

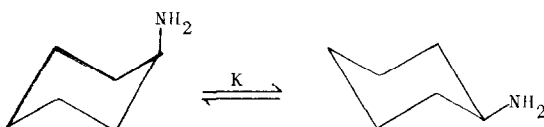
THE CONFORMATIONAL EQUILIBRIUM OF THE AMINO GROUP

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AMONG the numerous conformational equilibrium values reported in the literature<sup>1,2</sup> that of the amino group is conspicuously missing. Tichý, Jonáš and Sicher<sup>3</sup> some years ago determined  $pK_a$  data which indicate qualitatively that the  $-\Delta G$  value for the equilibrium



is comparable in magnitude with that for methyl (1.7 kcal./mole<sup>4</sup>) and these indications are now quantitatively supported as shown in the accompanying letter.<sup>5</sup>

In our laboratory, we were particularly interested in the  $-\Delta G$  value for the amino group because this group - unlike other groups

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<sup>1</sup> E. L. Eliel, Stereochemistry of Carbon Compounds, p. 236. Mc-Graw Hill, New York (1962).

<sup>2</sup> E. L. Eliel, J. Chem. Educ. 27, 126 (1960).

<sup>3</sup> M. Tichý, J. Jonáš and J. Sicher, Coll. Czech Chem. Comm. 24, 3434 (1959).

<sup>4</sup> A survey of literature data to be published elsewhere suggests that this value is better in the liquid phase than the commonly used value of 1.8 kcal./mole.

<sup>5</sup> J. Sicher, J. Jonáš and M. Tichý, Tetrahedron Letters 13, 825 (1963).

previously investigated<sup>1,2,6</sup> - contains a single free pair in its outer shell of electrons. We have determined the conformational equilibrium value for  $\text{NH}_2$  by two different methods previously described, *viz.* a kinetic method<sup>7,8</sup> and a nuclear magnetic resonance method.<sup>9,10</sup> The kinetic method involved a spectroscopic study of the rate of reaction of appropriate cyclohexylamines with 2,4-dinitrochlorobenzene to give 2,4-dinitrochloroanilines<sup>11</sup>. Since the specific rate for cyclohexylamine ( $k$ ) was too close to that for *trans*-4-*t*-butylcyclohexylamine ( $k_e$ ) to allow adequate calculation of the conformational equilibrium constant  $K$  from the equation<sup>8</sup>  $K = (k_a - k)/(k - k_e)$ , we calculated, instead, the corresponding equilibrium constant for *cis*-4-methylcyclohexylamine  $K^* = (k_a - k^*)/(k^* - k_e)$  where  $k^*$  is the rate constant for *cis*-4-methylcyclohexylamine and  $k_a$  that for *cis*-4-*t*-butylcyclohexylamine.  $\Delta G^\ddagger = -RT \ln K^*$  is then set equal to  $\Delta G_{\text{NH}_2}^\ddagger + 1.7$ , it being assumed that the free energies for shifting the amino and the methyl groups in the conformational equilibrium of *cis*-4-methylcyclohexylamine are additive.<sup>2</sup>

The substituted cyclohexylamines were prepared by published methods<sup>3</sup> and were converted to their N(2,4-dinitro)phenyl derivatives by treatment with 2,4-dinitrochlorobenzene in ethanol. The resulting

<sup>6</sup> See E. L. Eliel and B. Thill, Chemistry & Industry (London) in press (1963) for -SH.

<sup>7</sup> S. Winstein and N. J. Holness, J. Amer. Chem. Soc. 77, 5562 (1955).

<sup>8</sup> E. L. Eliel and C. Lukach, J. Amer. Chem. Soc. 79, 5986 (1957).

<sup>9</sup> E. L. Eliel, Chemistry & Industry (London), 568 (1959).

<sup>10</sup> E. L. Eliel and M. Gianni, Tetrahedron Letters, 97 (1962).

<sup>11</sup> e.g. J. F. Bunnett and J. J. Randall, Amer. Chem. Soc. 80, 6020 (1958).

2,4-dinitroanilines had the following physical properties and compositions:

Cyclohexyl Group	m.p.	Formula	Analysis			
			Calculated		Found %	
			C	H	C	H
4-H	155-155.5° <sup>12</sup>				-	-
cis-4-methyl	147-148°	C <sub>13</sub> H <sub>17</sub> N <sub>3</sub> O <sub>4</sub>	55.90	6.14	56.04	6.52
cis-4-t-butyl	142-142.5°	C <sub>16</sub> H <sub>23</sub> N <sub>3</sub> O <sub>4</sub>	59.79	7.21	59.97	7.53
trans-4-t-butyl	200-201°	C <sub>16</sub> H <sub>23</sub> N <sub>3</sub> O <sub>4</sub>	59.79	7.21	60.02	7.30

Kinetic data were obtained by the method of Bunnett and coworkers<sup>11</sup> for the reaction of the amines with 2,4-dinitrochlorobenzene in 98% ethanol at two temperatures and are shown in Table 1.

Table 1.

Amine	t°C	k <sub>2</sub> (1.mole <sup>-1</sup> sec. <sup>-1</sup> )	ΔH <sup>‡</sup> (kcal. mole <sup>-1</sup> )	ΔS <sup>‡</sup> cal.deg. <sup>-1</sup> mole <sup>-1</sup>
cyclohexyl	25.10	1.28x10 <sup>-4</sup>	13.63	-30.70
	56.60	1.14x10 <sup>-3</sup>		
cis-4-t-butyl- cyclohexyl	25.10	2.71x10 <sup>-4</sup>	13.09	-30.93
	56.60	2.23x10 <sup>-3</sup>		
cis-4-methyl- cyclohexyl	25.10	1.90x10 <sup>-4</sup>	13.35	-30.82
	56.60	1.61x10 <sup>-3</sup>		
trans-4-t-butyl- cyclohexyl	25.10	1.22x10 <sup>-4</sup>	13.65	-30.70
	56.60	1.10x10 <sup>-3</sup>		

All data were obtained in duplicate or triplicate, sometimes at two different concentrations of amine. From the data at either 25.10°C or 56.60°C one may calculate K<sup>‡</sup> = 1.2 whence ΔG<sup>‡</sup> = -0.1 kcal./mole and -ΔG<sub>NH<sub>2</sub></sub> = 1.7 - ΔG<sup>‡</sup> = 1.8 kcal./mole in 98% ethanol. This value is in excellent agreement with that of Sicher and coworkers.<sup>5</sup>

<sup>12</sup> J. J. Blanksma and G. F. Wilink, *Rec. trav. chim.* 66, 445 (1947).

It is noteworthy that the axial amine, cis-4-t-butylcyclohexylamine, reacts over twice as fast as its equatorial (trans) epimer. This is in contrast to the relative reactivity of axial and equatorial groups in almost any other reaction involving an exocyclic functional group and may reflect an unusual stabilization of the equatorial (vs. the axial) amino group through solvation.

Nuclear magnetic resonance studies<sup>9,10</sup> permitted an evaluation of  $-\Delta G_{\text{NH}_2}$  as a function of solvent. Here, again, the signal of the lone proton on the carbon bearing the amino group in cyclohexylamine was too close to that of the corresponding proton in trans-4-t-butylcyclohexylamine to allow evaluation of the conformational equilibrium constant by means of the equation<sup>10</sup>  $K = (\delta_a - \delta_e) / (\delta - \delta_e)$ ; therefore  $K^*$  for cis-4-methylcyclohexylamine was computed using the corresponding shift  $\delta^*$  in that compound. From  $K^*$ ,  $-\Delta G_{\text{NH}_2}$  was calculated as explained above. The NMR data and  $-\Delta G$  values derived from them are shown in Table 2. Shifts are in c./s. downfield from tetramethylsilane at 60 mc./s.

The following facts emerge regarding the conformational free preference of the amino group: (1) In solvents which are not hydrogen-donors,  $-\Delta G_{\text{NH}_2}$  is  $1.15 \pm 0.05$  kcal./mole. Polarity or hydrogen-acceptor properties of solvent seem to be unimportant. (2) In hydrogen-donor solvents,  $-\Delta G_{\text{NH}_2}$  is  $1.45 \pm 0.07$  kcal./mole. For reasons unknown, this value is somewhat lower than the kinetic value and the value<sup>5</sup> derived from pK measurements, but the discrepancy is not large. (3) In protonic solvents,  $-\Delta G_{\text{NH}_3^+}$  is  $1.70 \pm 0.16$  kcal./mole. The value seems to be lowest in the least solvating medium, trifluoroacetic acid, the value for adequately solvated  $\text{NH}_3^+$  lying between 1.7 and 1.8 kcal./mole. (This value, also, may be somewhat too low.)

Table 2

Solvent	$-\delta$	$-\delta_e$	$-\delta_a$	$-\delta'$	$-\Delta G_{\text{NH}_2}^{\text{G}}$ kcal./mole
Cyclohexane	150.1	148.3	188.9	177.7	1.13 <sup>a</sup>
Carbon tetrachloride <sup>b</sup>	153.2	148.5	187.0	176.7	1.10
Acetonitrile	150.6	145.0	183.8	172.6	1.16
Pyridine	157.0	146.4	189.6	176.8	1.19
Deuteriochloroform	158.8	153.6	189.5	176.2	1.38
95% Ethanol	153.4	150.4	185.4	172.0	1.42
90% <i>t</i> -Butyl Alcohol	155.0	151.6	187.3	172.4	1.50
<i>t</i> -Butyl Alcohol	154.4	149.5	185.6	170.6	1.52
Trifluoroacetic Acid <sup>c</sup>	201.0	197.6	230.9	216.4	1.55
Acetic Acid <sup>c</sup>	192.5	188.0	218.4	203.2	1.70
Trifluoroacetic $\bar{c}$ Acetic acid (1:8) <sup>c</sup>	192.5	189.5	220.8	205.3	1.70
Trifluoroacetic acid $\bar{c}$ <i>t</i> -Butyl Alcohol (1:8) <sup>c</sup>	181.3	181.5	210.3	193.9	1.86

<sup>a</sup> Independent of concentration from 2½% to 25%.

<sup>b</sup> Spectrum recorded before precipitation occurred.

<sup>c</sup> The much larger shifts in these solvents confirm that the amino group is protonated.

The trend of the three values is unmistakable and clearly shows that unbonded  $\text{NH}_2$  is smaller than hydrogen-bonded  $\text{NH}_2$  which, in turn, is smaller than solvated  $\text{NH}_3^+$ . The reasons for this in terms of the preferred rotational conformations of the axial  $\text{NH}_2$ -group and the space-demand of the free electron pair will be discussed fully elsewhere.

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