Ring Inversion Barrier in 5,5-Difluoro-1,3-dioxane

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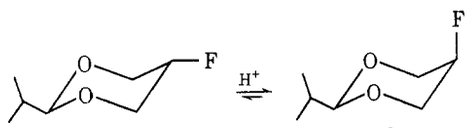
In recent publications[2,3] we have reported that the equilibrium between the 2-isopropyl-5-fluorodioxanes (**1** ⇄ **2**) favors the axial (cis) isomer (Scheme I) and

SCHEME I

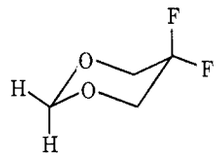


1 **2**

Solvent	$\Delta G°$, kcal/mol
CCl_4	−0.36
$(C_2H_5)_2O$	−0.62
C_6H_6	−0.83
$CHCl_3$	−0.87
CH_3CN	−1.22

this result has been confirmed qualitatively by comparison of the ^{19}F nmr spectra of the equatorial and axial models, **1** and **2**, with the corresponding spectrum of the conformationally mobile 5-fluoro-1,3-dioxane (**3**); the ^{19}F chemical shift of **3** is much closer to that of **2** than to that of **1**.[4] The situation is in contrast to that with the chlorine and bromine analogs of **1** and **2**, for which the equatorial isomer is favored;[2,3] it is reminiscent of that existing in the 1,2-haloethanes, where the gauche isomer predominates for the 1,2-difluoro compound, whereas in 1,2-dichloro- and 1,2-dibromoethane the anti isomer is favored, at least in the gas phase.[5,6]

Because of recent interest[7-9] in possible attractive interactions between heteroatoms, we desired to obtain independent evidence that the greater stability of **2** as compared with **1** was due to a fluorine–oxygen attraction. To that end, we determined the inversion barrier in 5,5-difluoro-1,3-dioxane (**4**); we argued that ground-state stabilization in **4** by fluorine–oxygen attraction should reflect itself in an enhanced barrier to inversion, since we had hoped that the transition state



4

would not be affected in a major way by the fluorine substituents at C-5.[10]

The barrier in **4** was measured by low-temperature proton nmr observing coalescence of the AB pattern at C-2. To check our experimental technique, especially the accuracy of the temperature measurement, we also repeated the measurement of the known[11-14] barriers in 1,3-dioxane (**5**) itself and in the 5,5-dimethyl homolog (**6**). The data are summarized in Table I. Our data for **5** and **6** are within the range of those determined by other groups; clearly, the barrier for **4** is appreciably lower than that for **5** and **6**.

By way of further confirmation of the lower barrier for **4** we also measured the coalescence of the ^{19}F nmr spectrum. Because of the large relative chemical shift of the geminal fluorines (ϕ_a 113.2 ppm, ϕ_e 115.2 ppm) the spectrum at coalescence was extremely broad, but the coalescence could nevertheless be determined to occur at −84°, corresponding to $\Delta G^{\ddagger}$ = 8.2 kcal/mol. Because of the discrepancy of 0.6 kcal/mol between the activation barriers determined by ^1H and ^{19}F, we simulated the line shape of the proton spectrum in the vicinity of the coalescence temperature by the program QUABEX[15] varying the rate constant from that computed by the approximative equation 1 (which had

$$k = \frac{\pi}{\sqrt{2}}\sqrt{\Delta\nu_{AB}^2 + 6J_{AB}^2} \qquad (1)$$

been used to calculate the data in Table I). The line fit at coalescence for k = 55.2 sec^{-1} (for which $\Delta G^{\ddagger}$ = 8.8 kcal/mol) was the best obtainable but was not perfect, probably because of neglect of the long-range coupling constant $J_{H_{2e}F_{5e}}$. We can thus not claim the highest accuracy for our data, but it is nevertheless clear that the barrier of 8.5 ± 0.3 kcal/mol for **4**, far from being enhanced as we might have expected, is lower than that of **5** by about 1 kcal/mol and lower than that of **6** by about 2 kcal/mol.

Several possible explanations suggest themselves. (1) Rather than there being a stabilization in **2**, there might be a destabilization in **1** (Scheme I). This could best be explained by the existence of four gauche-vicinal hydrogen atoms in **1** but only two such atoms in **2**. It would thus amount to postulating a repulsive F–H gauche interaction. In view of other recent findings,[16] such an explanation would appear exceedingly

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(2) E. L. Eliel and M. K. Kaloustian, *Chem. Commun.*, 290 (1970).

(3) R. J. Abraham, H. D. Banks, E. L. Eliel, O. Hofer, and M. K. Kaloustian, *J. Amer. Chem. Soc.*, **94**, 1913 (1972).

(4) S. Mager and E. L. Eliel, *Rev. Roum. Chim.*, in press. A low-temperature nmr study of **3** has been reported [L. D. Hall and R. N. Johnson, *Org. Magn. Resonance*, **4**, 369 (1972)] and leads to the same conclusion.

(5) R. J. Abraham and R. H. Kemp, *J. Chem. Soc. B*, 1240 (1971), and Table III in ref 3.

(6) Since these equilibria involve highly polar substituents and the conformers differ greatly in dipole moment, there is a strong solvent dependence. There is no question that the gauche isomer of FCH_2CH_2F predominates in the liquid phase, but the gas-phase preference rests on an older infrared determination [P. Klaboe and J. R. Nielsen, *J. Chem. Phys.*, **33**, 1764 (1960)] and should probably be put on a firmer experimental basis, especially since quantum mechanical calculations suggest the anti isomer to be more stable.[7]

(7) L. Radom, W. A. Lathan, W. J. Hehre, and J. A. Pople, *J. Amer. Chem. Soc.*, **95**, 693 (1973).

(8) L. Phillips and V. Wray, *Chem. Commun.*, 90 (1973).

(9) N. D. Epiotis and W. Cherry, *Chem. Commun.*, 278 (1973); N. D. Epiotis, *J. Amer. Chem. Soc.*, **95**, 3087 (1973).

(10) The barrier in 1,1-difluorocyclohexane is about 0.5–0.9 kcal/mol lower than that in cyclohexane; *cf.* G. Binsch, *Top. Stereochem.*, **3**, 158 (1968). Of this difference, 0.15–0.28 kcal/mol may be ascribed to ground-state compression by axial fluorine; *cf.* J. A. Hirsch, *Top. Stereochem.*, **1**, 200 (1967); F. J. Jensen, C. H. Bushweller, and B. H. Beck, *J. Amer. Chem. Soc.*, **91**, 344 (1969).

(11) H. Friebolin, S. Kabuss, W. Maier, and A. Lüttringhaus, *Tetrahedron Lett.*, 683 (1962).

(12) H. Friebolin, H. G. Schmid, S. Kabuss, and W. Faist, *Org. Magn. Resonance*, **1**, 67 (1969).

(13) J. E. Anderson and J. C. D. Brand, *Trans. Faraday Soc.*, **62**, 39 (1966).

(14) E. Coene and M. Anteunis, *Bull. Soc. Chim. Belg.*, **79**, 37 (1970).

(15) G. Binsch, *Top. Stereochem.*, **3**, 180 (1968).

(16) *Cf.* R. D. Norris and G. Binsch, *J. Amer. Chem. Soc.*, **95**, 182 (1973).

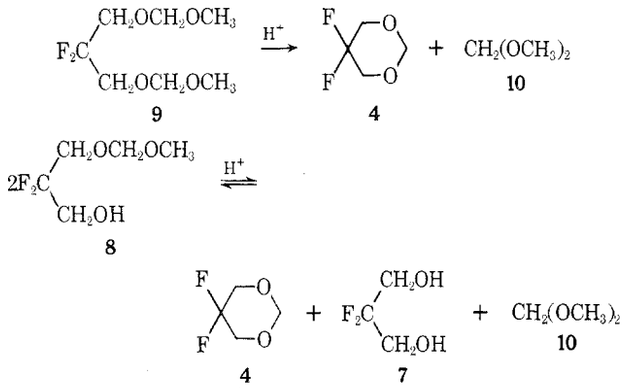
TABLE I
RING INVERSION BARRIERS

Compd	4	5	5	5	5	5	6	6	6	6	6
$\Delta G^{\ddagger}$, kcal/mol	8.8	9.6	9.7	9.9	9.0	9.7	10.7	11.2	11.1	10.5	10.5
Ref	*a*	*a*	11	12	13	14	*a*	11	12	13	14

[a] This work. Coalescence temperatures: **4**, −96°; **5**, −80°; **6**, −57°.

implausible. (2) The stabilization of **2** over **1** might be caused largely by differential solvation; no corresponding differential solvation occurs between **4** and the transition state for its inversion. This explanation has a fair measure of plausibility, in as much as it has been calculated[3] that, in the gas phase, **1** should actually be *more stable* than **2** by 0.5 kcal/mol.[17] (3) Our *a priori* assumption that comparison of the inversion barrier of the difluoro compound **4** with that of the parent dioxane **5** should not be dominated by a lowering of the transition-state energy might be incorrect. This factor probably contributes, since the relative effect of introducing a geminal difluoro group on the barrier height varies from system to system. For example, the inversion barrier of 518 cm^{-1} (1.48 kcal/mol) in puckered cyclobutane[18] drops to less than half, 241 cm^{-1} (0.69 kcal/mol), in 1,1-difluorocyclobutane[19] and the already very small analogous barrier in oxetane (15.3 cm^{-1})[20] disappears completely in (planar) 3,3-difluorooxetane.[21] A combination of 2 and 3 may well be responsible for our findings. Unfortunately, since the relative importance of the two factors is not known, the barrier measurement in **4**, as it turns out, throws no light on the equilibrium shown in Scheme I.

2,2-Difluoro-1,3-propanediol (**7**) was obtained by lithium aluminum hydride reduction of diethyl difluoromalonate.[22] Acid-catalyzed condensation of **7** with dimethoxymethane, unlike similar condensations of other 1,3-diols, gave rise not only to the dioxane **4** but also to the mixed formals $CH_3OCH_2OCH_2CF_2CH_2OH$ (**8**) and $CH_3OCH_2OCH_2CF_2CH_2OCH_2OCH_3$ (**9**) (see Experimental Section). When **9** was distilled over polystyrenesulfonic acid, it was smoothly converted to



4 and dimethoxymethane (**10**). Compound **8**, under these circumstances, yielded starting material **7** in addition to **4** and **10**, as might be expected from the stoichiometry.

Condensation of **7** with isobutyraldehyde yielded 2-isopropyl-5,5-difluoro-1,3-dioxane (**11**). The ^1H and ^{19}F nmr chemical shifts for both **4** (at room temperature and below the coalescence point) and **11** are recorded in the Experimental Section. Not unexpectedly[23,24] the axial and equatorial fluorine signals in **11** are not the same as those in **4** at low temperature, nor do they average to the room-temperature fluorine signal in **4**.

Experimental Section

The fluorine nmr spectra were recorded on a Varian XL-100-12 instrument at 94.1 MHz, the proton spectra on a Varian A-60A instrument at 60 MHz. ^{19}F chemical shifts are reported in the ϕ scale.[25] Microanalyses were performed by Midwest Microlab, Indianapolis, Ind.

2,2-Difluoro-1,3-propanediol (**7**).—Lithium aluminum hydride (12 g, 0.32 mol) was partially dissolved in anhydrous ether with good stirring and 40 g (0.20 mol) of diethyl difluoromalonate in 400 ml of ether was added slowly, maintaining gentle reflux. The solution was boiled for 2 hr and cooled, 7.5 ml of water was added cautiously to destroy excess hydride, and the mixture was poured into 500 ml of 10% sulfuric acid. The solution was saturated with ammonium sulfate and extracted four times with 500-ml portions of ether. The ether was dried over magnesium sulfate, filtered, and concentrated; the residue was dissolved in a 1:1:1 mixture of benzene, ethyl acetate, and Skellysolve F (petroleum ether, bp 30–60°). Cooling and further addition of Skellysolve F produced crystals which were collected and washed with Skellysolve F, mp 51–52° (lit.[26] mp 54.5°), yield 14.3 g (63%). Additional material may be obtained by concentration and vacuum distillation of the mother liquor. The proton nmr spectrum, δ 3.83 ppm (in D_2O from $Me_3SiCH_2CH_2CH_2SO_3^-Na^+$), showed a rather small H–F vicinal coupling constant, J = 14 Hz, confirmed by the ^{19}F spectrum, ϕ 117.7 ppm.

2-Isopropyl-5,5-difluoro-1,3-dioxane (**11**).—A solution of 0.3 g (2.7 mmol) of diol **7**, 2.25 g (31 mmol) of isobutyraldehyde, and 0.05 g of *p*-toluenesulfonic acid in 30 ml of Skellysolve F was boiled at reflux with a Dean–Stark trap until no more water was given off (15 hr). After neutralization with 0.05 g of sodium acetate (stirring for 30 min), the solution was filtered, the residue was washed with 20 ml of ether, and the combined filtrates were washed twice with 10 ml of water, dried over magnesium sulfate, and concentrated. The residue was purified by glpc using a 15 × 0.25 in. 20% Carbowax 20M on Chromosorb A (45–60 mesh) column at 164° with a 260-ml/min flow of helium, retention time 168 sec. Material of mp 32° was obtained in 55% yield.

Anal. Calcd for $C_7H_{12}F_2O_2$: C, 50.59; H, 7.28. Found: C, 50.99; H, 7.55.

^{19}F nmr spectrum: ϕ_a 114.1, ϕ_e 118.3 ppm, $J_{F_aF_e}$ = 252, $J_{F_aH_{4(6)e}}$ = 27, $J_{F_aH_{4(6)e}}$ = 11, $J_{F_eH_{4(6)a}}$ = 5, $J_{F_eH_{4(6)e}}$ = 0.7, $J_{F_aH_{2a}}$ = 0.7 Hz. ^1H nmr spectrum: 0.94 (d, J = 6 Hz, 6 H), 1.53–2.15 (m, 1 H), 3.28–4.1 (AB split by fluorines, J_{gem} = 12 Hz, 4 H), 4.24 ppm (d, J = 4.8 Hz, 1 H).

5,5-Difluoro-1,3-dioxane (**4**).—A solution of 2 g (18 mmol) of diol **7** in 20 ml of dimethoxymethane was boiled for 4 hr in the presence of a catalytic amount of Amberlyst-15 (beaded polystyrenesulfonic acid). Excess dimethoxymethane was distilled,

(17) Preliminary experimental results by N. C. Craig tend to confirm this prediction.
(18) F. A. Miller and R. J. Capwell, *Spectrochim. Acta, Part A*, **27**, 947 (1971).
(19) A. C. Luntz, *J. Chem. Phys.*, **50**, 1109 (1969).
(20) S. I. Chan, T. R. Borgers, J. W. Russell, H. L. Strauss and W. D. Gwinn, *J. Chem. Phys.*, **44**, 1103 (1966).
(21) G. L. McKown and R. A. Beaudet, *J. Chem. Phys.*, **55**, 3105 (1971).
(22) H. Gershon, J. A. A. Renwick, W. K. Wynn, and R. D'Ascoli, *J. Org. Chem.*, **31**, 916 (1966).
(23) *Cf.* E. L. Eliel and R. J. L. Martin, *J. Amer. Chem. Soc.*, **90**, 682 (1968).
(24) See also S. L. Spassov, D. L. Griffith, E. S. Glazer, K. Nagarajan, and J. D. Roberts, *J. Amer. Chem. Soc.*, **89**, 88 (1967).
(25) G. Filipovich and G. V. D. Tiers, *J. Phys. Chem.*, **63**, 761 (1959). The reference substance is CCl_3F.
(26) L. S. Boguslavskaya, V. S. Etlis, K. V. Yarovykh, and A. B. Bulovyatova, *Zh. Org. Khim.*, **7**, 1338 (1971).

the residue was transferred to a small distillation flask, and fresh Amberlyst was added. The residue was heated for 3–4 hr at 135° and the material which distilled was collected. To the residue, fresh dimethoxymethane (20 ml) and Amberlyst was added, the solution was boiled for 3 hr, and the above procedure was repeated. At the end, the bath temperature was increased to 150°. The combined distillates were purified by glpc on the column mentioned above at 110°, with 330-ml/min He flow, retention time 6 min: yield 0.52 g (23%); mp 19°; n^{20}D 1.3752.

Anal. Calcd for $C_4H_6F_2O_2$: C, 38.71; H, 4.87. Found: C, 38.78; H, 4.88.

^{19}F nmr spectrum (−124°): ϕ_a 113.2, ϕ_e 115.2, ϕ_{av} (room temperature) 114.7 ppm; $J_{F_eF_e} = 253$, $J_{F_aH_{4(6)a}} = 25$, $J_{F_4H_{4(6)e}} = 10.9$ Hz. ^{1}H nmr spectrum (−112°): $\delta_{H_{2e}}$ 5.11, $\delta_{H_{2a}}$ 4.77 ppm, $J_{H_{2e}H_{2a}} = -5.75$ Hz; (room temperature) 3.92 (t, J = 11 Hz, 4 H), 4.89 ppm (d, J = 1.2 Hz, 2 H).

When the original residue after distillation of excess dimethoxymethane and **4** was subjected to gas chromatography in the above column at 190° with a 310-ml/min He flow, two compounds were obtained, **8**, retention time 6 min, and **9**, retention time 11 min. Proton nmr spectra and elemental analyses were in accord with the structures assigned. *Anal.* Calcd for $C_5H_{10}F_2O_3$ (**8**): C, 38.46; H, 6.45. Found: C, 38.88; H, 6.56. *Anal.* Calcd for $C_7H_{14}F_2O_4$ (**9**): C, 42.00; H, 7.05. Found: C, 42.55; H, 7.25.

When **9** was heated over Amberlyst in a distilling flask, it was converted entirely into **4** and dimethoxymethane, as evidenced by gas chromatographic analysis of both the distillate and the residue. In contrast, similar treatment of **8**, while giving the same distillate (**4** and dimethoxymethane), left a residue containing some unchanged **8** as well as $HOCH_2CF_2CH_2OH$ (**7**).

Barrier Measurement.—The nmr spectrum of **4** was measured in a solvent mixture of 80% acetone-d_6 and 20% trichlorofluoromethane with some TMS.[27] For the low-temperature runs, the temperature was measured by letting the probe, refrigerated by a stream of precooled nitrogen, come to equilibrium and replacing the sample with a copper–constantan thermocouple located inside an nmr tube. A period of 10 min was allowed to allow either the sample tube or the thermocouple tube come to temperature equilibrium with the probe. Temperature readings were reproducible to ±2°. The proton signals (AB pattern for the H-2's) were located at 283 (ν_1), 289 (ν_2), 304.5 (ν_3), and 310 Hz (ν_4), indicating a coupling constant of −5.75 ± 0.25 Hz, and the chemical shifts reported above were calculated by the usual equation, $\Delta\nu_{AB} = (\nu_4 - \nu_1)^{1/2}(\nu_3 - \nu_2)^{1/2} = 20.46$ Hz. The coalescence temperature was found to be −96° by varying the temperature first in intervals of 5° and then, near the coalescence temperature, in intervals of 2°. The rate constant was calculated from the computed chemical shifts and the coalescence temperature by the equation given in the discussion and was found to be 55.2 sec^{-1} at −96°. The activation energy $\Delta G^{\ddagger}$ was calculated to be 8.8 kcal/mol by application of the Eyring equation, $k = \mathbf{k}T/h)e^{-\Delta G^{\ddagger}/RT}$ or $\Delta G^{\ddagger} = -RT \ln hk/\mathbf{k}T$. To simulate the spectrum in the vicinity of the coalescence point we used the program QUABEX,[15] which in addition to ν_A, ν_B, and J_{AB} requires the relaxation time T_2 as input; T_2 was taken at $1/\pi W$ where W is the width (in hertz) at half height of the peak. Spectra were calculated by a Univac 1107 computer and plotted by a Calcomp 750 plotter.

The fluorine data were handled similarly. Chemical shifts and coupling constants have been reported above at low temperature. Coalescence to a very broad spectrum occurred at approximately −84°, at which temperature the rate constant was calculated to be 1437 sec^{-1} and the activation energy 8.2 kcal/mol.

Rate constants and activation energies for **5** and **6** were determined similarly from the H-2 proton spectra.

Acknowledgment.—We are grateful to Mr. Donald Schifferl for recording the low-temperature ^{1}H and ^{19}F spectra. One of us (S. M.) is indebted to the University Babes Bolyai, Cluj, Romania, for an academic leave. This work was supported by NSF Grant GP-24,910.

Registry No.—**4**, 36301-44-7; **5**, 505-22-6; **6**, 766-15-4; **7**, 428-63-7; **8**, 42116-92-7; **9**, 42116-93-8.

(27) We used the most polar solvent available which would not freeze at the low temperature required in the nmr experiment, since, as indicated in Scheme I, the axial preference of fluorine is greatest in the most polar solvents. From results on 5-methoxy-1,3-dioxane [O. Hofer in E. L. Eliel, *Angew. Chem., Int. Ed. Engl.*, **11**, 739 (1972), Table VIII] acetone should favor the axial isomer **2** more than ether and benzene but less than acetonitrile.

An Exceptionally Facile Reaction of α,α-Dichloro-β-keto Esters with Bases

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α,α-Dichloro-β-keto esters react rapidly with even relatively weak nucleophiles such as sodium bicarbonate, potassium acetate, and diethylamine to give products according to eq 1.

$$MeCOCCl_2COOEt + MeCOONa \xrightarrow{EtOH} MeCOOEt + CHCl_2COOEt \quad (1)$$

To our knowledge, such a facile fragmentation of an α,α-disubstituted β-keto ester derivative with a base (eq 1) is unprecedented.[1] This reaction proceeds under extremely mild conditions. For example, when a solution of ethyl α,α-dichloroacetoacetate in ethanol is stirred at 25° for 30 min in the presence of a catalytic quantity of sodium acetate, ethyl acetate and ethyl dichloroacetate are produced in nearly quantitative yield. The results on other representative reactions are summarized in Table I.

The present reaction appears to be an example of retro acetoacetic ester consensation.[2] The characteristics noteworthy of this novel fragmentation process are (1) there is no reaction between the dichloro compound and the alcohol in the absence of required base; (2) when ethyl α,α-dichloroacetoacetate and sodium acetate are stirred together in a solvent such as benzene, chloroform, or dimethyl sulfoxide, the formation of acetic anhydride is not detected (ir, glpc) (however, upon the addition of an alcohol to this reaction mixture, the expected products are produced rapidly); and (3) when ethyl α,α-dichloroacetoacetate is stirred with potassium benzoate or ethyl α,α-dichlorobenzoylacetate is stirred with potassium acetate in a solvent such as chloroform or dimethyl sulfoxide in order to achieve a redistribution according to eq 2, the starting materials are recovered unchanged in both cases.

$$C_6H_5COCCl_2COOEt + KOCOCH_3 \rightleftharpoons H_3CCOCCl_2COOEt + C_6H_5COOK \quad (2)$$

Although a study of the precise mechanism of this reaction has not been undertaken, it would appear likely that the present fragmentation proceeds *via* an attack of the nucleophile on the reactive carbonyl moiety of the dichloro compound.[3]

(1) For a recent report on a related reaction which results in the ring opening of certain α,α-dihalospirocyclobutanones with bases, see B. M. Trost and M. J. Bodganowicz, *J. Amer. Chem. Soc.*, **95**, 2038 (1973).

(2) For a discussion of the principles involved in the acetoacetic ester condensation, see H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., 1972, Chapter 11.

(3) For a discussion of the reactivity of α- and β-keto halides, see (a) E. W. Trachtenberg and T. J. Whall, *J. Org. Chem.*, **37**, 1494 (1972), and references cited therein; (b) R. G. Pews and R. A. Davis, *J. Chem. Soc., Chem. Commun.*, 269 (1973).