upfield by about 9.8 ppm compared to the nitrogen signal in **1a** and **1e**. This effect of a methyl group on the nitrogen resonances appeared to be roughly additive. For example, on comparison of **1a** with **1b** and **1d**, a difference was noted for the nitrogen resonance that amounted to 9.8 and 19.1 ppm, respectively. The nitrogen in **1c** was also shielded (~10.0 ppm, apparently due to the ethyl group) compared to the corresponding signal found for nitrogen in **1a**. A similar trend was also found in *trans*-2,*trans*-6-diphenyl-*cis*-3-ethylthian-*r*-4-amine (**1g**). The resonance positions of ^{15}N in systems with an equatorial C–NH_2 bond are also influenced by 3-alkyl substituents but to a much less extent. Generally, ^{15}N resonances are shielded by carbons in the γ-position in a manner analogous to ^{13}C NMR chemical shifts, and this may possibly be due to conformational influences on the stereoelectronic relationship between the lone pair of electrons on the nitrogen and the C–C bonds.[1b]

In regard to compounds with an equatorial C-NH_2 group, comparing **2b** with **2a** gives a nitrogen chemical shift difference of 5.1 ppm for ^{15}N in an equatorial NH_2 group. With the sulfur analogue, comparing **2e** with **2f** showed differences of 6.3 ppm for the equatorial amino group. It was noteworthy that the additivity principle of the methyl group (as compared with axial amines) was detected in the equatorial isomers also. For example, on comparison of **2a** with **2b** and **2d**, chemical shift differences of 5.1 and 10.2 ppm for the amino nitrogen were found (Table I). The nitrogen resonances in **2c** and **2g** were also shifted upfield by ~5 ppm compared to nitrogen resonance signals in **2a** and **2e**, respectively. However, a shielding effect of ~5 ppm due to the equatorial alkyl group at C(3) was small when compared to the upfield shift (~10 ppm) found in the axial isomer. This may result from greater steric compression experienced by the lone pair on an axial amino nitrogen compared to that of a lone pair on the equatorial amino nitrogen.

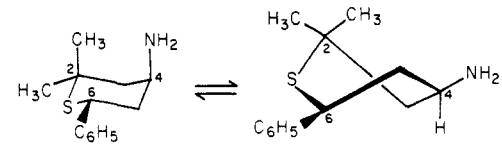


1b



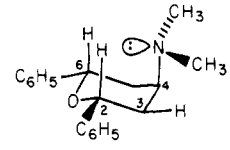
2b

The nitrogen chemical shift (39.8 ppm) in the axial isomer **3a** is not much smaller than the nitrogen resonance (42.7 ppm) for **4a**. Assuming 1,3 nonbonded steric interactions occur between axial methyl and axial NH_2 groups, one would expect an upfield shift of the nitrogen resonance for **3a** relative to that found for **1e**. Surprisingly, the nitrogen resonance in **3a** was shifted downfield (~6 ppm) compared to the ^{15}N resonance signal in **1e**. The downfield nitrogen resonance may be indicative of a possible nonchair conformation for **3a** wherein the syn-axial CH_3–NH_2 interactions can be relieved to some extent. The amino group in **3a** may acquire a pseudoequatorial orientation in the nonchair conformation **3a'** which could explain downfield shift of nitrogen resonance. Such a view is also supported by ^1H NMR and ^{13}C NMR spectral data[6] for **3a**.

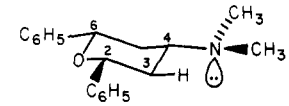


3a **3a'**

Conversion of primary amines to their *N,N*-dimethyl derivatives is accompanied by a shielding of the nitrogen resonance. The nitrogen resonance of tertiary amines appears to fall into two classes depending upon whether C(3) bears a hydrogen (as in **1h**) or an equatorial alkyl group (as in **1i**). In the former case, the nitrogen in the axial C–$N(CH_3)_2$ group (as in **1h**) is shielded more than that in the equatorial eipmer (**2h**).



1h

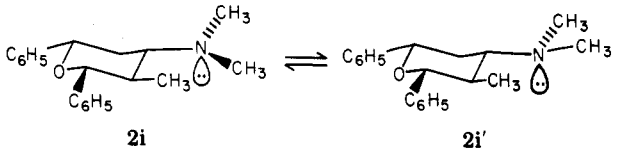


2h

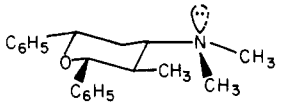
In the case of tertiary amines in which there is an equatorial alkyl substituent at C(3), the equatorial $N(CH_3)_2$ is more shielded than the axial epimer. For example, the nitrogen in the dimethylamino group in **1i** absorbs at 25.7 ppm while that in the dimethylamino group in **2i** appears at 20.1 ppm. The same trend is found in ethyl derivatives **1j** and **2j**. Likewise, the situation is similar in the sulfur analogues **1m**, **2m**, **1n**, and **2n**.

The marked upfield shift of the nitrogen resonance in **2i** may be rationalized in the following way. Tertiary amine **2i** could exist as an equilibrium mixture of **2i**, **2i'**, and **2i''** (C–N rotamers), (Scheme I). Rotamers **2i** and **2i''** can be precluded because there is a severe interaction between the dimethylamino methyl and the equatorial methyl group. Thus, the compound may chiefly exist in conformation **2i'**. In this conformation, the lone pair of electrons on the nitrogen atom of the equatorial dimethylamino group is probably oriented toward the equatorial methyl group at C(3). This results in an increased steric interaction of the lone pair with an equatorial methyl group, causing an *upfield* shift of nitrogen reso-

Scheme I

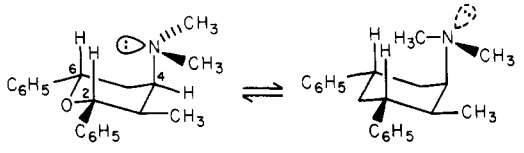


2i 2i'

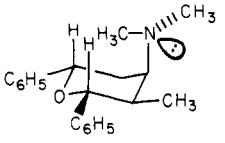


2i''

Scheme II



1i 1'



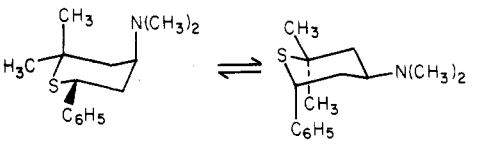
1''

nance. In the chair conformation of **1i**, an equilibrium may exist between three conformers **1i**, **1i'** and **1i''** because of free rotation around C–N bond (Scheme II).

Of the three possible conformations, conformers **1i'** and **1i''** have steric interactions between the dimethylamino methyl groups and the H(2) and H(6) protons. In conformer **1i**, the free electron pair points toward the center of the ring. With the lone pair so oriented as in **1i**, there may be comparatively less steric interaction with H(2) and H(6); thus **1i** might be expected to predominate in the equilibrium. Of course it is also possible that the higher field ^{15}N position in **2i** results from factors not directly related to steric compression.

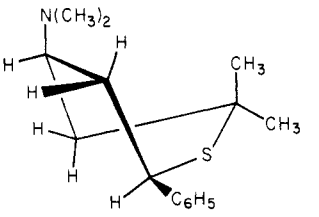
The observed upfield shift of the nitrogen resonance in **2i** compared with the corresponding nitrogen resonance in **1i** is in conformity with the relative rates of quaternization[7] of **1i**, **2i**, **1j**, and **2j** with CH_3I in CH_3CN at 30 °C. It is observed[7] that in the pair **1i** and **2i**, as well as in the pair **1j** and **2j**, the rates of quaternization of the axial isomer **1i** and **1j** are higher than those of the corresponding equatorial isomers **2i** and **2j**. This lowering of rates for **2i** may, therefore, be attributed again to the steric interaction between the nitrogen lone pair and the equatorial methyl group.

Interestingly, the nitrogen resonances in **3b** and **4b** are similar. This would suggest that the contribution to the equilibrium by conformer **3b** with a bulky dimethylamino group is small and that the compound largely exists in the chair conformation **3b'**. However, the syn-diaxial CH_3–C_6H_5 interaction in **3b'** should be severe enough to make



3b 3b'

the chair conformation highly strained. Consequently, the system may exist in a nonchair conformation or a twist conformation **3b''** in which the nonbonded steric interac-



3b''

tions are largely relieved. This conclusion also derives support from the ^1H NMR and ^{13}C NMR chemical shift data for **3b** and the kinetics of quaternization of **3b** with CH_3I in CH_3CN at 10 °C.[7]

Experimental Section

All spectra were recorded on a quadrature detection modified Bruker HX-270, operating at 27.4 MHz for ^{15}N with two-level broad-band decoupling (low level ~0.5 W, high level ~4 W) centered at ~4 ppm (at room temperature, i.e., 30 °C). A solution of $^{15}NH_4NO_3$ in aqueous HNO_3 in a capillary (δ 21.6 relative to anhydrous ammonia) was used as the reference for ^{15}N shifts. For primary amines, the number of scans was about 1000; a 60° pulse (45 ms) at a repitition rate of 4 s and a spectral window of 2000 Hz with $4K + 4K$ data points (zero filled to $8K$ real plus $9K$ imaginary data points before Fourier transformed) were used to give good spectra (signal/noise ratio >20). For tertiary amines, ~5000 scans at a repitition rate of 6 s gave reasonably good spectra.

Oxygen heterocycles **1a–d** and **2a–d** were prepared as reported.[5] The preparations of 4-aminothianes **1e–g**, **2e–g**, **3a**, and **4a** have been communicated.[6] The synthesis of compounds **1h–n**, **2h–n**, **3b**, and **4b** will be reported elsewhere.[8]

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Registry No. **1a**, 74854-71-0; **1b**, 74854-72-1; **1c**, 74854-73-2; **1d**, 74854-74-3; **1e**, 69832-20-8; **1f**, 78837-43-1; **1g**, 78837-44-2; **1h**, 81158-62-5; **1i**, 81158-63-6; **1j**, 81158-64-7; **1k**, 81158-65-8; **1l**, 81203-25-0; **1m**, 81158-66-9; **1n**, 81158-67-0; **2a**, 74854-79-8; **2b**, 74854-80-1; **2c**, 74854-81-2; **2d**, 74854-82-3; **2e**, 69832-19-5; **2f**, 78918-40-8; **2g**, 78918-41-9; **2h**, 81158-68-1; **2i**, 81158-69-2; **2j**, 81158-70-5; **2k**, 81158-71-6; **2l**, 81203-26-1; **2m**, 81203-27-2; **2n**, 81203-28-3; **3a**, 78837-45-3; **3b**, 81158-72-7; **4a**, 78837-47-5; 4b, 81158-73-8.

(8) Chandrasekara, N.; Ramalingam, K.; Satyamurthy, N.; Berlin, K. D., submitted for publication in *J. Org. Chem.*