

STEREOCHEMICAL STUDIES. LXXV.\*  
CONFORMATIONAL EQUILIBRIA IN SUBSTITUTED  
2-AMINOCYCLOHEXANOLS AND  
2-HYDROXYCYCLOHEXANECARBOXYLIC ACIDS  
IN HYDROXYLIC MEDIUM

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Conformational equilibria in some substituted 2-aminocyclohexanols and in *trans*-2-hydroxy-*cis*-4-isopropylcyclohexanecarboxylic acid have been determined in 80% Methyl Cellosolve on the basis of their  $pK_a$  values. The  $\Delta G$  values found for the equilibria agree well with that calculated on the assumption of additivity of substituents and no vicinal effects have been found.


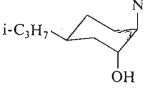
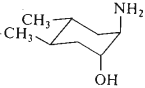

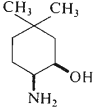
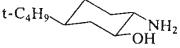



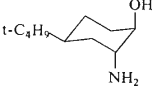
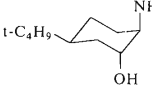
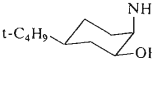
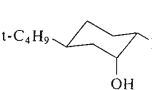
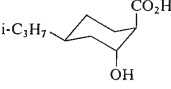

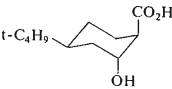
In the course of our stereochemical investigations we determined<sup>1</sup> conformational equilibria in a series of cyclohexane amino alcohols. For quantitative determination of concentration of certain conformers we used spectroscopic detection of intramolecular hydrogen bonding and therefore this approach required the use of non-polar aprotic solvents. Most of the biologically important systems, however, exist in aqueous solutions and therefore it was of interest to obtain information about the conformational equilibria in some our amino alcohols and hydroxy acids in an aqueous, or at least hydroxylic, medium. For the determination of conformational preferences of ionisable groups we have introduced<sup>2-4</sup> (simultaneously with Stolow<sup>5</sup>) a method based on measurement of apparent dissociation constants which gives information about conformational equilibria of ionised as well as non-ionised species. In the present communication we tried to apply this approach to the determination of conformational equilibria in compounds *I-V* and *XIV* in 80% ethylene glycol monomethyl ether (Methyl Cellosolve), which – as a solvent – should be similar to water.

#### EXPERIMENTAL

The determination of dissociation constants was carried out in 80% ethylene glycol monomethyl ether (Methyl Cellosolve) at 25°C using a glass electrode, exactly as described in our previous papers<sup>3,6</sup>. The compounds were homogeneous according to vapour phase chromatography

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TABLE I  
2-Amino Alcohols and 2-Hydroxy Acids and Their  $pK_a'$  Values

				
I	II <sup>a</sup>	III <sup>a</sup>	IV	V
8·87	8·75	8·64	9·07	8·87
				
VI	VII	VIII	IX	
8·86	8·86	8·87	8·85	
				
X	XI	XII	XIII	
8·42	8·42	8·65	9·10	
				
XIV	XV	XVI		
7·13	8·86	7·42		

<sup>a</sup> Compound depicted in one of the two possible conformations.

(the hydroxy acids were analysed as their esters). Hydrochlorides of the amino alcohols were purified by precipitation with ether from their ethanolic solution and are already described<sup>1,6</sup>, except for the hydrochloride of V. The acids XV and XVI are also already known<sup>6</sup>.

#### Hydrochloride of cis-2-Amino-5,5-dimethylcyclohexanol

This salt was prepared from the known<sup>7</sup> base; m.p. 248–250°C. For C<sub>8</sub>H<sub>18</sub>ClNO · 1/2 H<sub>2</sub>O (188·9) calculated: 51·03% C, 10·15% H, 7·44% N; found: 51·53% C, 10·01% H, 7·83% N.

*trans*-2-Ethynyl-*trans*-5-isopropylcyclohexanol

A mixture of *trans*-1,2-epoxy-4-isopropylcyclohexane<sup>1</sup> (1.0 g) and sodium acetylide (prepared from 3 g of sodium) in liquid ammonia (50 ml) was shaken in an autoclave for 36 hours at 20°C. The ammonia was distilled off, the residue taken between dilute hydrochloric acid and pentane, the organic layer dried, taken down and the residue distilled, b.p. 80°C/0.3 Torr. Redistillation at 115–117°C/15 Torr gave 0.7 g (59%) of a yellow liquid. For C<sub>11</sub>H<sub>18</sub>O (166.2) calculated: 79.46% C, 10.92% H; found: 79.35% C, 10.75% H.

*trans*-2-Hydroxy-*cis*-4-isopropylcyclohexanecarboxylic Acid (XIV)

A solution of the above ethynyl derivative (0.6 g) in ethyl acetate (20 ml) was treated at -70°C with a stream of ozonised oxygen. After the consumption of ozone had ceased, the reaction mixture was shaken with 10% aqueous sodium carbonate (10 ml) and 30% hydrogen peroxide (3 ml) for 1 hour. The solvent was distilled off, the residue made homogeneous by addition of ethanol and the mixture was boiled for 15 min. The ethanol was distilled off, the residue diluted with water and extracted with ether. The aqueous layer was acidified and the product taken up into ether, dried and the solvent distilled off, yielding 0.2 g of XIV, m.p. 128–129°C (ethyl acetate). According to the vapour phase chromatographic analysis of its ester, the acid is configurationally homogeneous. For C<sub>10</sub>H<sub>18</sub>O<sub>3</sub> (186.2) calculated: 64.49% C, 9.74% H; found 64.57% C, 9.64% H.

## RESULTS AND DISCUSSION

The measured  $pK'_a$  values of the amino alcohols and hydroxy acids are given in Table I. Some of them (for compounds VI, VII, X, XI, XV and XVI) have already been reported<sup>6</sup>: the recent redetermination shows a very good agreement with our previous data. The near-identity of the  $pK'_a$  values of various conformationally fixed compounds (VI–IX) supports, in accord with our previous results<sup>6</sup>, the implicit assumption of negligible polar effect of a remote alkyl substituent on the dissociation constant.

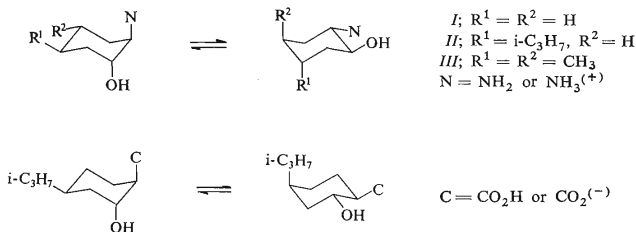
The conformational equilibrium constant was calculated using the previously derived<sup>2</sup> equations (1) and (2) for amines and analogous equations (3) and (4) for acids:

$$K^{NH_3^+} = \frac{K^e - K^{mob}}{K^{mob} - K^a} \quad (1), \quad K^{NH_2} = \frac{K^a}{K^e} K^{NH_3^+} \quad (2);$$

$$K^{CO_2H} = \frac{K^e - K^{mob}}{K^{mob} - K^a} \quad (3), \quad K^{CO_2^-} = \frac{K^a}{K^e} K^{CO_2H} \quad (4),$$

where  $K^{NH_3^+}$ ,  $K^{NH_2}$ ,  $K^{CO_2H}$  and  $K^{CO_2^-}$  are the conformational equilibrium constants for the species with ionised and non-ionised functional group denoted in the index, and  $K^e$ ,  $K^a$  and  $K^{mob}$  are the respective dissociation constants of the equatorial and axial standard and of the mobile compound.

From the energy differences between “diaxial”<sup>b</sup> and “diequatorial” conformers (Scheme 1) in the mobile compounds,  $\Delta G_{exp}$ , we may deduce the values of the gauche

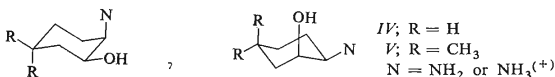


SCHEME 1

interactions between the equatorial hydroxyl and amino or carboxy group by comparison of  $\Delta G_{exp}$  with the values  $\Delta G_{calc}$ , computed under assumption of a strict additivity of conformational preferences of substituents. The difference  $\Delta G_{exp} - \Delta G_{calc}$  should then represent the interaction between equatorial hydroxyl and the corresponding substituent, as discussed in more detail in our previous papers<sup>1,2</sup>. Both  $\Delta G_{exp}$  and  $\Delta G_{calc}$  are given in Table II.

As expected, the  $pK_a$  value found for the parent *trans*-2-aminocyclohexanol (I) is identical with that of the conformationally fixed  $N^{\circ}O^e$  aminoalcohols VI–IX because (assuming additivity of conformational preferences) this compound should exist almost exclusively in the diequatorial conformation, both in the ionised as well as in the non-ionised form (the first being favoured<sup>4</sup> by  $\Delta G_{NH_3^+} + \Delta G_{OH} = 2.0 + 0.9 = 2.9$  kcal mol<sup>-1</sup> and the second by  $\Delta G_{NH_2} + \Delta G_{OH} = 1.7 + 0.9 = 2.6$  kcal mol<sup>-1</sup>). The introduction of isopropyl group (in II) or two methyl groups (in III) shifts the conformational equilibria into a more suitable region. As seen from the Table II, the calculated and found energy differences in these compounds are practically identical within the confidence limits of the measurements.

Let us consider now the conformational equilibrium in *cis*-2-aminocyclohexanol (IV). Here, on the basis of the additivity of conformational preferences, the  $N^{\circ}O^a$  conformer (Scheme 2) should be favoured by about 0.8 kcal mol<sup>-1</sup> ( $\Delta G_{NH_2} - \Delta G_{OH} = 1.7 - 0.9$  kcal mol<sup>-1</sup>) for the non-ionised and about 1.1 kcal mol<sup>-1</sup> ( $2.0 - 0.9$  kcal mol<sup>-1</sup>) for the ionised species. Here, too, the  $pK_a$  value in this com-



SCHEME 2

TABLE II

Free Energy Differences Found ( $\Delta G_{\text{exp}}$ ) and Calculated ( $\Delta G_{\text{calc}}$ ) for the Conformational Equilibria in Compounds *II*, *III*, *V* and *XIV*

No	System (Scheme 1 and 2)		$\Delta G_{\text{exp}}$ kcal mol <sup>-1a</sup>	$\Delta G_{\text{calc}}$ kcal mol <sup>-1b</sup>
<i>II</i>	N <sup>a</sup> O <sup>a</sup> ⇌ N <sup>c</sup> O <sup>c</sup>	NH <sub>2</sub>	-0.36 ± 0.2	-0.5
		NH <sub>3</sub> <sup>+</sup>	-0.96 ± 0.2	-0.8
<i>III</i>	N <sup>a</sup> O <sup>a</sup> ⇌ N <sup>c</sup> O <sup>c</sup>	NH <sub>2</sub>	+0.30 ± 0.2	0.0
		NH <sub>3</sub> <sup>+</sup>	-0.30 ± 0.1	-0.3
<i>V</i>	N <sup>a</sup> O <sup>c</sup> ⇌ N <sup>c</sup> O <sup>a</sup>	NH <sub>2</sub>	+0.34 ± 0.2	+0.3
		NH <sub>3</sub> <sup>+</sup>	-0.27 ± 0.2	0.0
<i>XIV</i>	C <sup>a</sup> O <sup>a</sup> ⇌ C <sup>c</sup> O <sup>c</sup>	CO <sub>2</sub> H	+0.34 ± 0.1	+0.2 <sup>c</sup>
		CO <sub>2</sub> <sup>-</sup>	-0.42 ± 0.1	-0.4 <sup>c</sup>

<sup>a</sup> Measured at 25°C in 80% Methyl Cellosolve; the conformational equilibrium constants in *II* and *III* were calculated using the values  $pK_a = 8.86$  for the diequatorial standard and  $pK_a = 8.42$  for the diaxial standard. <sup>b</sup> Calculated under assumption of complete additivity of conformational preferences of substituents; the values used are:  $\Delta G_{\text{OH}} = 0.9$  kcal mol<sup>-1</sup> (ref.<sup>8</sup>),  $\Delta G_{\text{NH}_2} = -1.7$  kcal mol<sup>-1</sup> (ref.<sup>4</sup>),  $\Delta G_{\text{NH}_3^+} = 2.0$  kcal mol<sup>-1</sup> (ref.<sup>4</sup>),  $\Delta G_{\text{CH}_3} = 1.7$  kcal mol<sup>-1</sup> (ref.<sup>8</sup>),  $\Delta G_{i-C_3H_7} = 2.1$  kcal mol<sup>-1</sup> (ref.<sup>8</sup>),  $\text{CH}_3/\text{OH}$  *syn*-axial interaction taken as 2.4 kcal mol<sup>-1</sup> (ref.<sup>9</sup>) and  $\text{CH}_3/\text{CH}_3$  vicinal interaction as 0.9 kcal mol<sup>-1</sup> (ref.<sup>10-13</sup>). <sup>c</sup> Calculated from the known energy difference<sup>3</sup> in *cis*-4-isopropylcyclohexanecarboxylic acid,  $\Delta G = 1.11$  kcal mol<sup>-1</sup> (CO<sub>2</sub>H<sup>a</sup> conformer favoured), and its anion,  $\Delta G = -0.48$  kcal mol<sup>-1</sup> (CO<sub>2</sub><sup>-</sup> — equatorial form predominating).

pound is shifted too closely to that of the N<sup>c</sup>O<sup>a</sup> standard making thus an exact evaluation impossible. We can very crudely estimate the preference of the N<sup>c</sup>O<sup>a</sup> conformer to be about 1.5 kcal mol<sup>-1</sup> for the ionised and about 1.0 kcal mol<sup>-1</sup> for the free aminoalcohol.

More reliable results were obtained from *cis*-5,5-dimethyl-2-aminocyclohexanol (*V*) where the N<sup>c</sup>O<sup>a</sup> conformation is destabilised by the CH<sub>3</sub>/OH *syn*-axial interaction and the energy differences between conformers are only several tenths of kcal mol<sup>-1</sup> (Table II). These energy differences are again in good accord with that calculated under assumption of additivity of conformational preferences (-0.3 kcal mol<sup>-1</sup> compared with 0.0 kcal mol<sup>-1</sup> for the ionised and +0.3 kcal mol<sup>-1</sup> compared with +0.3 kcal mol<sup>-1</sup> for the non-ionised aminoalcohol. The hydroxy acid *XIV* does not show any difference between  $\Delta G_{\text{calc}}$  and  $\Delta G_{\text{exp}}$ .

From these results we may conclude that in a hydroxylic solvent, such as 80% Methyl Cellosolve, the vicinal hydroxyl and amino or carboxy groups exhibit no appreciable additional effect (attraction or repulsion). This behaviour is in contrast to the relatively strong attractive forces observed in aprotic non-polar solvents and is undoubtedly connected with interactions of these groups with the hydroxylic solvent which offset the relatively weak intramolecular interactions between the groups. The results found for the *trans*-amino alcohols *II* and *III* and the hydroxy acid *XIV* indicate that the supposed intramolecular (presumably solvent-mediated) hydrogen bonds<sup>6,14,15</sup> which would be expected to stabilize the N<sup>o</sup>C<sup>o</sup> and C<sup>o</sup>O<sup>o</sup> conformations and thus cause the deviation from additivity, do not play any important role in the energetics of the molecules of the studied compounds.

*The autor is indebted to Mrs M. Snopková for carrying out the pK<sub>a</sub> measurements.*

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