CALORIMETRIC STUDY OF THE ANOMERIC EFFECT IN 2-CARBOETHOXY-1,3-DITHIANES

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The enthalpic contribution to the anomeric effect in r-2-carboethoxy-*trans*-4,*trans*-6- and r-2-carboethoxy-*cis*-4,*cis*-6-dimethyl-1,3-dithianes was determined by reaction–solution calorimetry. The enthalpy of solution of both isomers in pure p-dioxane and the enthalpy of solution and isomerization in the same solvent and in the presence of trifluoroacetic acid were experimentally measured. From these results the corresponding enthalpies of isomerization in solution were calculated, and were found to be $\Delta H_{ax \to eq} = -0\cdot16 \pm 0\cdot04$ kcal mol^{-1} ($-0\cdot67 \pm 0\cdot18$ kJ mol^{-1}) and $\Delta S_{ax \to eq} = -2\cdot68 \pm 0\cdot1$ cal K^{-1} mol^{-1} ($-11\cdot2 \pm 0\cdot4$ J K^{-1} mol^{-1}). The slightly negative ΔH term nevertheless reflects a substantial anomeric effect owing to the countervailing steric effects in the axial isomer. The significant entropy loss in the equatorial isomer was explained in terms of intramolecular electrostatic effects. The results are in agreement with those obtained from NMR studies of the conformational behaviour of 2-carboethoxy-5-methyl-5-aza-1,3-dithiacyclohexane.
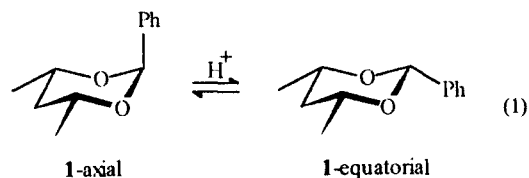
INTRODUCTION

The anomeric effect was discovered by Edward[1] and then defined by Lemieux and Chü[2] as the tendency of an electronegative substituent at C-1 of a pyranoid ring to assume an axial rather than an equatorial orientation, in contrast to the expected behaviour from steric considerations alone.

Most commonly, the thermodynamic study of this phenomenon has been restricted to the determination of equilibrium constants for the axial ⇌ equatorial process in various polar substituted six-membered heterocycles. The position of equilibrium (K) is usually established from spectroscopic analysis (mainly NMR spectroscopy), and calculation of the corresponding free energy change is made via the Gibbs relationship $\Delta G = -RT \ln K$. Comparison with the corresponding conformational free energies in monosubstituted cyclohexanes (A values) is then used to confirm or discount the operation of the anomeric effect.[3]

In this regard, Booth and Khedair[4] have stressed that entropy differences can contribute significantly to the conformational equilibria of interest, and that evaluations of the anomeric effect based exclusively on temperature-dependent ΔG (rather than ΔH) values are unsatisfactory.
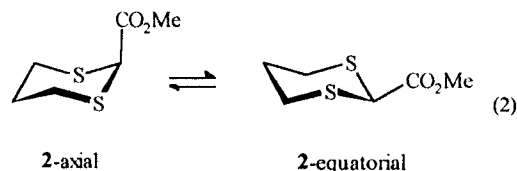
A few years ago, Bailey et al.[5] reported the calorimetric measurements of the heat of acid-catalysed isomerization of diastereoisomeric 2-phenyl-*cis*-4,*cis*-6-dimethyl-1,3-dioxanes [1, equation (1)], which indicated that the conformational free energy of a phenyl group at C-2 in 1,3-dioxane ($\Delta G = -3\cdot12 \pm 0\cdot002$ kcal mol$^{-1} = -13\cdot05 \pm 0\cdot08$ kJ mol^{-1}) is the result of a $\Delta H = -2\cdot01 \pm 0.2$ kcal mol$^{-1} = -8\cdot4 \pm 0\cdot8$ kJ mol^{-1}) favouring equatorial phenyl and a large conformational entropy ($\Delta S = +3\cdot9 \pm 0\cdot8$ cal K^{-1} mol$^{-1} = +16\cdot3 \pm 3\cdot3$ J K^{-1} mol^{-1}) also favouring the equatorial isomer.
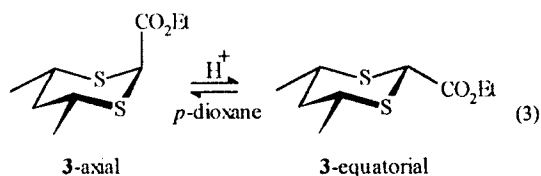

1-axial   1-equatorial   (1)

On the other hand, the existence of a substantial anomeric effect (axial preference) in 2-carbomethoxy-1,3-dithiane [2, equation (2)] was reported by Juaristi et al.[6] but no determination of the enthalpic and entropic contributions to ΔG was described.[7]

The aim of this work was to find the enthalpic contribution to the anomeric effect in the axial ⇌ equatorial

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(2)

2-axial   **2-equatorial**

equilibrium of 2-carboethoxy-1,3-dithiane, by direct calorimetric measurements for the isomerization process between the (axial) r-2-carboethoxy-trans-4,trans-6- and (equatorial) r-2-carboethoxy-cis-4,cis-6-dimethyl-1,3-dithianes [equation (3)]. This reaction is catalysed by acid and the equilibrium is reached from both sides, that is, starting from an excess of either isomer until equilibrium is reached.
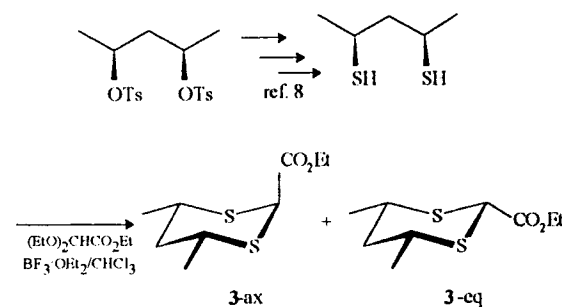

(3)

3-axial   **3-equatorial**

EXPERIMENTAL

General. Proton NMR spectra were recorded on Jeol GSX-270 (270 MHz) or Jeol PMX60-SI (60 MHz) instruments operated in the pulse Fourier transform mode and locked on solvent deuterium. ^{13}C NMR spectra were recorded on a Jeol GSX-270 (67·8 MHz) spectrometer.

r-2-Carboethoxy-trans-4,trans-6-dimethyl-1,3-dithiane (3-ax) and r-2-carboethoxy-cis-4,cis-6-dimethyl-1,3-dithiane (3-eq). meso-Pentane-2,4-diol ditosylate was converted into the corresponding meso-2,4-dithiol using the polysulphide–lithium aluminium hydride method,[8] and then condensed with ethoxyethyl acetate following the general procedure described by Eliel et al.[9] The crude product was purified by flash column chromatography [hexane–ethyl acetate (95 : 5)]. Fractional recrystallization from hexane–ethyl acetate (90 : 10) afforded the separated products (Scheme 1).

trans-Isomer (3-ax), m.p. 40–41 °C. ^{1}H NMR (270 MHz, CDCl₃), δ 1·12 (d, $^3J_{H-H} = 6·6$ Hz, 6 H, CH_3-CH), 1·30 (t, $^3J_{H-H} = 7·25$, 3 H, CH_3-CH₂,), 1·32 [dd, $^3J_{gem} = 13·86$ Hz, $^3J_{anti} = 11·88$ Hz, 1 H, C(5)-H$_{ax}$], 2·13 [dt, $J_{gem} = 13·86$ Hz, $^3J_{gauche} = 1·32$ Hz, 1 H, C(5)-H$_{eq}$], 3·5 [m, 2 H, C(4,6)-H], 4·20 (q, $^3J_{H-H} = 7·25$ Hz, 2 H, CH₂-O), 4·27 [s, 1 H, C(2)-H]. ^{13}C NMR (67·93 MHz, CDCl₃), δ 14·08 (CH₃CH₂), 21·51 (CH₃CH), 34·82, (CH₃CH), 42·78 (C-CH₂-C), 43·45 (S-CH-S), 61·60 (CH₂-O), 170·51, C=O).

cis-Isomer (3-eq), m.p. 37–37·5 °C. ^{1}H NMR (270

Scheme 1

MHz, CDCl₃), δ 1·29 (d, $^3J_{H-H} = 6·6$ Hz, 6 H, CH_3-CH), 1·31 (t, $^3J_{H-H} = 7·26$ Hz, 3 H, CH_3-CH₂), 1·65 [dt, $^3J_{gem} = {}^3J_{anti} = 13·86$ Hz, C(5)-H$_{ax}$], 2·12 [dt, $^3J_{gem} = 13·86$ Hz, $^3J_{gauche} = 1·98$ Hz, 1 H, C(5)-H$_{eq}$], 2·95 [m, 2 H, C(4,6)-H], 4·27 (q, $^3J_{H-H} = 7·26$ Hz, 2 H, CH₂-O], 4·95 [s, 1 H, C(2)-H]. ^{13}C NMR (67·93 MHz, CDCl₃), δ 14·06 (CH₃CH₂), 21·38 (CH₃CH), 40·22 (CH₃-CH), 43·38 (C-CH₂-C), 51,36 (S-CH-S), 62·49 (CH₂-O), 167·54 (C=O).

Measurements. The calorimetric measurements were made using 1,4-dioxane (Aldrich Chemical) as solvent, chosen because of its zero dipole moment and low dielectric constant, thus expecting an increase in the anomeric effect.[3] The solvent was dried prior to the calorimetric experiments by slow distillation over lithium aluminium hydride, in order to avoid any isomerization or hydrolysis during the dissolution of pure axial or equatorial samples. The trifluoracetic acid (Aldrich Chemical) used as a catalyst was not additionally purified prior to use.

Measurements were carried out on an LKB-8700 precision calorimetric system with a reaction cell of 100 cm³, which was modified to introduce a quartz crystal probe. Samples were introduced in glass ampoules of 1 cm³. Time–temperature curves were obtained using a quartz crystal thermometer (HP 2804A) coupled to an HP-85 computer for automatic data collection. The corrected temperature rise was calculated by the Regnault–Pfaundler method.[10] The enthalpy changes were determined by electrical calibration before and after the main experiments. The calorimeter constant was taken as the average from these two experiments. The instrument was tested by determining the dissolution enthalpy of tris(hydroxymethyl)amino methane (THAM) in aqueous NaOH. All the measurements were made at 298·15 K.

Figure 1 shows the thermochemical cycle used to determine the enthalpy change of the anomeric effect. $\Delta_{sol}H$(ax) and $\Delta_{sol}H$(eq) are the experimentally determined values of the enthalpy of solution of pure crystalline axial and equatorial isomers in pure dioxane,
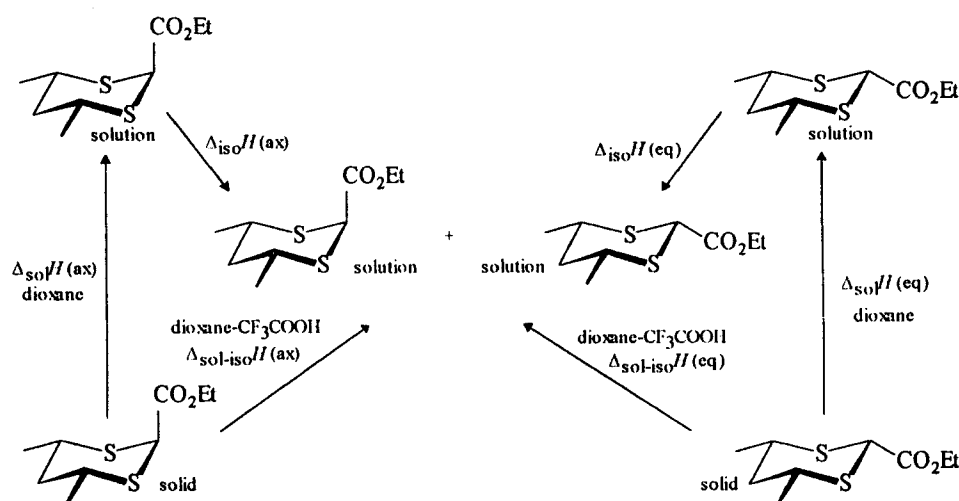
Figure 1. Diagrammatic presentation of thermochemical data

respectively. Following each experiment, the solution was analysed by NMR spectroscopy in order to verify that no isomerization had occurred. $\Delta_{sol-iso}H(ax)$ and $\Delta_{sol-iso}H(eq)$ are the experimentally determined values of the enthalpy change when pure axial or equatorial compounds are dissolved in dioxane, acidified with trifluoracetic acid and allowed to equilibrate. In these cases the reaction reaches the equilibrium in less than 2 min as revealed by the calorimetric curve. The composition of the final calorimetric solution was determined by integration of appropriate signals in the NMR spectra in order to ascertain the molar enthalpy change. From these measurements the enthalpy change $\Delta_{iso}H$ for the isomerization process in solution could be determined.

RESULTS

The results of the calorimetric measurements are given in Tables 1–4. The uncertainties are the standard deviation of the mean. The enthalpy of solution of the axial isomer in pure dioxane was determined as $\Delta_{sol}H(ax) =$

$4 \cdot 44 \pm 0 \cdot 004$ kcal mol^{-1} $\quad (18 \cdot 539 \pm 0 \cdot 015$ kJ mol$^{-1})$ and $\Delta_{sol-iso}H(ax) = 4 \cdot 42 \pm 0 \cdot 003$ kcal mol$^{-1}(18 \cdot 453 \pm 0 \cdot 013$ kJ mol$^{-1})$. From these results, the enthalpy of isomerization in solution, $\Delta_{iso}H(ax)$, when n_{iso} (determined from integration of appropriate ^{1}H NMR signals in the equilibrium samples) of the total number of moles n_t, of the axial isomer are transformed to the equatorial compound can be calculated from the equation

$$n_{sol-iso}\Delta_{sol-iso}H(ax) = n_t\Delta_{sol}H(ax) + n_{iso}\Delta_{iso}H(ax)$$

$$(4)$$

leading to a value of $\Delta_{iso}H(ax) = -0 \cdot 087$ kcal mol^{-1} $(-0 \cdot 363$ kJ mol$^{-1})$. In a similar fashion, the enthalpy of solution of the equatorial isomer in pure dioxane was determined as $\Delta_{sol}H(eq) = 5 \cdot 447 \pm 0 \cdot 012$ kcal mol^{-1} $(22 \cdot 768 \pm 0 \cdot 049$ kJ mol$^{-1})$, and the enthalpy of solution and isomerization for the same compound was $5 \cdot 559 \pm 0 \cdot 012$ kcal mol^{-1} $(23 \cdot 238 \pm 0 \cdot 049$ kJ mol$^{-1})$. From these values, the enthalpy of isomerization in solution of the equatorial to axial compound

Table 1. Experimental enthalpy of solution of r-2-carboethoxy-$trans$-4,$trans$-6-dimethyl-1,3-dithiane in 1,4-dioxane

| Experiment | ε(cal K^{-1}) | Mass | | $\Delta T/$(K) | Q(cal) | $\Delta_{sol}H$(kcal mol^{-1}) |
		g	mol $\times 10^4$			
1	56·296	0·04229	1·9193	0·01510	0·8501	4·429
2	57·024	0·04216	1·9134	0·01486	0·8474	4·429
3	57·592	0·03854	1·7491	0·01340	0·7717	4·435
						Av. 4·431 ± 0·003

Table 2. Experimental enthalpy of solution and isomerization of r-2-carboethoxy-trans-4,trans-6-dimethyl-1,3-dithiane in acidified 1,4-dioxane

| Experiment | ε(cal K^{-1}) | Mass | | K_{eq} | Isomerization (%) | ΔT/(K) | Q(cal) | $\Delta_{sol-iso}H$(kcal mol^{-1}) |
		g	mol × 10^4					
1	56·422	0·04395	1·9946	0·295	22·762	0·01558	0·8790	4·407
2	55·928	0·04171	1·8929	0·321	24·271	0·01439	0·8048	4·411
3	55·442	0·03232	1·4668	0·317	24·087	0·01148	0·6479	4·413
								Av. 4·410 ± 0·003

Table 3. Experimental enthalpy of solution of r-2-carboethoxy-cis-4,cis-6-dimethyl-1,3-dithiane in 1,4-dioxane

| Experiment | ε(cal K^{-1}) | Mass | | ΔT/(K) | Q(cal) | $\Delta_{sol}H$(kcal mol^{-1}) |
		g	mol × 10^4			
1	56·887	0·03543	1·6079	0·01538	0·8749	5·441
2	56·371	0·04074	1·8489	0·01785	1·0062	5·442
						Av. 5·441 ± 0·012

Table 4. Experimental enthalpy of solution and isomerization of r-2-carboethoxy-cis-4,cis-6-dimethyl-1,3-dithiane in acidified 1,4-dioxane

| Experiment | ε(cal K^{-1}) | Mass | | K_{eq} | Isomerization (%) | ΔT/(K) | Q(cal) | $\Delta_{sol-iso}H$(kcal mol^{-1}) |
		g	mol × 10^4					
1	57·928	0·03231	1·4663	0·320	75·901	0·01408	0·8156	5·562
2	56·392	0·03670	1·6656	0·324	75·755	0·01638	0·9237	5·546
								Av. 5·554 ± 0·012

was calculated as $\Delta_{iso}H$(eq) = +0·148 kcal mol^{-1} (+0·620 kJ mol^{-1}).

The direct measurement of the enthalpy of isomerization was then attempted. In this case the calorimetric cell was filled with dioxane mixed with trifluoroacetic acid, and the ampoule was filled with ca 300 mg of the axial isomer previously dissolved in dioxane. The evolved heat was within the detection limit of the instrument; however, this experiment showed that the process is effectively exothermic and the enthalpy change from one experiment was estimated as $\Delta_{iso}H$(ax, sol) = −0·202 kcal mol^{-1} (−0·846 kJ mol^{-1}). The same procedure was applied to the equatorial isomer, leading to an endothermic enthalpy value determined as $\Delta_{iso}H$ (eq, sol) = +0·119 kcal mol^{-1} (+0·497 kJ mol^{-1}), as estimated from three experiments.

The equilibrium constant K of interest was determined from the isomeric composition of the final

Table 5. Summary of the experimental and derived thermodynamic parameters for the isomerization of r-2-carboethoxy-trans-4,trans-6-dimethyl-1,3-dithiane and r-2-carboethoxy-cis-4,cis-6-dimethyl-1,3-dithiane in 1,4-dioxane

Process	$\Delta_{sol}H$ (kcal mol^{-1})	$\Delta_{sol-iso}H$ (kcal mol^{-1})	$\Delta_{iso}H$ (cal mol^{-1})	K_{eq}	$\Delta_{iso}G$ (kcal mol^{-1})	$\Delta_{iso}S$ (cal K^{-1} mol^{-1})
3-ax to 3-eq	4·431	4·410	−86·7	0·311	0·69	−2·61
3-eq to 3-ax	5·442	5·554	148·2	3·137	−0·68	2·77

calorimetric solution. The derived quantities $\Delta_{iso}G$ and $\Delta_{iso}S$ were calculated from the relationships $\Delta G_{iso} = -RT \ln K$ and $\Delta_{iso}G = \Delta_{iso}H - T\Delta_{iso}S$. The results of this calculation are shown in Table 5.
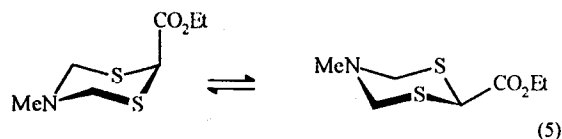
DISCUSSION

The enthalpy of solution for both the axial and equatorial isomers was found to be endothermic, although this value is greater for the equatorial isomer. This might be due to a decrease in crystal lattice inter-molecular distances for the equatorial isomer, increasing the molecular interactions and therefore the lattice energy, which is destroyed upon solvation.

The small but exothermic enthalpy change associated with the isomerization from the axial to equatorial carboethoxy $\Delta H_{ax \to eq} = -0.16 \pm 0.04$ kcal mol^{-1} $(-0.67 \pm 0.18$ kJ mol$^{-1})$ can be explained in terms of steric repulsion between the substituent and the *syn* axial protons. Nevertheless, an enthalpy value close to zero suggests the existence of an enthalpic anomeric effect compensating the repulsion which would otherwise be reflected in a more substantial negative enthalpy value.

On the other hand, the estimated entropy change $\Delta_{iso}S(ax) = -2.59$ cal K^{-1} mol^{-1} $(-10.81$ J K^{-1} mol$^{-1})$ for the isomerization from axial to equatorial (3) indicates that in the equatorial isomer there exists rotational restriction around the C-2—carboethoxy bond. The similar value of $\Delta_{iso}S(eq) = +2.77$ cal K^{-1} mol^{-1} $(+11.58$ J mol^{-1} K$^{-1})$ for the isomerization from equatorial to axial confirms that in the latter isomer the rotation of the substituent is less restricted.

A possible explanation of this entropy change may be related to the local dipole–dipole interactions present in the axial and equatorial epimers as reported by Juaristi *et al.*[11] Indeed, values of $\Delta H° = -0.03 \pm 0.04$ kcal mol^{-1} $(-0.12 \pm 0.17$ kJ mol$^{-1})$ in CD$_2$Cl$_2$ and -0.04 ± 0.11 kcal mol^{-1} $(-0.17 \pm 0.46$ kJ mol$^{-1})$ in acetone-d_6 have been measured in the conformational study of 2-carboethoxy-5-methyl-5-aza-1,3-dithiacyclo-hexane[11] [equation (5)]. The corresponding entropy changes for these equilibria were $\Delta S° = -1.70 \pm 0.23$ cal K^{-1} mol^{-1} $(-7.11 \pm 0.96$ J K^{-1} mol$^{-1})$ and -1.38 ± 0.57 cal K^{-1} mol^{-1} $(-5.77 \pm 2.38$ J K^{-1} mol$^{-1})$, respectively.

(5)

When the substituent is in the axial position the dipole of the substituent is antiparallel to the dipole of the ring in such a way that any of the rotamers is almost equally probable from an electrostatic point of view, as shown in Figure 2(a). In the case of the equatorial isomer only the rotamers where the dipole of the substituent is pointing in the opposite direction to the dipole of the ring is favoured. Therefore, this configuration is more restricted [see Figure 2(b)] [one of the referees has cautioned against the advancement of *any* explanation for the (small) entropy change observed in this work].

At temperatures higher than 33 K the axial isomer is more abundant because the $T\Delta S$ term dominates the equilibrium.
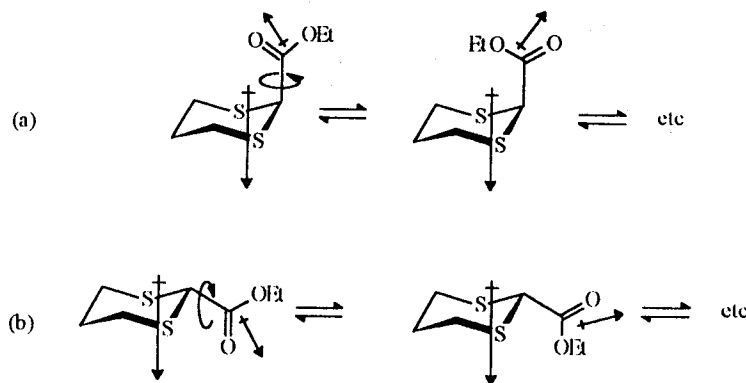
Figure 2. Bond dipole orientations in the axial equatorial conformers of 2

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