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Registry No. **2a**, 81158-62-5; **2b**, 81158-63-6; **2c**, 81158-64-7; **2d**, 81158-65-8; **4a**, 81158-68-1; **4b**, 81158-69-2; **4c**, 81158-70-5; **4d**, 81158-71-6; **5a**, 85318-63-4; **5b**, 85318-64-5; **5c**, 85318-65-6; **5d**, 85318-66-7; **6a**, 85318-67-8; **6b**, 85318-68-9; **6c**, 85318-69-0; **6d**, 85318-70-3.

Base Strengths of 4-Aminooxanes (Tetrahydropyrans), (Methylamino)oxanes, (Dimethylamino)oxanes, (Methylamino)thianes, and (Dimethylamino)thianes

Nallappan Chandrasekara,[1] Pullachipatti K. Subramanian,[2] and Kondareddiar Ramalingam*

Department of Chemistry, PSG College of Arts and Sciences, Coimbatore 641 014, India

Nagichettiar Satyamurthy[3] and K. Darrell Berlin*

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74078

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The pK_a values of a series of epimeric 4-aminooxanes (tetrahydropyrans), (methylamino)oxanes, (dimethylamino)oxanes, (methylamino)thianes and (dimethylamino)thianes have been determined in 80% 2-methoxyethanol at 27 ± 0.1 °C. Alkyl groups on the carbon α to the C–N group reduce the basicity of the nitrogen in the 4-aminooxanes, apparently due to reduced stability of the conjugate acid because of steric factors. Possible twist conformations are suggested for *trans*-2,6-diphenyl-*cis*-3-methyl-*r*-4-(dimethylamino)oxane (**1l**), *trans*-2,6-diphenyl-*cis*-3-ethyl-*r*-4-(dimethylamino)oxane (**1m**), *trans*-2,6-diphenyl-*cis*-3,5-dimethyl-*r*-4-(dimethylamino)oxane (**1n**), *cis*-2,6-diphenyl-*trans*-3,5-dimethyl-*r*-4-(dimethylamino)oxane (**2n**), *trans*-2,6-diphenyl-*cis*-3-methyl-*r*-4-(dimethylamino)thiane (**4e**), 2,2-dimethyl-*trans*-6-phenyl-*r*-4-(methylamino)thiane (**6a**), 2,2-dimethyl-*trans*-6-phenyl-*r*-4-(dimethylamino)thiane (**6b**), and 2,2-dimethyl-*trans*-6-(4-chlorophenyl)-*r*-4-(dimethylamino)thiane (**6c**). Such a twist form avoids severe nonbonded interactions between the C–N bond(s) and axial C(2,6)–H or C(2,6)–C bonds or between C–N bond(s) and equatorial C(3,5)–C bonds, depending upon the system involved. Solvation of the free amine is suggested to be favored over solvation of the protonated amine since the latter may experience rather strong nonbonded interactions in the ground state with concomitant retardation of solvation compared to that with the free amine. ^{1}H NMR data are also presented which support a nonchair form for several of the molecules. The study is the first in which a systematic investigation is described concerning the basicity of the amine group in 4-aminooxanes and 4-aminothianes and the configuration at the carbon bonded to the nitrogen atom.

Although assignments of configurations of carbons bonded to amino groups in six-membered cyclic systems[4-7] and alicyclic systems[8] have been made via analysis of pK_a determinations, such a study on six-membered heterocycles has apparently not been recorded. Certain aminooxanes[9] appear to exist in biased chair conformations. We report herein the first systematic study of the relationship of the basicity of selected 4-aminooxanes and 4-aminothianes to the configuration at carbon bonded to nitrogen. Systems 1–8 were those investigated at 27 ± 0.1 °C in 80% 2-methoxyethanol. All values are the average of at least two independent measurements for each compound. Both the synthesis and ^{1}H and ^{13}C NMR analysis have been described.[10]

Table I. pK_a Values for the Aminooxanes in 80% 2-Methoxyethanol (v/v) at 27 ± 0.1 °C[a]

compd	pK_a (axial amines)	compd	pK_a (equatorial amines)
1a	7.96	2a	8.40
1b	7.60	2b	8.09
1c	7.70	2c	8.15
1d	7.38	2d	7.98
1e	7.11	2e	7.71
1f	7.10	2f	7.72
1g	6.84	2g	7.49
1h	7.81	2h	8.27
1i	7.40	2i	8.03
1j	7.08	2j	8.00
1k	6.54	2k	7.40
1l	6.88	2l	7.18
1m	6.65	2m	6.85
1n	6.55	2n	5.85
		3	8.33

[a] The values were reproducible to within ±0.01 of a pK_a unit.

(1) Taken in part from the Ph.D. dissertation of N.C., submitted to the University of Madras, India.
(2) Taken in part from the Ph.D. dissertation of P.K.S., submitted to the University of Madras, India.
(3) Research associate 1980–1981.
(4) Bird, C. W.; Cookson, R. C. *J. Chem. Soc.* **1960**, 2343.
(5) Sicher, J.; Jonas, J.; Tichy, M. *Tetrahedron Lett.* **1963**, 825.
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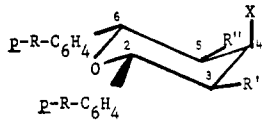
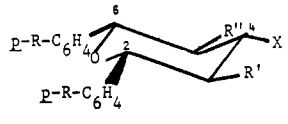
The pK_a values of pairs of epimeric amines **1a–n**, **2a–n**, and **3** are listed in Table I. With one exception (i.e., **1n**),



1



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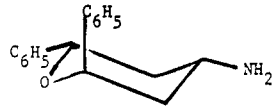
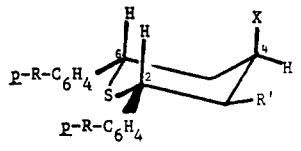


3

	X	R	R'	R''
a	NH_2	H	H	H
b	NH_2	H	CH_3	H
c	NH_2	OCH_3	CH_3	H
d	NH_2	H	C_2H_5	H
e	NH_2	H	CH_3	CH_3
f	NH_2	OCH_3	CH_3	CH_3
g	NH_2	Cl	CH_3	CH_3
h	$NHCH_3$	H	H	H
i	$NHCH_3$	H	CH_3	H
j	$NHCH_3$	H	C_2H_5	H
k	$N(CH_3)_2$	H	H	H
l	$N(CH_3)_2$	H	CH_3	H
m	$N(CH_3)_2$	H	C_2H_5	H
n	$N(CH_3)_2$	H	CH_3	CH_3

the 4-amino-, 4-(methylamino)-, and 4-(dimethylamino)-oxanes were the weaker bases when the amine group was in an axial position than when it was in a equatorial position. A similar situation for epimeric pairs **4a,b**, **5a,b**, and **6a,7a** as well as for **4c,5c**, **4d,5d**, **4e,5e**, **4f,5f**, **6b,7b**,



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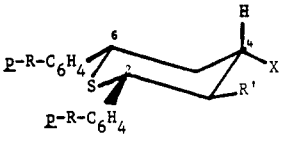
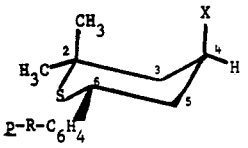


5

	R	R'	X
a	H	H	$NHCH_3$
b	H	CH_3	$NHCH_3$
c	H	H	$N(CH_3)_2$
d	Cl	H	$N(CH_3)_2$
e	H	CH_3	$N(CH_3)_2$
f	H	C_2H_5	$N(CH_3)_2$

and **6c,7c** persists in terms of the data for the aminothianes in Table II. Thus, although the C–S bond in thiane derivatives (1.815–1.830 Å)[11a] is longer than the C–C bond



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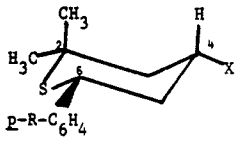
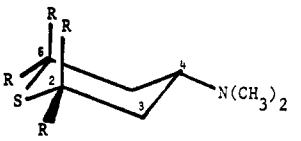


7

	R	X
a	H	$NHCH_3$
b	H	$N(CH_3)_2$
c	Cl	$N(CH_3)_2$



8

a R = H

b R = CH_3

in cyclohexane (1.528 Å)[11b] and the C–S–C bond angle is considerably smaller in thianes (98.9–99.8°)[11a] than the C–C–C bond angle in cyclohexane (111.5°),[11b] steric crowding of the type from axial 1,3-interactions must still obtain. This is in accord with observations[4-7] in cyclohexylamines, the rationale being that an axial ammonium ion experiences more steric interference from 1,3-interactions and is thus less accessible for solvation than the equatorial counterpart.

Some interesting observations made on these systems deserve a brief analysis. The introduction of a methyl (as in **1b,2b**, **1i,2i**, **4b,5b**, and **4e,5e**) or ethyl group (as in **1d,2d**, **1j,2j**, **1m,2m**, and **4f,5f**) in the equatorial position at C(3) reduces the basicity of the nitrogen. Apparently, any increase in bulkiness near the nitrogen atom (whether it be attached via an equatorial or axial bond to the ring) retards solvation of the protonated amine group and lowers the pK_a in both the oxane and thiane. N-Methylation also results in the formation of weaker bases regardless of the position of the amino group (equatorial or axial) as can be seen in **1a** vs. **1h** or **1k**, **1b** vs. **1i** or **1l**, **1d** vs. **1j** or **1m**, **2a** vs. **2h** or **2k**, **2b** vs. **2i** or **2l**, **4a** vs. **4c**, **4b** vs. **4e**, **5a** vs. **5c**, **5b** vs. **5e**, **6a** vs. **6b**, and **7a** vs. **7b**. This leads us to a tentative conclusion that solvation of the protonated amine may be greater than solvation of the free amine since the N-methylation resulted in formation of a weaker base whether or not an axial or equatorial C–N bond existed in the system. Steric parameters are, of course, still difficult to predict, however, and other unknown forces may be important here.

In the case of (methylamino)oxanes, introduction of an equatorial methyl group at the 3-position lowers the basicity. However, the decrease in basicity in the secondary amine due to the introduction of an equatorial alkyl group is much greater in the axial *N*-methyl derivative than in the equatorial *N*-methyl compound. (Methylamino)oxanes **1i** and **1j** are weaker amines than the "parent" amine, *trans*-2,6-diphenyl-*r*-4-(methylamino)oxane (**1h**); the difference for **1i** is 0.41 pK_a unit, and that for **1j** is as much

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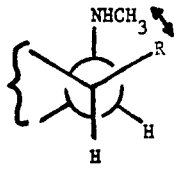
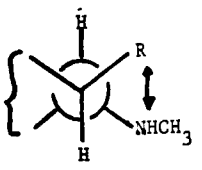


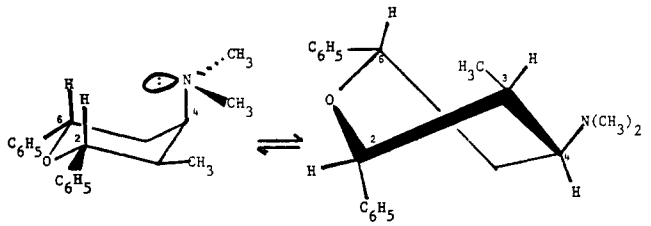
1i R = CH_3
1j R = C_2H_5



2i R = CH_3
2j R = C_2H_5

as 0.73 pK_a unit. The all-equatorial *N*-methyl amines **2i** and **2j** are again weaker bases than the parent amine **2h**, the former by 0.24 and the latter by 0.27 pK_a unit. It is known now that the cyclohexane ring is slightly flattened, rather than being a perfect chair.[12] The tetrahydropyran ring is more flattened than cyclohexane.[13,14] The flattening of the ring is accompanied by a change in torsional angles[15] in such a way that 1,2 equatorial–equatorial bonds diverge whereas 1,2 equatorial–axial bonds converge.[16] In view of this, one would expect that the separation between an equatorial alkyl group and the *N*-methylamino group in the secondary aminooxanes **2i** and **2j** would be larger than in the axial equatorial isomer **1i** and **1j**. Hence, an equatorial alkyl group in the 3-position should have a greater steric effect on the dissociation constants of the axial *N*-methylamino group than on the pK_a of an equatorial *N*-methylamino group. This was indeed found to be the case (Table I).

The dramatic fall in pK_a values of **1k–n** and **2k–n** shows that tertiary amines are more weakened by steric hindrance to solvation than are primary or secondary aminooxanes. The (dimethylamino)oxane **1l** with an equatorial methyl group at C(3) is a stronger base than the "parent" *trans*-2,6-diphenyl-*r*-4-(dimethylamino)oxane (**1k**) by 0.34 pK_a unit. In contrast, (dimethylamino)oxane **2l** with an equatorial methyl group at C(3) is a weaker base than the corresponding "parent" *cis*-6-diphenyl-*r*-4-(dimethylamino)oxane (**2k**) by 0.22 pK_a unit. The difference in pK_a between the epimers is also considerably smaller (0.3 pK_a unit) than that observed (0.86 pK_a unit) for the "parent" amines **1k** and **2k**. The base-weakening effect for the all-equatorial isomer **2l** results from the steric interactions between the equatorial methyl and equatorial dimethylamino groups. The increase in pK_a in **1l** cannot be due to the inductive effect of the methyl, since the inductive effect of the methyl group should be the same for the epimers **1l** and **2l**, and so the difference in pK_a should be steric in origin. The dimethylamino group in **1l** will be severely hindered by the equatorial methyl group (gauche interaction), in addition to the axial hydrogens H(2) and H(6).



1l 1l'

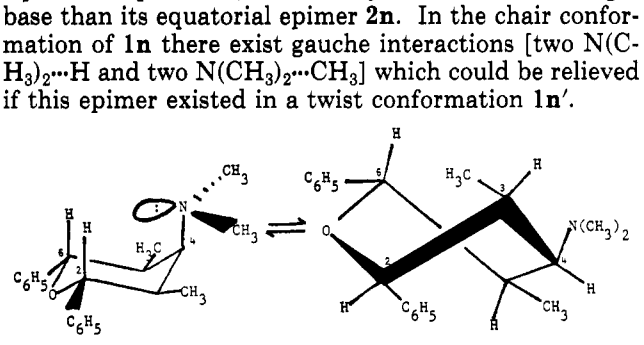
Table II. pK_a Values for the (Methylamino)- and (Dimethylamino)thianes in 80% 2-Methoxyethanol at 27 ± 0.1 °C[a]

compd	pK_a (ax)	compd	pK_a (eq)
4a	7.51	5a	8.23
4b	7.14	5b	7.90
4c	6.25	5c	7.31
4d	6.02	5d	7.09
4e	6.52	5e	6.87
4f	6.22	5f	6.46
6a	8.07	7a	8.23
6b	7.26	7b	7.47
6c	7.21	7c	7.47
		8a	7.86
		8b	7.62

[a] The values were reproducible to within ±0.02 of a pK_a value.

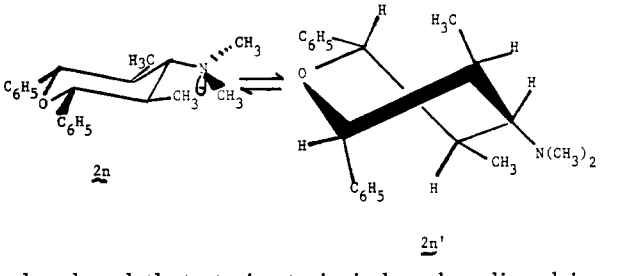
The molecule, therefore, may not exist in the chair conformation. A twist conformation may relieve the steric strain. In a conformation of this type, the $N(CH_3)_2$ group no longer remains axial but has some equatorial-like orientation, and hence an increase in pK_a is observed. Such a view is supported by ^{1}H NMR data[10] for **1l**. The dissociation constant data for **1m** is higher compared to **1k** indicating that **1m** also probably adopts a twist conformation.

cis-2,6-Diphenyl-*trans*-3,5-dimethyl-*r*-4-(dimethylamino)oxane (**2n**) and its epimer **1n** present a particularly interesting anomaly. *trans*-2,6-Diphenyl-*cis*-3,5-dimethyl-*r*-4-aminooxane (**1e**) is a weaker base than its equatorial epimer **2e**, but tertiary amine **1n** is a stronger base than its equatorial epimer **2n**. In the chair conformation of **1n** there exist gauche interactions [two $N(CH_3)_2\cdots H$ and two $N(CH_3)_2\cdots CH_3$] which could be relieved if this epimer existed in a twist conformation **1n'**.



1n 1n'

In the twist conformation **1n'**, the 3,5-dimethyl groups are axial-like, and the dimethylamino group will be in a pseudoequatorial position and may offer lesser steric hindrance for solvation. An inspection of models suggest that the equatorial dimethylamino group in **2n** is highly



2n 2n'

hindered and that steric strain is largely relieved in a distorted chair or twist form. However, in the twist conformation **2n'**, the methyl groups at C(3,5) and also the dimethylamino group acquire a pseudoaxial orientation. The pseudoaxial methyl groups and the pseudoaxial dimethylamino group in the twist conformation **2n'** could strongly hinder solvation, and this could explain the anomalous decrease in basicity for **2n**. A twist conformation for **1n** and **2n** is also supported by ^{1}H NMR

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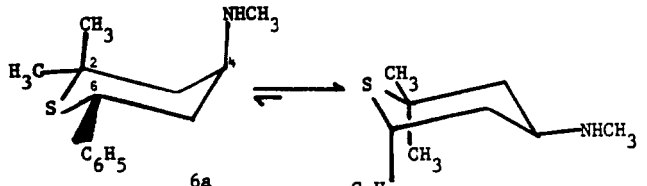
(15) Wohl, R. A. *Chimia* **1964**, *18*, 219.
(16) (a) Eliel, E. L.; Schroeter, S. H.; Brett, T. J.; Biros, F. J.; Richer, J.-C. *J. Am. Chem. Soc.* **1966**, *88*, 3327. (b) Eliel, E. L.; Biros, F. J. *J. Am. Chem. Soc.* **1966**, *88*, 3334.

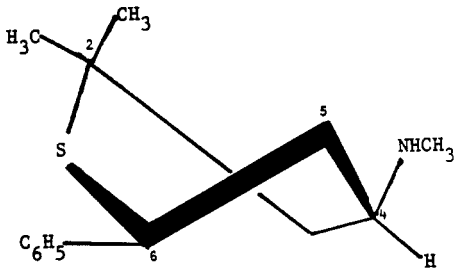
data.[10b] An abnormal coupling constant (J = 9.0 Hz) was observed[10b] for H(2,6) protons in **1n** and **2n**. In the thianes **4** and **5**, trends similar to those found in the corresponding oxanes are observed.

Introduction of an equatorial methyl group at C(3) reduces the basicity of (methylamino)thiane. For example, *trans*-2,6-diphenyl-*cis*-3-methyl-*r*-4-(methylamino)thiane (**4b**) is a weaker base than the "parent" *trans*-2,6-diphenyl-*r*-4-(methylamino)thiane (**4a**). This is probably due to the steric interaction of the methyl group with the amino function since the solvation of ammonium ion is more sensitive to steric hindrance. A similar trend is also observed for **5b**.

The basicity of **7a** is almost identical with that of **5a**. It is reasonable to expect that an axially placed 3-methyl group will not have any polar effect on the equatorial *N*-methylamino group. Such an axial group may also be expected to have a negligible steric effect on the equatorial *N*-methylamino group, provided the ring is not distorted. The observed pK_a of **7a** (pK_a = 8.23) is only slightly higher than that of **6a** (pK_a = 8.07). 2,2-Dimethyl-*trans*-6-phenyl-*r*-4-(methylamino)thiane (**6a**) can exist as an equilibrium mixture of conformers **6a** and **6a′**. The small



6a ⇌ **6a′**

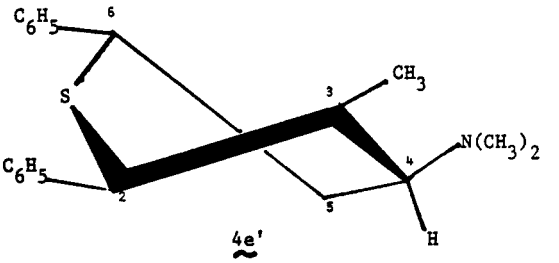


6a″

difference in pK_a values suggests that, at equilibrium, conformation 6a′ may persist with a minor contribution from **6a**. However, **6a′** will have one CH_3–C_6H_5, one C_6H_5–H, and one CH_3–H interaction. Consequently, the chair form **6a′** could be severely distorted, or compound **6a** might prefer a twist conformation, **6a″**. ^1H NMR studies on **6a** also led to a similar conclusion.[10]

An inspection of Table II shows that *cis*-2,6-diphenyl-*r*-(dimethylamino)thiane (**5c**) is much less basic than 4-(dimethylamino)thiane (**8a**). This lowering in basic strength may be attributed to the polar effect of the phenyl groups which could be transmitted along a σ bond.[17] The pK_a values of tertiary amines **4c** and **5e** are much less compared with the pK_a values of the corresponding secondary amines **4a** and **5b**. This suggests that tertiary amines are more weakened by steric hindrance than are secondary amines.

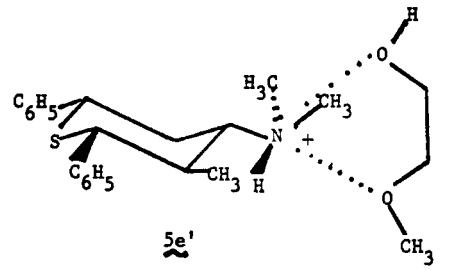
The tertiary amine **4e** is a stronger base than **4c** by 0.27 pK_a unit whereas the all-equatorial isomer **5e** is a weaker base than the corresponding "parent" amine **5c** by 0.44 pK_a unit. The increase in basicity for **4e** cannot be due to the inductive effect of the methyl group, for the inductive effect of the methyl group should be same for both the epimers **4e** and **5e**. The dimethylamino group in **4e** will be severely hindered by the equatorial methyl group (gauche interaction) in addition to 1,3-interactions with H(2) and H(6). The molecule, therefore, may not exist in regular chair conformation. A twist conformation, **4e′**, may



4e′

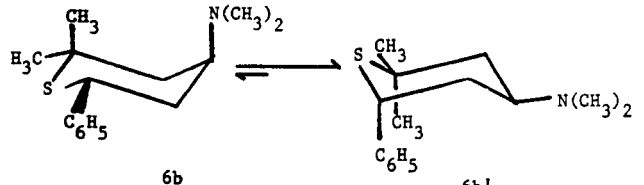
well relieve the steric strain. In a conformation of this type, the $N(CH_3)_2$ group no longer remains truely axial but has pseudoequatorial orientation, and hence an increase in basicity is observed for **4e**.

In the case of tertiary amine **5e**, the most stable conformation of the dimethylammonium ion in **5e′** might

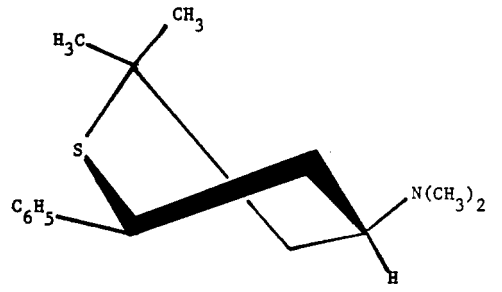


5e′

expectedly be that with the N^+–H bond pointing toward the methyl and possibly with the hydrogen atom bonded to solvent. In **5e′**, the hydrogen (N^+–H) is not easily accessible to the solvent, and this could possibly explain the lowering of basicity in **5e** compared to that in **5c**. The basicity (pK_a = 7.26) of the tertiary amine **6b** is not much lower than that (pK_a = 7.47) of its equatorial isomer **7b**. This might initially suggest that the contribution to the equilibrium of conformation **6b**, with an axial dimethylamino group, is small, and the compound chiefly exists as **6b′**. However, conformation **6b′** also has a number of



6b ⇌ **6b′**



6b″

severe 1,3-interactions, all of which are relieved in the twist conformation **6b″**. The twist conformation **6b″** is expected

(17) A comparable situation exists in the case of γ-phenylpropylamine (pK_a = 10.39) which is less basic than *n*-propylamine (pK_a = 10.59). See: Lange, N. A. "Handbook of Chemistry"; McGraw-Hill: New York, 1967; p 1215.

to be more stable than either **6b** or **6b′**. Since the conformation **6b″** has a dimethylamino group in a pseudoequatorial position, the observed increase in basicity is not unreasonable.

The dissociation constant of the tertiary amine **6c** is quite similar to that of **6b**, suggesting that the two bases may have similar conformations. The basicity of the tetramethyl derivative **8b** is less than that of **8a**. In **8b**, the axial methyl groups at the 2,6-positions may hinder solvation of $^{+}NH(CH_3)_2$, and hence the basicity of the amino group may be reduced.

Experimental Section

4-Aminooxanes **1a,b,d,e**, **2a,b,d,e**, and **3** were prepared as reported.[9] Preparation of compounds **1c,f–n**, **2c,f–n**, **4a–f**, **5a–f**, **6a–c**, **7a–c**, and **8a**, will be reported elsewhere.[10]

General Procedure for the Measurement of Dissociation Constants.[4] The amines were purified by either repeated crystallizations or distillation under reduced pressure. Methyl Cellosolve (2-methoxyethanol) was purified initially by distillation over quick lime and subsequently by fractionation using a Dufton column [bp 124 °C (760 mm)]. Distilled water, free from carbon dioxide, was prepared, and 80% 2-methoxyethanol was used as the solvent.

The amine (about 15 mg) was dissolved in 80% 2-methoxyethanol (25 mL). While the solution was stirred under nitrogen, 0.05 N hydrochloric acid was added dropwise from a buret that could be read to 0.005 mL. The pH values were measured in a pH meter, precalibrated with buffers at pH 4.0 and 9.2 with a glass electrode and a saturated calomel electrode as the reference electrode. All measurements were made at 27 ± 0.1 °C. The equivalence point was determined from a plot of pH against volume of HCl added. An average value (pK_a) of one-fourth, one-half, and three-fourths neutralizations was taken, and at least two independent titrations were carried out on each compound. The pH meter was an Elico Digital pH meter (Model LI-120) with an accuracy of ±0.01 pH units.

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Registry No. **1a**, 74854-71-0; **1b**, 74854-72-1; **1c**, 85336-31-8; **1d**, 74854-73-2; **1e**, 74854-74-3; **1f**, 85336-32-9; **1g**, 85336-33-0; **1h**, 85336-34-1; **1i**, 85336-35-2; **1j**, 85336-36-3; **1k**, 81158-62-5; **1l**, 81158-63-6; **1m**, 81158-64-7; **1n**, 81158-65-8; **2a**, 74854-79-8; **2b**, 74854-80-1; **2c**, 85336-37-4; **2d**, 74854-81-2; **2e**, 74854-82-3; **2f**, 85336-38-5; **2g**, 85336-39-6; **2h**, 85336-40-9; **2i**, 85336-41-0; **2j**, 85336-42-1; **2k**, 81158-68-1; **2l**, 81158-69-2; **2m**, 81158-70-5; **2n**, 81158-71-6; **3**, 74854-70-9; **4a**, 85336-43-2; **4b**, 85336-44-3; **4c**, 81203-25-0; **4d**, 85404-41-7; **4e**, 81158-66-9; **4f**, 81158-67-0; **5a**, 85404-42-8; **5b**, 85404-43-9; **5c**, 81203-26-1; **5d**, 85404-44-0; **5e**, 81203-27-2; **5f**, 81203-28-3; **6a**, 85336-45-4; **6b**, 81158-72-7; **6c**, 85336-46-5; **7a**, 85336-47-6; **7b**, 81158-73-8; **7c**, 85336-48-7; **8a**, 85336-49-8; **8b**, 85336-50-1.

Substituent Effects on ^{15}N and ^{17}O Chemical Shifts in Nitrobenzenes: Correlations with Electron Densities

David J. Craik,*[1a] George C. Levy,[1b] and Robert T. C. Brownlee[1c]

Departments of Chemistry, Syracuse University, Syracuse, New York 13210, and La Trobe University, Bundoora, Victoria 3083, Australia

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^{15}N and ^{17}O NMR spectra have been measured for a series of para- and meta-substituted nitrobenzenes, and the derived substituent chemical shifts (SCS) have been correlated with σ_I and σ_R substituent constants by using the dual substituent parameter (DSP) equation. The polar nature of the substituent is most important in determining the nitrogen chemical shifts, which follow a "reverse" trend; i.e., electron-withdrawing substituents induce *upfield* ^{15}N shifts. This observation is consistent with a π-polarization mechanism in which the N=O bonds are polarized by the dipole of the substituent. The proposal that this mechanism is transmitted through space and is not dependent on conjugation between the substituent and side-chain nitro group is confirmed by the observation that substituent effects on ^{15}N SCS values are ~25% larger in the meta series compared with the para series. Substituent chemical shifts at the oxygen atom are an order of magnitude larger than those at nitrogen and depend strongly on both polar and resonance substituent effects. The ^{17}O shifts follow a normal direction (i.e., donor substituents induce upfield shifts) and are smaller in the meta series than in the para series. Calculated ab initio π-electron densities reproduce the ^{15}N and ^{17}O chemical shift trends.

Over the last decade, NMR chemical shifts have been used extensively as probes of electronic substituent effects.[2-4] Although ^{1}H chemical shifts show small but systematic changes with molecular substitution, the larger chemical shift range of ^{13}C and ^{19}F nuclei makes them more useful probes, as has been demonstrated recently in studies of substituent effects at ring[4-6] and side-chain sites[7-9] in

(1) (a) To whom correspondence should be addressed at the School of Pharmaceutical Chemistry, Victorian College of Pharmacy Ltd., Parkville, Victoria 3052, Australia. (b) Camille and Henry Dreyfus Teacher Scholar, 1976–1981. (c) La Trobe University.

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