

THE A-VALUES OF THE AMINO AND DIMETHYLAMINO GROUPS

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VALUES for the free energy change involved in moving an equatorial substituent on a cyclohexane chair into the axial position (A-values¹) have, in the past several years, become known for almost all the more common substituents.² The one important group for which this value remains essentially unknown is the amino group. Only approximate estimates are available; according to these the A-value of the amino group is equivalent to, or only slightly larger than, that of hydroxyl^{3,4}; dissociation measurements carried out in this Laboratory⁵ some time ago indicated, however, that the A-value of the amino group must be considerably larger than this.

We now report the A-values for the amino and dimethylamino groups, as well as their protonated forms, based on

¹ S. Winstein and N.J. Holness, J. Amer. Chem. Soc. 77, 5562 (1956).

² For a list of A-values see: E.L. Eliel: Stereochemistry of Carbon Compounds, McGraw-Hill, New York, 1962.

³ P.R. Jefferies and E.W. Della, Australian J. Chem. 14, 610 (1961).

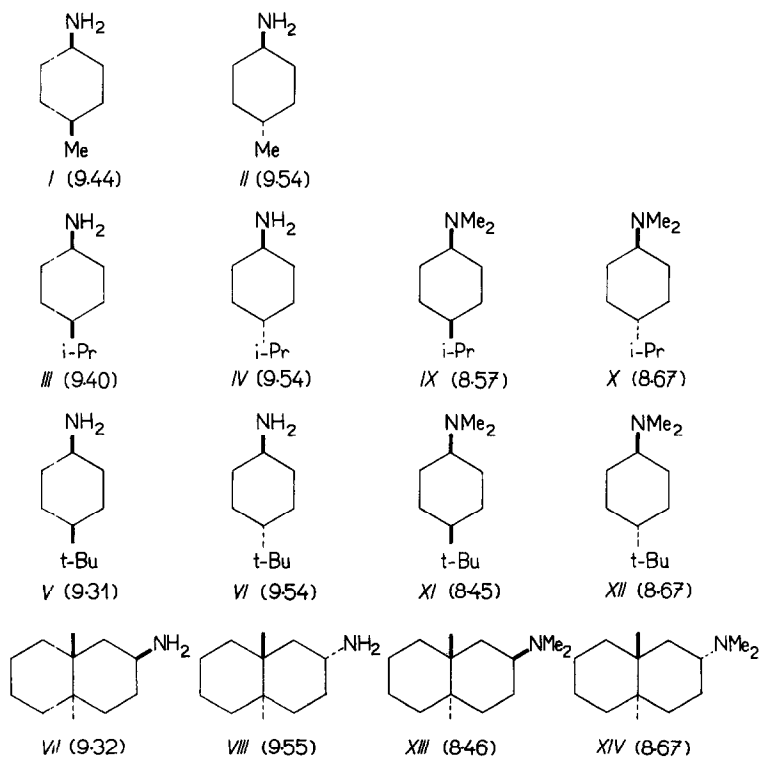
⁴ A. Streitwieser, Jr., and C.E. Coverdale, J. Amer. Chem. Soc. 81, 4275 (1959).

⁵ M. Tichý, J. Jonáš, and J. Sicher, Coll. Czech. Chem. Comm. 24, 3434 (1959).

accurate measurements of dissociation constants of the amines I - VIII and the dimethylamines IX - XIV (Table 1).

Table 1

The figures given in parentheses are values of pK'_a , determined on the hydrochlorides in "80%" methylcellosolve at 20°. The values are averages of 4 to 10 independent measurements for each compound. For the technique of measurement see ref. 6.

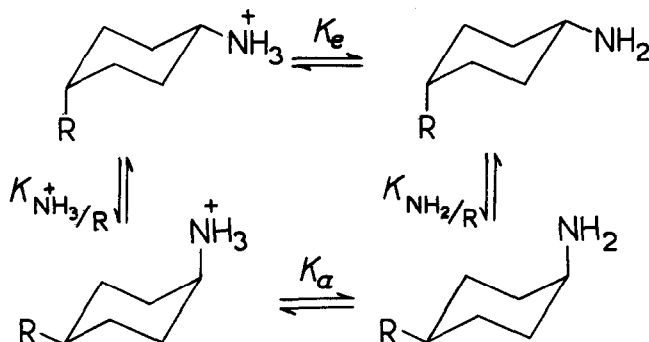


⁶ M. Svoboda, J. Jonáš, and J. Sichter, Coll. Czech. Chem. Comm. **23**, 1551 (1958).

The compounds III, IV, IX, X, XIII and XIV are new; their synthesis, carried out by standard methods, will be reported subsequently.

The procedure used was quite analogous to that which had been developed, independently by Stolow⁷ and ourselves⁵, for the determination of the A-value of the carboxyl group. Consider the system of equilibria for a "conformationally mobile" cis-4-alkylcyclohexylamine (Scheme 1). From this

Scheme 1



scheme we readily deduce the relationships

$$K_{\text{NH}_3^+/\text{R}} = \frac{K_e - K_R}{K_R - K_a} \quad (1) \quad \text{and} \quad K_{\text{NH}_2/\text{R}} = \frac{K_a}{K_e} K_{\text{NH}_3^+/\text{R}} \quad (2)$$

where K_R is the measured acid dissociation constant of the "conformationally mobile" cis-4-alkylcyclohexylamine. For K_e and K_a , the dissociation constants for an equatorial and axial

⁷ R.D. Stolow, J. Amer. Chem. Soc. **81**, 5806 (1959).

amine, the values of the experimentally determined dissociation constants of the "conformationally rigid" trans- and cis-4-t-butylcyclohexylamine (VI and V), respectively, were used; the fact that these are in very good agreement with the constants found, on the one hand, for II, IV and VIII and, on the other, for VII represents good evidence for the correctness of the values employed for K_e and K_a .

From the conformational equilibrium constants $K_{\text{NH}_3^+/\text{R}}$ and $K_{\text{NH}_2/\text{R}}$, as obtained from (1) and (2), we calculate the values of the corresponding free energy differences, $\Delta F_{\text{NH}_3^+/\text{R}}$ and $\Delta F_{\text{NH}_2/\text{R}}$. Assuming that $\Delta F_{\text{NH}_2/\text{R}} = \Delta F_{\text{NH}_2} - \Delta F_{\text{R}}$, we obtain from the definition of A-values¹, that $A_{\text{NH}_2} = \Delta F_{\text{NH}_2/\text{R}} + A_{\text{R}}$ (3).

A completely analogous procedure was used to determine the A-value of the dimethylamino group. cis-4-Isopropylcyclohexyldimethylamine (IX) served as the mobile species; the values of K_e and K_a were here obtained from the dissociation constants of XII and of XI, respectively.

Values of K_{R} for two "conformationally mobile" cis-4-alkylcyclohexylamines, cis-4-methyl and cis-4-isopropylcyclohexylamine (I and III) were available for the determination of the A-value of the amino group; cis-4-isopropylcyclohexyldimethylamine (IX) was used as the "conformationally mobile" cyclohexyldimethylamine. The A-value for methyl⁸ was taken as 1.7 kcal.mole⁻¹ and that for isopropyl⁹ as 2.1 kcal.mole⁻¹.

⁸ The value of 1.7 kcal.mole⁻¹ is used in preference to the more commonly employed² value of 1.8 kcal.mole⁻¹ (cf. footnote 4 in the accompanying letter).

⁹ N.L. Allinger, L.A. Freiberg, and S.-E. Hu, J. Amer. Chem. Soc. **84**, 2836 (1962).

Table 2 lists values of the free energy differences of the type $\Delta F_{\text{NH}_2/\text{R}}$ and the values of A_{NH_2} , $A_{\text{NH}_3^+}$, A_{NMe_2} and $A_{\text{NHMe}_2^+}$ derived from them using equation (3).

Table 2

(Values are given in kcal.mole⁻¹)¹⁰

$\Delta F_{\text{NH}_2/\text{Me}}$	=	0.0 ;	A_{NH_2}	=	1.7
$\Delta F_{\text{NH}_2/\text{iPr}}$	=	-0.4 ;	A_{NH_2}	=	1.7
$\Delta F_{\text{NH}_3^+/\text{Me}}$	=	0.3 ;	$A_{\text{NH}_3^+}$	=	2.0
$\Delta F_{\text{NH}_3^+/\text{iPr}}$	=	-0.1 ;	$A_{\text{NH}_3^+}$	=	2.0
$\Delta F_{\text{NMe}_2/\text{iPr}}$	=	0.0 ;	A_{NMe_2}	=	2.1
$\Delta F_{\text{NHMe}_2^+/\text{iPr}}$	=	0.3 ;	$A_{\text{NHMe}_2^+}$	=	2.4

The value of 1.7 kcal.mole⁻¹ may be seen to be in very good agreement with the value of 1.8 kcal.mole⁻¹ now established by a kinetic method by Eliel and coworkers (cf. accompanying letter¹¹).

With respect to the cyclohexane chair, the amino group is thus - in the aqueous solvent employed - sterically practically equivalent to methyl, and the dimethylamino

¹⁰ An analysis of the experimental pK_a results shows that the accuracy of the values of $F_{\text{NH}_2/\text{R}}$ derived from them is about ± 0.1 kcal.mole⁻¹; in view of the relatively large latitude^{2,12} in the choice of the values of A_{Me} and A_{iPr} this accuracy is regarded as sufficient.

¹¹ E.L. Eliel, E.W. Della, and T.H. Williams, Tetrahedron Letters, 13, 831 (1963).

¹² A.H. Lewin and S.W. Winstein, J. Amer. Chem. Soc. 84, 2464 (1962).

group to isopropyl. Protonation (and the attendant enhanced solvation) lead to an increase of the A-value of $0.3 \text{ kcal.mole}^{-1}$ for both the amino and dimethylamino group. The implications of these findings, which may also have some bearing on the interesting problem of the rotational conformation of the axial amino group,¹³ will be discussed in the full paper, to be published in Coll. Czech. Chem. Comm.

We are indebted to Dr W. Simon, Eidgenössische Technische Hochschule, Zürich, for running a parallel series of pK_a measurements on the amines I - XIV on his apparatus.

¹³ M. Tichý, F. Šipoš, and J. Sicher, Coll. Czech. Chem. Comm. 27, 2907 (1962).