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Short Communication

On the nature of conformational preferences of 4-fluoromethylated groups in 1,3-dioxanes

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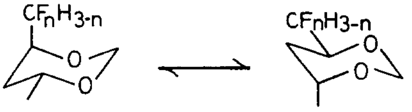
Using NMR parameters, we have previously reported[1] the equilibria that exist between the conformers in *trans*-4-CF_nH_{3-n}-6-methyl-1,3-dioxanes, (I) $\rightleftharpoons$ (II). Only free energy differences at 300°K were obtained. Corresponding derivatives with 2-methyl groups also may be equilibrated under acid conditions, and the equilibrium between the configurational isomers, (III) $\rightleftharpoons$ (IV), may thus be evaluated accurately by quantitative GLC.



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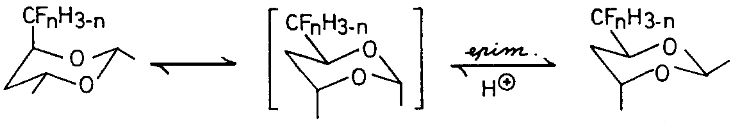

III IV

We now report the results obtained by this chemical epimerization at several temperatures, from which some estimates of the thermodynamic parameters $\Delta H°$ and $\Delta S°$ may be derived. The present data obtained for $\Delta G°$ are in complete agreement with our previously reported[1] results.

Experimental and results

The preparation and separation of the compounds will be published later[2]. The preparative separation of the 2,6-dimethyl-4-difluoromethyl-1,3-dioxanes was impossible however (although on capillary columns the three isomers are nicely resolved) and only one of the two isomers (*e.g.* (IV), $n = 2$) could be isolated in the pure state. All other pairs ((III) and (IV)) have been equilibrated, starting from both sides (either pure (III) or pure (IV)).

Equilibrations were done in carbon disulfide with trifluoroacetic acid (TFA) as the catalyst. Variations in concentration of both the dioxanic compounds and TFA had to be considered. Therefore, three procedures were checked: (a) using 1 vol. % of dioxane in CS_2 with 0.1 equiv. TFA; (b) using 0.2 vol. % of dioxane in CS_2 and an equivalent amount of TFA and (c) using 1 vol. % of dioxane in CS_2 and an equivalent amount of TFA. These checks were necessary because only the last procedure allows equilibration at low temperatures in an acceptable time. The two first procedures, (a) and (b), were checked in order to observe the results of possible changes in dielectrical behaviour of the solution with temperature, which could greatly affect the equilibrium between isomers differing in polar character, as was actually found to be the case.

TFA is noted[3,4] for its very pronounced $d\varepsilon/dT$ value. Using 0.0032 mole of TFA in CS_2, however, we calculated from additivity principles that the maximum change of ε between $-30°$ and $+60°$ should only be from 2.822 to 2.716. The change of ε caused by a change in composition of the equilibrating species is of much greater importance. Procedures (a) and (c) may only be used safety, provided that the same molar concentration is used at the different temperatures, after taking into account the volume change of the medium. A further important point concerns the quantitative application of GLC analyses. Packed columns were found to cause serious preferential absorption of one the isomeric compounds. Therefore capillary columns had to be used. However, this necessitates the use of a splitter, unless "on-column" injection is used. Splitter ratios have a considerable influence upon the results obtained using standard mixtures. With *r*-2-methyl-, *trans*-4-trifluoromethyl-, *cis*-6-methyl-1,3-dioxane and *r*-2-methyl-, *cis*-4-trifluoromethyl-, *trans*-6-methyl-1,3-dioxane the following data were found (split ratio–% *trans*/*cis*): 1/34–67.3; 1/60–70.75; 1/73–71.8 and 1/86–72.8. It is easily seen by extrapolation that still more pronounced ratios would be necessary in order to get representative results[4]. In principle, therefore, the only precise method consists in "on-column" injections. Besides the difficulty in introducing small sample values (e.g. $< 0.5\ \mu l$) it is important not to overload the column, because this causes tailing, thus affecting the electronic counts in the detector. The number of counts is best held between 3×10^4 and 1×10^5. Typical results obtained for the same standard mixture as above are: 75.27 (9000 counts); 74.5 (25 000 counts); 73.75 (35 000 counts) and 73.0 (260 000 counts). The results of equilibrium compositions are gathered in Table 1 and are mean values of at least five integrations. Those giving a number of counts outside the 3×10^4–10^5 range were discarded.

Discussion

In general, the results from epimerization are in complete agreement with previously[1] obtained data from NMR studies. In those studies, rather variable values for the monofluoro derivative were obtained but 0.923 was proposed as the best value for *K*. This is now confirmed.

TABLE 1

EQUILIBRIA AT SEVERAL TEMPERATURES OBTAINED IN CS_2 BY GLC ANALYSIS[a] BETWEEN EPIMERIZABLE DIOXANES (III) $\rightleftharpoons$ (IV)

Starting compound	% axial $CF_nH_{3-n}(\alpha)$	$K = \frac{(100-\alpha)}{\alpha}$	T (°K)	$\Delta G^{\circ c}$ (cal mole^{-1})	ΔG° (from NMR^b) ΔH° and ΔS°
(III) $n=3^a$	73.40	0.357	293	600	(695/588)
(IV) $n=3$	74.00				
(IV) $n=2$	60.51	0.652_6	240	204	(294/299)
	61.40	0.628_7	275	254	$\Delta H^\circ = -114$ cal mole^{-1}
	61.70	0.620_8	306	290	$\Delta S^\circ = -1.33$ e.u.
	62.04	0.610_9	326	320	$r = 0.9989^d$
(III) $n=1$	51.18	0.953_5	240	$22._7$	
(IV) $n=1$	51.19				
(III) $n=1$	52.75	0.898_6	275	$58._4$	(—57 to 128)
(IV) $n=1$	52.58				
(III) $n=1$	53.77	0.857_0	306	94	$\Delta H^\circ = -234$ cal mole^{-1}
(IV) $n=1$	53.96				$\Delta S^\circ = -1.07$ e.u.
(III) $n=1$	54.33	0.838_9	326	114	$r = 0.9996$
(IV) $n=1$	54.45				

[a] Capillary columns[8], $l = 55$ m, coated with SE-30, analyses at 70–90°, for $n = 3$ and $n = 2$; capillary columns[8], $l = 90$ m coated with Carbowax, analyses at 160° for $n = 1$.

[b] ΔG° values previously obtained from NMR data in CS_2 and to be compared with actual values at 300°K.

[c] Positive values, *i.e.* favouring axial CF_nH_{3-n} group.

[d] r = Regression coefficient.

It is difficult to obtain reliable values of ΔH° and ΔS°, but due to the good reproducibility obtained by on-column injections, the results obtained may be regarded as significant estimates. It is clear that the axial orientation of the CF_nH_{3-n} group is preferred not only for enthalpy reasons, but that entropy contributions are also important. Calculations[5] of external rotational entropy contributions show that a substantial part of the observed difference between axial and equatorial conformers might be simply the result of differences in moments of inertia (evaluated at 0.5–1.0 e.u. in favour of the axial CF_nH_{3-n} substituent). However, some other contributions presumably operate as well.

Table 2 gathers the theoretical (calculated) dipole moments for different rotamers (including eclipsed conformations). This has been done for 4-CF_nH_{3-n} substituted dioxanes in respectively axial (constant values for all rotamers) and equatorial positions possessing extreme μ values. These values clearly illustrate how the polar groups influence the equilibrium state, other than by mere steric requirements. The dipoles operate at least at two stages. Firstly, there is an enthalpic favouring arising from intrinsic dielectric repulsion*. By virtue of this

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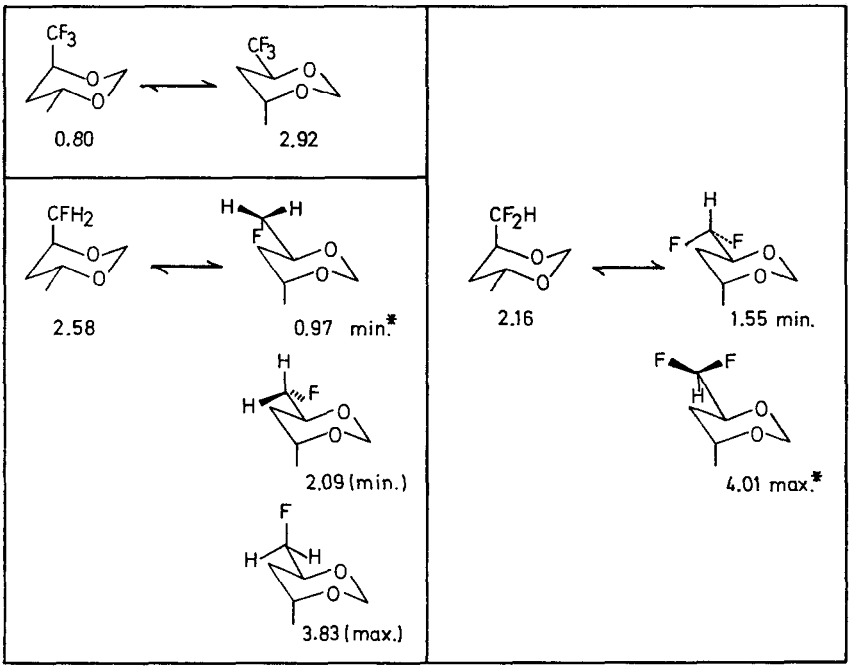
* This might be expressed quantitatively by Jeans' equation[7] $E_\mu = \mu_1 . \mu_2(\cos x - 3 \cos d_1 . \cos d_2 / Dr^3)$. However, the problem is to define the parameters exactly.

TABLE 2

CALCULATED DIPOLE MOMENTS FOR AXIAL AND EQUATORIAL 4-CF_nH_{3-n}-SUBSTITUTED 1,3-DIOXANES[a]



[a] The Table shows extreme values for different rotameric distributions. Values marked with asterisk correspond to eclipsed forms.

effect alone, we expect an axial preference for the CF_3 group (smallest μ), but an equatorial preference for CF_2H and to a lesser extent also for CFH_2. This is indeed roughly what is found from our equilibria parameters (Table 1) considering only $\Delta H°$. As the result of the isotropic behaviour of a CF_3 group we may accept that $\Delta G°(CF_3) \simeq \Delta H°(CF_3)$. However, some rotameric situations in the equatorial position are also less probable because of their high polar character. This too must influence entropy contents *. For these reasons we would expect an axial preference for CF_2H and to a lesser extent for CFH_2. This is indeed reflected by the respective $\Delta S°$ (Table 1) values.

It is therefore clearly understood that both contributions result in the observed trends in $\Delta G°$. Electric contributions for non-isotropic groups influence both $\Delta H°$ and $\Delta S°$ values, sometimes with opposite trends.

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* Only the negative effect of electric contributions is discussed here. It is clear that for steric reasons also some of the axial rotameric forms are less probable. For electric reasons, however, all of the axial rotamers behave identically because of their equal dipole moments.

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