# Experimental Studies of the Anomeric Effect. Part VI.<sup>1</sup> Ring Inversion Equilibria in Cyclohexane, Tetrahydropyran and Piperidine Rings Substituted by a Carbomethoxy or a Cyano Group.

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Abstract: The ring inversion equilibrium in carbomethoxycyclohexane is compared with those in 2-carbomethoxytetrahydropyran and 2-carbomethoxypiperidine through a variable temperature nmr study of the positions of equilibria. The derived  $\Delta H^{o}_{a\to e}$  values (kcal mol<sup>-1</sup>) of -1.24 (cyclohexane), -1.69 (tetrahydropyran) and -0.54 (piperidine) can be rationalised in terms of competition between steric effects and endo-anomeric effects of the ring heteroatom. Variable temperature studies have also given  $\Delta H^{o}_{a\to e}$  values (kcal mol<sup>-1</sup>) for ring inversions in cyanocyclohexane, 2-cyanotetrahydropyran and 2-cyanopiperidine as -0.18, +0.36 and +2.22. Steric effects are small for CN, and the trend in  $\Delta H^{o}$  values is consistent with the expected increase in stabilising endo-anomeric effect along the series C, O, N.

In the ring inversion equilibrium  $(1 \neq 2)$  for a tetrahydropyran substituted at 2 by an electronegative group XR, both conformations are stabilised by the exo-anomeric effect illustrated, in which an exocyclic lone pair orbital overlaps with the antibonding orbital of an anticoplanar carbon-heteroatom bond.<sup>2,3</sup> The concept has been supported<sup>3</sup> by values of bond lengths from crystallographic studies, and by values of coupling constants from <sup>1</sup>H and <sup>13</sup>C nmr spectra of solutions.<sup>4</sup>



The theoretically analogous endo-anomeric effect, <sup>3</sup> which stabilises only the axial conformation, as in (3), has been supported<sup>3</sup> largely by values of bond lengths, although Pinto and Wolfe<sup>5</sup> provided evidence from a comparison of equilibria in water of glucose ( $5 \neq 6$ ) and the nitrogen analogue nojirimycin ( $7 \neq 8$ ). <sup>1</sup>H nmr spectroscopy gave the proportions of (7) in ( $7 \neq 8$ ) as 63%, a marked increase over the 36% of (5) present in ( $5 \neq 6$ ), and although the figures do not represent  $\Delta H^{\circ}$  values, it seems unlikely that entropy factors would disturb the situation substantially.



The increase in stability of the axial conformation probably reflects an increase in endo-anomeric effect caused by replacement of ring oxygen by the more powerful electron-donating nitrogen. The purpose of the present study was to submit the endo-anomeric effect to further scrutiny by a comparison of the thermodynamic parameters for the equilibration of 2-substituted piperidines and 2-substituted tetrahydropyrans with those of the corresponding cyclohexanes. The substituents  $CO_2Me$  and CN were deliberately chosen because exo-anomeric effects are expected to be negligible. However, in view of the large amount of data available for the equilibrium in 2-methoxytetrahydropyran, it was logical to examine first the equilibrium in 2-methoxypiperidine. However, the instability of the piperidine precluded the proposed study. Although the amine was released at 195K by addition of solid Na<sub>2</sub>CO<sub>3</sub> to a suspension of the amine hydrochloride<sup>6</sup> in CFCl<sub>3</sub>/CDCl<sub>3</sub>, a carbon-13 spectrum of the resulting solution at 220K showed that little or no 2-methoxypiperidine was present. The likely product of decomposition was a mixture of  $\alpha$ - and  $\beta$ -tripiperidines produced from the amine *via* self condensation of  $\Delta'$ -piperideine.<sup>7</sup>

Attention was then directed to rings with substituents  $CO_2Me$  and CN. The  $\Delta H^o$  and  $\Delta S^o$  values for ring inversion in cyanocyclohexane have already been determined by Höfner, Lesko and Binsch.<sup>8</sup> The required carbomethoxycyclohexane was a commercial sample and the remaining compounds were synthesised by standard techniques (see Experimental).



Jensen, Bush and Beck<sup>9</sup> studied the conformational equilibrium in carbomethoxycyclohexane (9  $\rightleftharpoons$  10) in CS<sub>2</sub> by <sup>1</sup>H nmr spectroscopy at a single temperature (195K). The equilibrium constant K (= 10/9) of 29±5 gave a  $\Delta G^{\circ}_{a\rightarrow e}$  value of -1.31kcal mol<sup>-1</sup>, whilst Tichy *et al.* determined a  $\Delta G^{\circ}_{a\rightarrow e}$  value of -1.28 kcal mol<sup>-1</sup> at 363K from the equilibration of *cis*-4-t-butyl-1-carbomethoxycyclohexane in methanol.<sup>10</sup>

We analysed the carbon-13 nmr spectra of  $(9 \neq 10)$  (see Table 1) in ether/toluene-d<sub>8</sub> (75/25, v/v) at 165K, 170K and 175K, with integration, and in the range 215 to 235K by application of a line-broadening technique.<sup>11</sup> The latter method gave equilibrium constants at 220K and 228K. Values of K (= 10/9) varied from 34.1 at 165K to 11.2 at 228K.

Table 1. Carbon-13 chemical shifts (δ/ppm from Me<sub>4</sub>Si) at 62.9MHz for
(9), (10) and (9 ≠ 10) in ether/toluene-d<sub>8</sub> (3/1; v/v)

Species	T/K	1-C	2,6-C	3,5-C	4-C	CH <sub>3</sub> O	C=0
(9 ≓ 10)	260 <sup>a</sup>	43.28	29.57	25.99	26.36	51.16	175.42
(9)	165	39.16	27.71	23.48	26.53	51.62	174.71
(10)	165	42.95	29.44	25.88	26.06	51.62	175.83
(9)	170	39.18	27.72	23.47	26.53	51.59	174.70
(10)	170	42.98	29.45	25.90	26.07	51.59	175.80
(9)	175	39.19	27.73	23.46	26.53	51.57	174.69
(10)	175	43.01	29.45	25.91	26.06	51.57	175.80

<sup>a</sup> assignments follow the work of Pehk and Lippmaa<sup>12</sup>

The derived thermodynamic parameters are listed in Table 4, and show a substantial preference for the equatorial conformation in enthalpy terms ( $\Delta H^{o}_{a\rightarrow e} = -1.24$ kcal mol<sup>-1</sup>), although the axial conformation is slightly favoured by entropy ( $\Delta S^{o}_{a\rightarrow e} = -0.63$  cal K<sup>-1</sup> mol<sup>-1</sup>). The calculated  $\Delta G^{o}_{a\rightarrow e}$  value at 195K is -1.18kcal mol<sup>-1</sup> (*cf.* experimental value of -1.31 in CS<sub>2</sub><sup>10</sup>).



 $\Delta G_{a \to e}^{o}$  values for the equilibrium in 2-carbomethoxytetrahydropyran (11=12) have been determined by at least two groups. Anderson and Sepp<sup>13</sup> equilibrated 2-carbomethoxy-6-t-butyltetrahydropyran in methanol at 298K and obtained a  $\Delta G_{a \to e}^{o}$  value of -1.62kcal mol<sup>-1</sup>. Eliel *et al.*, <sup>14</sup> after measuring the equilibrium constant in 2-carbomethoxy-5-methyltetrahydropyran at 163K in CD<sub>2</sub>Cl<sub>2</sub>, used the previously recorded  $\Delta G^{o}$  value of methyl in 3-methyltetrahydropyran to deduce that  $\Delta G_{a \to e}^{o}$  (2-CO<sub>2</sub>Me) was -1.38kcal mol<sup>-1</sup>. In the present investigation, we recorded the carbon-13 spectra of (11=12) (see Table 2) in ether/toluene-d<sub>8</sub> (3/1, v/v) at 150K and 160K, with integration, and in the range 170-202K by application of the line-broadening method.<sup>11</sup> The latter gave equilibrium constants (K) at 193K, 195K and 196K. Values of K (=12/11) varied from 25.0 at 150K to 8.56 at 196K. The derived thermodynamic parameters are listed in Table 4, where the large errors in  $\Delta S^{o}$  for the cyclohexane and tetrahydropyran compounds are in part a reflection of the required extrapolation of steep plots of lnK against T<sup>-1</sup>. For 2-carbomethoxytetrahydropyran, the value of -1.69kcal mol<sup>-1</sup> for  $\Delta H_{a\to e}^{o}$  indicates a particularly strong preference shown by the carbomethoxy group for the equatorial orientation at C-2 in tetrahydropyran.

Table 2. Carbon-13 chemical shifts ( $\delta$ /ppm from Me<sub>4</sub>Si) at 62.90MHz for (11), (12) and (11 = 12) in ether/toluene-d<sub>8</sub> (3/1; v/v)

Species	T/K	2-C	3-C	4-C	5-C	6-C	CH <sub>3</sub> O	C=O
(11≓12)	296 <sup>a</sup>	76.46	29.22	23.21	26.20	67.79	51.38	171.57
(11)	150	72.47	27.55	b	25.65	63.94	52.10	172.65
(12)	150	75.94	29.44	23.50	25.65	68.05	52.10	172.01
(11)	160	77.47	29.53	b	25.64	63.93	52.08	172.64
(12)	160	75.97	29.43	23.49	25.64	68.05	52.08	171.98

<sup>a</sup> assignments by comparisons with shifts reported for CDCl<sub>3</sub> as solvent<sup>15</sup>

<sup>b</sup> hidden by  $CD_3$  (toluene-d<sub>8</sub>)

The equilibrium  $(13 \neq 14)$  in 2-carbomethoxypiperidine has not hitherto been examined. We have now recorded the carbon-13 spectra (Table 3) of  $(13 \neq 14)$  in ether/toluene-d<sub>8</sub> (3/1, v/v) at 165K, 170K and 175K with integration, and in the range 215-227K by the line-broadening method. The latter gave equilibrium

constants (K) at 221K and 222K. Values of K (=14/13) varied from 7.4 at 165K to 4.5 at 221K. The derived thermodynamic parameters are listed in Table 4. The value of -0.54kcal mol<sup>-1</sup> for  $\Delta H^0_{a\to c}$  shows that 2-carbomethoxypiperidine (13  $\rightleftharpoons$  14) shows a reduced preference, in the enthalpy terms, for the equatorial conformation (14), in comparison with carbomethoxycyclohexane (9  $\rightleftharpoons$  10).

Table 3.	Carbon-13 chemical shifts <sup>a</sup> ( $\delta$ /ppm from Me <sub>4</sub> Si) at 62.9MHz for
	(13), (14) and (13 $\rightleftharpoons$ 14) in ether/ toluene-d <sub>g</sub> (3/1; v/v)

Species	T/K	2-C	3-C	4-C	5-C	6-C	CH <sub>3</sub> O	C=O
(13 <b>≓1</b> 4)	294	59.06	29.66	24.80	26.78	46.27	51.26	173.62
(13)	165	55.80	27.24	22.65	26.20	42.81	51.81	175.08
(14)	165	58.91	29.73	25.25	26.20	46.57	51.81	173.78
(13)	170	55.87	27.26	22.68	26.28	42.90	51.77	175.01
(14)	170	58.95	29.79	25.27	26.28	46.63	51.77	173.74
(13)	175	55.86	27.24	22.66	26.26	42.89	51.72	175.02
(14)	175	58.96	29.78	25.26	26.26	46.61	51.77	173.70

<sup>a</sup> assignments by comparisons with shifts calculated from observed shifts in piperidine,<sup>19</sup> together with substituent shift parameters<sup>15</sup> for the CO<sub>2</sub>Me group in tetrahydropyrans.

Table 4. Thermodynamic parameters<sup>a</sup> ( $\Delta$ H<sup>o</sup> and  $\Delta$ G<sup>o</sup> in kcal mol<sup>-1</sup>;  $\Delta$ S<sup>o</sup> in cal K<sup>-1</sup> mol<sup>-1</sup>) for equilibration of carbomethoxy derivatives of cyclohexane, tetrahydropyran (at 2-C) and piperiding (at 2-C) in ether/tolyane d. (2/1) w(x)

	and piperionic (at 2-C) in emeritoric-log (3/1; $v/v$ ).					
Ring:	cyclohexane	tetrahydropyran	piperidine			
Parameter						
∆H <sup>°</sup> <sub>a→e</sub>	-1.24	-1.69	-0.54			
± error	0.15	0.25	0.07			
∆S° <sub>a→e</sub>	-0.63	-4.50	0.72			
± error	0.80	1.45	0.37			

<sup>a</sup> from computer plots of lnK against  $T^{-1}$ .

The experimentally derived  $\Delta H^{o}_{a \to e}$  values in Table 4 may be rationalised by reference to (a) the steric effect of the relatively bulky CO<sub>2</sub>Me substituent, and (b) the endo-anomeric effects of the ring hetero-atoms. The replacement of a ring carbon of carbomethoxycyclohexane by a hetero-atom X(X=O,N) is likely to lead to a puckering of the C-X-C fragment of the chair conformation, as the C-X bond is appreciably shorter than the C-C bond (~0.154nm). The extent of ring puckering will be greater for a tetrahydropyran (C-O bond ~0.143nm) than for a piperidine (C-N bond ~0.147nm). Evidence supporting these predictions comes from the increasing disinclination of a methyl group to adopt the axial orientation along the series methylcylohexane<sup>16</sup> ( $\Delta G^{o}_{a \to e} = -1.74$ kcal mol<sup>-1</sup>), 2-methylpiperidine ( $\Delta G^{o}_{a \to e} = -2.47$ kcal mol<sup>-1</sup>) and 2-methyltetrahydropyran ( $\Delta G^{o}_{a \to e} = -2.47$ kcal mol<sup>-1</sup>)

-2.75kcal mol<sup>-1</sup>). The 2-methylpiperidine value is obtained, albeit by making assumptions of additivity and of negligible conformational entropy differences, from the equilibria in 4-methylpiperidine<sup>17</sup> ( $\Delta G^o_{a\to c} = -1.93$ kcal mol<sup>-1</sup>) and in *trans*-2,4-dimethylpiperidine<sup>18</sup> ( $\Delta G^o$ , 2a 4e  $\rightarrow$  2e 4a, -0.54kcal mol<sup>-1</sup>). Similar assumptions are involved in the calculation of the 2-methyltetrahydropyran value from equilibria in 4-methyltetrahydropyran<sup>3</sup> ( $\Delta G^o_{a\to c} = -1.86$ kcal mol<sup>-1</sup>) and in *trans*-2,4-dimethyltetrahydropyran<sup>14</sup> ( $\Delta G^o$ , 2a 4e  $\rightarrow$  2e4a, -0.89kcal mol<sup>-1</sup>).

The predicted ring puckering will inevitably bring an axial substituent at position 2 closer to axial hydrogen atoms at positions 4 and 6. The resulting destabilisation of the axial conformations (11) and (13) will lead to a relatively increased stability for the corresponding equatorial conformations (12) and (14), compared to the situation for the corresponding cyclohexane conformations. On the other hand, replacement of a ring carbon by the more electron donating oxygen and nitrogen should enhance the endo-anomeric effect, thus increasing the stability of the axial conformations (11) and (13). The  $\Delta H^{\circ}$  values of Table 4 indicate quite clearly that steric effects have outweighed endo-anomeric effects in the case of 2-carbomethoxytetrahydropyran (11 $\neq$ 12), leading to an increased preference in  $\Delta H^{\circ}$  terms, for the *equatorial* conformation (12), when compared to the cyclohexane case. This result is opposite to that deduced for the carboethoxy group by Tschierske, Köhler, Zaschke and Kleinpter,<sup>20</sup> who, however, base their conclusions on  $\Delta G^{\circ}$  values at a single temperature. Evidently the case of 2-carbomethoxypiperidine (13 $\neq$ 14) is different. Here the more powerful electron donation from ring nitrogen ensures a very strong endo-anomeric effect, which outweighs steric factors and causes an increased preference, in  $\Delta H^{\circ}$  terms, for the *axial* conformation (13).



The conformational equilibrium  $(15 \neq 16)$  for cyanocyclohexane has been studied on several occasions by direct analysis, <sup>8,9,21</sup> by analysis of the complex with a lanthanide shift reagent,<sup>22</sup> and by base-catalysed equilibrations of *cis*- and *trans*-4-t-butyl-1-cyanocyclohexane.<sup>10,23,24</sup> Single temperature determinations of equilibrium constants have given  $\Delta G^{o}_{a\rightarrow e}$  values of  $-0.25^{24}$  (339K; solvent Bu<sup>t</sup>OH),  $-0.19^{10}$  (349K; Bu<sup>t</sup>OH),  $-0.24^{9}$  (194K; CS<sub>2</sub>),  $-0.24^{21}$  (178K; CFCl<sub>3</sub>; <sup>1</sup>H nmr), and  $-0.21^{21}$  (178K; CFCl<sub>3</sub>; <sup>13</sup>C nmr). A variable temperature study by Rickborn and Jensen<sup>23</sup> gave, for Bu<sup>t</sup>OH as solvent,  $\Delta H^{o}_{a\rightarrow e}$  as 0.04kcal mol<sup>-1</sup> and  $\Delta S^{o}_{a\rightarrow e}$ as 0.66cal K<sup>-1</sup> mol<sup>-1</sup>, whilst the variable temperature study by Höfner, Lesko and Binsch<sup>8</sup> gave for CFCl<sub>3</sub> as solvent,  $\Delta H^{o}_{a\rightarrow e}$  as -0.18 kcal mol<sup>-1</sup> and  $\Delta S^{o}$  as zero. The weak conformational preference shown by CN reflects its linear, non-bulky character.



We have now recorded the carbon-13 spectra (Table 5) of 2-cyanotetrahydropyran ( $17 \rightleftharpoons 18$ ) in CFCl<sub>3</sub>/CDCl<sub>3</sub> (85/15, v/v) at 155K, 165K, 172K and 180K with integration, and in the range 190 to 220K by the line-broadening technique (Experimental). The axial conformation (17) is preferred, with values of the equilibrium constant K (=18/17) varying from 0.203 at 155K to 0.252 at 200K.

Table 5. Carbon-13 chemical shifts<sup>a</sup> (δ/ppm from Me<sub>4</sub>Si) at 62.9MHz for (17), (18) and (17 ≠ 18) in CFCl<sub>2</sub>/CDCl<sub>3</sub> (85/15; v/v).

Species	T/K	2-C	3-C	4-C	5-C	6-C	CN
(17 <b>≓1</b> 8)	275	65.19	29.51	20.47	25.38	66.08	117.69
(17)	165	64.60	28.39	19.27	24.96	65.01	117.91
(18)	165	65.77	29.92	22.24	24.96	68.90	118.47

a assignments made by comparisons with shifts calculated from observed shifts in tetrahydropyran<sup>15</sup> and substituent shift parameters for the CN groups in cyclohexane.<sup>21</sup>

The thermodynamic parameters for the equilibrium  $(17 \neq 18)$  are shown in Table 7 and reveal a situation quite different from that in cyanocyclohexane  $(15 \neq 16)$ . In 2-cyanotetrahydropyran it is the *axial* conformation (17) which has the lower enthalpy due in part to the stabilising endo-anomeric effect. It is also expected that the relatively lower dipole moment of (17), as against (18), will ensure its lower enthalpy when a non-polar solvent such as CFCl<sub>3</sub>/CDCl<sub>3</sub> is employed ( $\epsilon$  for CFCl<sub>3</sub> 2.28 at 29°C;  $\epsilon$  for CDCl<sub>3</sub> 4.75 at 25°C).

The conformational equilibrium in 2-cyanopiperidine  $(19 \neq 20)$ , dissolved in CFCl<sub>3</sub>/CDCl<sub>3</sub> (85/15, v/v), was investigated by low temperature carbon-13 nmr spectroscopy. Spectra of  $(19 \neq 20)$  (see Table 6) were recorded at 190K and 195K, with integration, and in the range 222-232K by the line-broadening technique (Experimental). The *axial* conformation (19) was very strongly preferred, with the equilibrium constant K (=20/19) varying from 0.057 at 190K to 0.116 at 227K.

Species	T/K	2-C	3-C	4-C	5-C	6-C	CN
(19≓20)	270	46.87	29.28	21.89	25.61	43.54	119.97
(19)	190	46.24	28.18	21.06	25.05	42.58	120.15
(20)	190	46.97	30.17	23.81	25.05	42.58	120.73
(19)	195	46.27	28.21	21.08	25.06	42.59	120.13
(20)	195	47.01	30.20	23.81	25.06	42.59	120.72

Table 6.	Carbon-13 chemical shifts <sup>a</sup> ( $\delta$ /ppm from Me <sub>4</sub> Si) at 62.9MHz for
	(19), (20) and (19 $\Rightarrow$ 20) in CFCl <sub>3</sub> /CDCl <sub>3</sub> (85/15; v/v).

<sup>a</sup> assignments relied on observed chemical shifts for piperidine, <sup>19</sup> together with empirical substituent shift parameters for the CN group in cyclohexanes.<sup>21</sup>

Table 7. Thermodynamic parameters<sup>a</sup> ( $\Delta H^{\circ}$  and  $\Delta G^{\circ}$  in kcal mol<sup>-1</sup>;  $\Delta S^{\circ}$  in cal K<sup>-1</sup> mol<sup>-1</sup>) for equilibration of cyano derivatives of cyclohexane, tetrahydropyran (at 2-C) and piperidine (at 2-C)

Ring:	cyclohexane <sup>b</sup>	tetrahydropyran <sup>c</sup>	piperidine <sup>c</sup>
Parameter			
∆H <sup>°</sup> a→e	-0.182 <sup>d</sup>	0.36	2.22
± error	0.007	0.07	0.56
0			
∆S <sub>a→e</sub>	0 <sup>a</sup>	-0.84	5.65
± error	0.04	0.38	2.67

<sup>a</sup> from computer plots of lnK against T<sup>-1</sup>.

- <sup>b</sup> solvent CFCl<sub>3</sub>
- <sup>c</sup> solvent CFCl<sub>3</sub>/CDCl<sub>3</sub> (85/15; v/v)
- <sup>d</sup> reference 8

The thermodynamic parameters for  $(19 \neq 20)$  are given in Table 7 and show a very strong preference in enthalpy terms for the axial conformation (19). As with the corresponding tetrahydropyran (17), conformation (19) is preferentially stabilised over its equatorial isomer by both endo-anomeric and polar effects, although the latter are less effective in the piperidine case.

In trying to rationalise the trends in conformational enthalpy differences  $(\Delta H_{a\rightarrow e}^{o})$  for the cyanoderivatives of cyclohexane, piperidine and tetrahydropyran, steric effects may be ignored: they are likely to be small and in any case should favour the equatorial conformation for the puckered hetero-rings. The unmistakable trend of increasing stability of axial conformations along the series cyanocyclohexane, 2cyanotetrahydropyran and 2-cyanopiperidine is almost certainly due to the gradually increasing endo-anomeric effects which accompany the increase in electron donation when ring carbon is changed to oxygen and then nitrogen. This conclusion is not undermined by the fact that the equilibrium in  $(15 \rightleftharpoons 16)$  was examined in neat

#### Experimental

General - see Part 1.3

2-Carbomethoxytetrahydropyran - Sodium 3,4-dihydro-2H-pyran-2-carboxylate (2.0g) was hydrogenated in methanol (100cm<sup>3</sup>) over 10% palladised charcoal (0.2g) during 24h, when  $325cm^3 H_2$  (theory  $300cm^3$ ) were absorbed. The catalyst was removed by filtration and the filtrate was evaporated to give sodium tetrahydropyran 2-carboxylate (1.99g, 98%). The <sup>1</sup>H nmr spectrum (250MHz, D<sub>2</sub>O, reference DOH at 84.80) showed signals at 84.29 (d,  ${}^{3}J_{2,3}$  11.05 Hz; 2-H), 3.75 (m; 6-H), 3.39-3.49 (m; 6-H), 1.77-1.89 (m; 3-H), 1.37-1.55 (m 4,5-H). The above compound (0.76g), dissolved in HMPA (25cm<sup>3</sup>) was treated with iodomethane (1.42g) and the suspension was stirred overnight at room temperature.<sup>25</sup> The resulting orange solution was treated with hydrochloric acid (50cm<sup>3</sup>, 1M) and extracted with ether (4 x 25cm<sup>3</sup>). The combined ether extracts were washed with saturated brine (10x20cm<sup>3</sup>), dried (MgSO<sub>4</sub>), filtered and evaporated to remove ether. Distillation of the residue gave 2-carbomethoxytetrahydropyran (0.56g, 78%), b.p. 110° at 15mmHg (lit.<sup>15</sup> 118° at 25mmHg). The <sup>1</sup>H nmr spectrum (250MHz, CDCl<sub>3</sub>) included signals at 83.99-4.12 (m; 2,6-H), 3.76 (s; OMe), 3.46-3.56 (m; 6-H), 1.86-2.00 (m; 3-H) and 1.52-1.70 (m; 4,5-H).

2-Carbomethoxypiperidine - Thionyl chloride (3.45g) was added dropwise, with cooling, to anhydrous methanol (50cm<sup>3</sup>). The mixture was stirred at 20° for 5 min, after which piperidine-2-carboxylic acid (2.50g) was added. The solution was stirred at 20° for 16hr. and then evaporated at 20°/10mm to remove methanol. The residual solid was dissolved in water (2cm<sup>3</sup>) and the solution was basified with an excess of saturated aqueous sodium hydrogen carbonate. The mixture was extracted with ether (5x20cm<sup>3</sup>) and the combined ether extracts were dried (MgSO<sub>4</sub>), filtered and evaporated. Distillation of the residual oil gave 2-carbomethoxypiperidine (1.32g, 48%), b.p. 86° at 10mmHg (Found, M<sup>+</sup> 143.0957; calc. for C<sub>7</sub>H<sub>13</sub>NO<sub>2</sub>: M143.0945). The infrared spectrum (liquid film) included  $v_{max}$  3360 (N-H str) and 1735cm<sup>-1</sup> (C=O str) The <sup>1</sup>H nmr spectrum (250MHz, CDCl<sub>3</sub>) showed signals at  $\delta$ 3.72 (s; OCH<sub>3</sub>), 3.37 (dd, J values 9.82 and 3.08Hz; 2-H), 3.10 (ddd, J values 11.53, 3.52 and 2.20Hz; 6-H), 2.66 (dt, J values 3.18 and 11.53 Hz; 6-H), 1.95-2.02 (m; 3-H, N-H), 1.78-1.83 (m; 3-H), and 1.39-1.64 (m; 4,5-H).

2-Cyanopiperidine - 2-Carbomethoxypiperidine (0.37g) in aqueous ammonia (5cm<sup>3</sup>, d 0.88), was stirred at 20°C for 18hr. The solvent was removed *in vacuo* to give piperidine-2-carboxamide as a white solid, M<sup>+</sup> 128.0952 (calc. for  $C_6H_{12}N_2O$ : M 128.0948). The <sup>1</sup>H nmr spectrum (250MHz, CDCl<sub>3</sub>) showed signals at  $\delta 6.64$  (bs; N-H), 5.48 (bs; N-H), 3.17 (dd, J values 9.90 and 3.31Hz; 2-H), 2.98 (ddd, J values 11.82, 3.27 and 2.06Hz; 6-H), 2.62 (dt, J values 3.01 and 11.82Hz; 6-H), 1.71-1.95 (m, 3-H, N-H) and 1.31-1.55 (m; 4,5-H). The foregoing product (1.29g) was dissolved in a mixture of dry tetrahydrofuran (30cm<sup>3</sup>) and anhydrous pyridine (1.62cm<sup>3</sup>).<sup>26</sup> To the mixture, at 3-5°, was slowly added, with stirring, trifluoroacetic anhydride (2.32g). The solution was stirred at room temperature for 4hr. and then evaporated to dryness *in vacuo*. The residue was dissolved in chloroform (50cm<sup>3</sup>), washed successively with water (40cm<sup>3</sup>) and

saturated brine (50cm<sup>3</sup>), dried (MgSO<sub>4</sub>), filtered and heated to remove solvent. The residue was distilled with petroleum ether (b.p. 60-80°C, 100cm<sup>3</sup>) to remove traces of pyridine. The residual oil was 1-trifluoroacetyl-2-cyanopiperidine (1.65g, 79%). The infrared spectrum (liquid film) included  $v_{max}$  2240cm<sup>-1</sup> (C=N str), 1695cm<sup>-1</sup> (C=O str) and 1130-1220cm<sup>-1</sup> (C-F str). The <sup>1</sup>H nmr spectrum (250MHz, CDCl<sub>3</sub>) showed signals at  $\delta$ 5.61 (bs; 2-H), 3.95 (m; 6-H), 3.40 (m; 6-H), 2.07 (m; 5-H), 1.70-1.95 (m; 3,4,5-H), 0.72 (m; 4-H).

The preceding product (1.63g) was dissolved in a mixture of methanol (12cm<sup>3</sup>) and saturated aqueous sodium hydrogen carbonate (12cm<sup>3</sup>) and the suspension was stirred at room temperature for 2hr. The solution was evaporated to remove methanol and then extracted with ether (4x40cm<sup>3</sup>). The combined extracts were dried (MgSO<sub>4</sub>), filtered and evaporated to give 2-cyanopiperidine (0.36g, 32%) as a yellow oil, b.p. 100° at 15mmHg (lit.<sup>27</sup> 130° at 25mmHg), M<sup>+</sup> 110.0853 (Calc. for C<sub>6</sub>H<sub>10</sub>N<sub>2</sub>: M110.0842). The infrared spectrum (liquid film) included  $v_{max}$  3340 (N-H str) and 2230cm<sup>-1</sup> (C=N str). The <sup>1</sup>H nmr spectrum (250MHz, CDCl<sub>3</sub>) shows signals at 84.02 (t, J value 4.15Hz, 2-H), 2.98 (dd, J values 9.68 and 3.01Hz; 6-H), 2.92 (t, J values 4.18Hz; 6-H), 1.47-1.87 (m; 3,4,5-H).

2-Cyanotetrahydropyran - Freshly distilled 2-chlorotetrahydropyran<sup>3</sup> (3.66g) was added dropwise to a stirred suspension of silver cyanide (4.1g) in refluxing anhydrous diethyl ether (50cm<sup>3</sup>). Finally the mixture was refluxed for 3hr., cooled and filtered. Distillation of the filtrate gave 2-cyanotetrahydropyran as a colourless liquid (1.12g, 33%), b.p. 70-72° at 18mmHg (lit.<sup>28</sup> 77-83° at 16mmHg). (Found: M<sup>+</sup> 111.0683. Calc. for C<sub>6</sub>H<sub>9</sub>NO: M11.0684). The infrared spectrum (liquid film) included  $v_{max}$  2240cm<sup>-1</sup> (C=N str). The <sup>1</sup>H nmr spectrum (250MHz, CDCl<sub>3</sub>) showed signals at 84.63 (t; 2-H), 3.71-3.96 (m; 6-H) and 1.51-2.00 (m; 3,4,5-H).

#### Determination of Thermodynamic Parameters

See Part I.<sup>3</sup>

#### Data Treatment

(a)

Data treatment employed computer drawn plots of lnK (K = e/a) against T<sup>-1</sup> (method B of Part I).

1. The equilibrium in carbomethoxycyclohexane  $(9 \neq 10)$  in ether/toluene-d<sub>8</sub> (3/1; v/v).

equilibrium constant K = 10/9 = e/a

low temperature integ	ration		
T/K	165	170	175
К	34.15	24.28	27.97
± error	3.25	1.63	2.08

(b) li

line broadening method at intermediate temperatures.<sup>11</sup> w = maximum line width (corrected for line width of TMS)

Carbon Signal	T/K	w/Hz	К	±error
C1	228	20.4	11.23	0.05
C3,5	220	13.4	10.88	0.08
C2,6	220	7.4	14.22	0.18

## Data Treatment

Plot of lnK against T<sup>-1</sup> (6 points) gave

 $\Delta H^{o}_{a \to e} = -1.24 \pm 0.15 \text{ kcal mol}^{-1} \text{ and}$  $\Delta S^{o}_{a \to e} = -0.63 \pm 0.80 \text{ cal K}^{-1} \text{ mol}^{-1}$ 

2. The equilibrium in 2-carbomethoxytetrahydropyran (11=12) in ether/toluene-d<sub>8</sub> (3/1; v/v). equilibrium constant K = 12/11 = e/a

(a)	low temperature integration				
	T/K	150	160		
	K	25.00	26.51		
	± error	3.13	2.24		

(b) line broadening method at intermediate temperatures.

w = maximum line width (corrected for line width of TMS)

Carbon Signal	T/K	w/Hz	К	±error
C6	196	28.8	8.56	0.03
C2	195	27.6	7.51	0.03
C3	193	14.6	7.73	0.05

# Data Treatment

Plot of lnK against T<sup>-1</sup> (5 points) gave

$$\Delta H^{o}_{a \to e} = -1.69 \pm 0.25 \text{ kcal mol}^{-1} \text{ and}$$
  
 $\Delta S^{o}_{a \to e} = -4.50 \pm 1.45 \text{ cal } \text{K}^{-1} \text{ mol}^{-1}$ 

3. The equilibrium in 2-carbomethoxypiperidine  $(13 \neq 14)$  in ether/toluene-d<sub>g</sub> (3/1; v/v). equilibrium constant K = 14/13 = e/a

(a)	low temperature integr	ration		
	T/K	165	170	175
	K	7.43	6.95	7.30
	± error	0.29	0.32	0.33

(b)

line broadening method at intermediate temperatures.

w = maximum line width (corrected for line width of TMS)

Carbon Signal	T/K	w/Hz	K	±error
C6	222	41.5	5.281	0.012
C2	222	35.3	5.154	0.015
C3	221	32.8	4.525	0.015
C4	222	31.9	4.764	0.017

#### Data Treatment

Plot of lnK against T<sup>-1</sup> (7 points) gave

 $\Delta H^{\circ}_{a \to e} = -0.54 \pm 0.07 \text{ kcal mol}^{-1} \text{ and}$  $\Delta S^{\circ}_{a \to e} = 0.72 \pm 0.37 \text{ cal K}^{-1} \text{ mol}^{-1}$ 

4. The equilibrium in 2-cyanotetrahydropyran ( $17 \Rightarrow 18$ ) in CFCl<sub>3</sub>/CDCl<sub>3</sub> (85/15; v/v). equilibrium constant K = 18/17 = e/a

(a)	low temperature integration				
	T/K	155	165	172	180
	К	0.203	0.217	0.225	0.232
	± error	0.013	0.018	0.010	0.018

# (b) line broadening method at intermediate temperatures.

w = maximum line width (corrected for line width of TMS)

Carbon Signal	T/K	w/Hz	К
C3	195	24.38	0.274
C4	200	43.50	0.252

# Data Treatment

Plot of lnK against T<sup>-1</sup> (6 points) gave

 $\Delta H^{o}_{a \to e} = 0.36 \pm 0.07 \text{ kcal mol}^{-1} \text{ and}$  $\Delta S^{o}_{a \to e} = -0.84 \pm 0.38 \text{ cal K}^{-1} \text{ mol}^{-1}$ 

# 5. The equilibrium in 2-cyanopiperidine $(19 \neq 20)$ in CFCl<sub>3</sub>/CDCl<sub>3</sub> (85/15; v/v). equilibrium constant K = 20/19 = e/a

(a)	low temperature integration			
	T/K	190	195	
	К	0.057	0.045	
	±error	0.001	0.003	

(b) line broadening method at intermediate temperatures.

w = maximum line width (corrected for line width of TMS)

Carbon Signal	T/K	w/Hz	K	±error
C3	225	15.8	0.132	0.001
C4	227	19.2	0.116	0.001

## Data Treatment

Plot of lnK against T<sup>-1</sup> (4 points) gave

 $\Delta H^{0}_{a \rightarrow e} = 2.22 \pm 0.56 \text{ kcal mol}^{-1} \text{ and}$  $\Delta S^{0}_{a \rightarrow e} = 5.65 \pm 2.67 \text{ cal } \text{K}^{-1} \text{ mol}^{-1}$ 

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