Chair–Chair Interconversion in Some Highly Substituted 1,2,4-Trioxanes and 1,3-Dioxanes. A Dynamic NMR Study of a Striking Effect of Skeletal Substitution

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A dynamic NMR determination of barriers to chair–chair interconversion in some tetra- and hexa-substituted 1,2,4-trioxanes and 1,3-dioxanes is reported. Two comparisons of trioxanes and equivalently substituted dioxanes show that trioxane barriers are strikingly higher, and this is attributed to the high barrier to rotation about the oxygen–oxygen bond in the trioxane series.

The chair–chair interconversion of saturated six-membered rings and particularly the effect of substitution, both on the ring and in the ring skeleton, have been much studied.[1] In the first, rate-determining step, concerted rotation, constrained by the ring, takes place about several adjacent bonds to attain a set of twist conformations of relatively high energy. Some connection, albeit not simple, between ring inversion barriers and rotational barriers for molecules R–X–Y–R′, the acyclic equivalents of the various X–Y bonds in the ring is thus expected. The twist conformations are more flexible, so further bond rotations little constrained by the ring and so reflecting mainly the substituents on the bond take place relatively easily, until a reversal of the original concerted rotation leads to the original or to an inverted chair. The barrier in cyclohexane[2,3] is 10.1 kcal mol^{-1} and most simple substitutions have little effect on, or lower, this barrier, since statistically molecules choose rotation about the lowest-barrier bonds in the rate-determining step. We now report ring inversion studies where comparisons show how introducing bonds with high rotational barriers can lead to high ring inversion barriers.

High inversion barriers are already known in highly substituted molecules, with no 'low-barrier' bonds. For example, all *cis*-1,2,3,4,5,6-hexamethylcyclohexane[4] has a barrier of 17.4 kcal mol^{-1}, while that for dodecamethylcyclohexane[5] is 16.4 kcal mol^{-1}. Interactions between 1,3-diaxial methyl groups flatten the ring and lead to a lower ring inversion barrier in the latter case, even though all skeletal bonds, being hexa-substituted, have higher intrinsic rotational barriers. With ring flattening, skeletal bonds are already significantly rotated away from the staggered towards the eclipsed conformation even in the ground state.

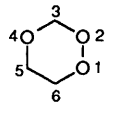
Results and Discussion

We treat two sets of compounds with an intermediate degree of substitution, from the recently available[6] 1,2,4-trioxane **1** and the structurally similar 1,3-dioxane **2** series. To the best of our knowledge there is no previous information on the solution phase conformations of 1,2,4-trioxanes and the present results may have a wider significance, given the current interest in these compounds as potential antimalarial drugs.[7] Ring inversion barriers as determined from the temperature-dependence of NMR spectra are shown in Table 1 along with those previously reported for some other 1,3-dioxanes and relevant cyclohexanes. The NMR behaviour of compound **1b** is typical. At −48 °C six methyl group signals are seen in both the proton and carbon-13 NMR spectra, showing that interchange of axial and equatorial methyl groups by ring inversion is slow on the NMR timescale. As the temperature is raised, methyl signals broaden and at about 0 °C, depending on the relative chemical shift, coalesce to give a single peak for the two methyl groups at each ring position, then finally become narrow again. From the low temperature relative shift of exchanging signals, the rate constant for ring inversion at the coalescence temperature can be determined.[8] The free energy of activation for ring inversion at this temperature can then be calculated,[8] assuming a transmission coefficient of 0.5, since the set of twist conformations form an unstable intermediate minimum symmetrically placed between the two chair conformations on the potential energy surface.

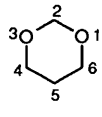
Table 1 Barriers (kcal mol^{-1}) to ring inversion in series of 1,2,4-trioxanes **1**, 1,3-dioxanes **2** and cyclohexanes **3**

Substituents	Coalescence temperature T_c/°C	Barrier at T_c	Ref.
1,2,4-Trioxanes			
1a 5,5,6,6-Me	+2	12.2	*a*
1b 3,3,5,5,6,6-Me$_6$	−5	12.3	*a*
1c 5,5,6,6-Me$_4$-3,3(–CH$_2$–)$_5$	−18	11.6	*a*
1c 5,5,6,6-Me$_4$-3,3,Ad[b]	−17	11.6	*a*
1,3-Dioxanes			
2a None	−70	9.9	9
2b 2,2-Me$_2$	−70	7.8	10
2c 4,4-Me$_2$	−70	8.6	9
2d 5,5-Me$_2$	−70	11.2	9
2e 2,2,4,4-Me$_4$	< −150	< 5.5	11
2f 2,2,5,5-Me$_4$	−70	8.9	9
2g 4,4,6,6-Me$_4$	−148	5.9	11
2h 4,4,5,5-Me$_4$	−73	10.1	*a*
2i 2,2,4,4,5,5-Me$_6$	−133	6.5	*a*
Cyclohexanes			
3a None		10.1	2,3
3b 1,1-Me$_2$		10.3	20
3c 1,1,4,4-Me$_4$		11.4	14, 16
3d 1,1,3,3-Me$_4$		8.7	14

[a] This work. [b] Ad = spiro[2.2]adamantyl.



1



2

Some polymethyl-1,3-dioxanes have been shown by molecular mechanics[12] calculations to prefer twist-boat conformations. However, we confirmed using Allinger's MM3 molecular mechanics program[13] which is parametrised for the peroxide bond, that the chair conformation is more stable than any boat conformation by several kcal mol^{-1} for the compounds

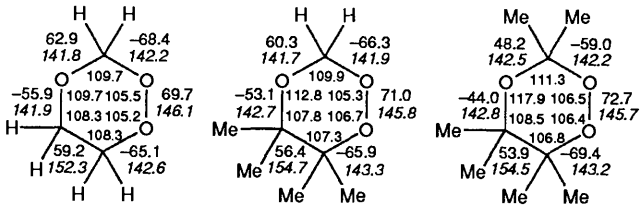


Fig. 1 Bond lengths (pm; italic numbers), internal bond angles (small numbers), and torsional angles for bonds in 1,2,4-trioxane rings as calculated by MM3

2e, **h** and **i**, and the same is true for compounds **1a** and **b**. Calculations in the 1,2,4-trioxane series do not seem to have been reported previously so some bond lengths, bond angles and torsion angles are shown in Fig. 1. The succession of oxygen–carbon and oxygen–oxygen bonds, short compared with carbon–carbon bonds, induces ring-puckering, that is torsion angles greater than 60°. Substitution with geminal methyl groups produces slight bond lengthening and closing down of bond angles internal to the ring. In the hexamethyl compound, methyl–methyl 1,3-diaxial interactions flatten one part of the ring as shown by noticeably reduced torsion angles and increased puckering in the rest of the ring.

Results in Table 1 for simple 1,3-dioxanes show clearly from several comparisons how introducing axial substituents in the 2, 4 or 6-positions produces substantial lowering of barriers, even though the substitution constrains rotation of two bonds in the ring skeleton. Syn-diaxial interactions are particularly marked because of the four short carbon–oxygen bonds in 1,3-dioxanes compared with the equivalent carbon–carbon bonds of cyclohexanes, and produce these barrier reductions. Our present results for **2h** and **i** provide further examples of this effect (compare **2h** with **2d**, and **2i** with **2h** or **2f**) but also illustrate a contrasting effect. Introducing a hexasubstituted bond in the 4–5 position leads to ring inversion barriers higher by more than 1 kcal mol^{-1} in **2h** and **i** compared with **2c** and **e** respectively.

The barriers to ring inversion for each of the 1,2,4-trioxanes **1a–d** are surprisingly similar, and higher than any in the 1,3-dioxane series. The extra substituents at the OCO position in **1b–d** compared with **1a** have little effect on the barrier although the equivalent substitution in the above 1,3-dioxane series lowers the barrier by more than 3 kcal mol^{-1}. The slightly lower barriers in **1c** and **d** compared with **1a** and **b** may reflect the cyclic substituents being less able to distort to accommodate strain in the ground state.

The striking comparisons in our present results are thus between the two series. The barrier in **1a** is 2.1 kcal mol^{-1} higher than that in **2h**, while that in **1b** is 5.8 kcal mol^{-1} higher than that in **2i**. In both cases a CH_2-group in the dioxane has been replaced by an oxygen atom in the trioxane. It is difficult to predict whether the replacement increases or reduces transannular interactions, for the parent 1,3-dioxane (9.9) and cyclohexane (10.1) barriers are very similar, but it does introduce a bond with a high rotational barrier, the oxygen–oxygen bond, and this is the likely cause of the contrasting high barriers in the 1,2,4-trioxanes. Thus, the 1,3-dioxanes **2h** and **2i** have substituents located in the 2,3,4,5-part of the molecule so the 'low barrier' rate-determining rotation step of the ring inversion is presumably in the 5,6,1,2-part. Introducing an oxygen atom into the 6-position to give the 1,2,4-trioxanes **1a** and **1b** with a high barrier oxygen–oxygen bond, removes the 'low barrier' section of the molecule and thus leads to high barriers regardless of the substitution pattern. There is a precedent for enhanced barriers when oxygen–oxygen bonds are introduced as shown by the comparison of the ring inversion barrier for 1,1,4,4-tetramethylcyclohexane[14–16] of 11.4 kcal mol^{-1} with the higher barriers for both 3,3,6,6-tetramethyl-1,2-dioxane[17] (14.6 kcal mol^{-1}), and 3,3,6,6-tetramethyl-1,2,4,5-tetroxane[18,19] (15.4 kcal mol^{-1}).

While we do not doubt that even for the 1,2,4-trioxanes, rotation about individual bonds and the overall flatness of the ground state ring conformation are the dominating influences on barrier sizes, these effects operate in opposite directions and their relative importance when there are so many heteroatoms, and when all carbons are substituted, is too complicated to elucidate.

Experimental

1,2,4-Trioxanes **1a–1d** were prepared by the reported 'one-pot' method[6] involving mercury(II) acetate-mediated cyclisation of hemiperacetals derived from 2,3-dimethylbut-1-en-3-yl hydroperoxide and the appropriate ketone, followed by reduction *in situ* with sodium borohydride. 1,3-Dioxane **2h** was prepared from dimethoxymethane and 1,1,2,2-tetramethylpropane-1,3-diol as previously described,[21,22] and 1,3-dioxane **2i** (b.p. 145–146 °C) Found: C, 69.6; H, 11.0. $C_{10}H_{20}O_2$ requires C, 69.71; H, 11.70%) was prepared by a similar transacetalisation reaction with 2,2-dimethoxypropane.

NMR spectra (Varian VXR400 spectrometer) are for approximately 0.1 mol dm^{-3} solutions in deuteriochloroform for spectra at temperatures above −60 °C, and in an approximately 2:2:1 $CHCl_2F$–$CHClF_2$–CD_2Cl_2 mixed solvent for spectra below −60 °C. Solvent effects on spectra and entropies and enthalpies of activation for the ring inversion were not determined in this work. Barriers were calculated[8] from the coalescence of appropriate NMR signals as the temperature varied. Chemical shifts (δ) at fast and slow rates of ring inversion for **1a–1d**, **2h** and **2i** are as follows.

δ_H(400 MHz). **1a**, +25 °C, 5.279 (3-H_2), 1.220 and 1.266 (5-Me_2 and 6-Me_2); −58 °C, 4.944, 5.554 (*J* 8.36, 3-H_2), 0.964, 1.114, 1.349 and 1.985 (5-Me_2 and 6-Me_2). **1b**, +42 °C, 1.460 (3-Me_2) and 1.240 (5-Me_2 and 6-Me_2); −48 °C, 1.310, 1.619 (3-Me_2), 1.044, 1.081, 1.380 and 1.435 (5-Me_2 and 6-Me_2). **1c**, +25 °C, 1.42–1.65 (3-'cyclohexyl') and 1.230 (5-Me_2 and 6-Me_2); −58 °C, 1.38–1.90 (3-'cyclohexyl'), 1.055, 1.085, 1.386 and 1.448 (5-Me_2 and 6-Me_2). **1d**, +25 °C, 1.51–2.11 (3-'adamantyl') and 1.235 (5-Me_2 and 6-Me_2); −58 °C, 1.43–2.04 (3-adamantyl'), 0.982, 1.048, 1.359 and 1.395 (5-Me_2 and 6-Me_2).

δ_H(200 MHz). **2h**, +21 °C, 4.93 (2-H_2), 3.58 (6-H_2), 1.22 (4-Me_2) and 0.96 (5-Me_2); −80 °C, 4.92, 4.96 (2-H_2), 3.36, 3.79 (6-H_2), 1.22, 1.37 (4-Me_2), 0.76 and 1.23 (5-Me_2). **2i**, +20 °C, 0.926 (5-Me_2), 1.185 (4-Me_2), 1.342 (2-Me_2) and 3.481 (6-H_2); −142 °C, 0.79, 1.12 (5-Me_2), 0.94, 1.20 (4-Me_2), 1.39 (2-Me_2), 3.20 and 3.96 (6-H_2).

δ_C NMR (100 MHz). **1a**, +42 °C, 91.25 (C-3), 74.53 (C-5), 83.59 (C-6), 21.29 and 21.83 (5-Me_2 and 6-Me_2); −58 °C, 91.08 (C-3), 74.38 (C-5), 83.56 (C-6), 19.22, 19.18, 21.11 and 24.14 (5-Me_2 and 6-Me_2). **1b**, +42 °C, 101.74 (C-3), 26.47 (3-Me_2), 74.78 (C-5), 81.38 (C-6), 21.56 and 25.76 (5-Me_2 and 6-Me_2); −49 °C, 101.62 (C-3), 25.08, 27.37 (3-Me_2), 74.31 (C-5), 81.31 (C-6), 21.04, 24.40, 25.08 and 26.04 (5-Me_2 and 6-Me_2). **1c**, +25 °C, 101.98 (C-3), 25.43, 26.09, 35.36 (C-3-'cyclohexyl'), 74.65 (C-5), 81.57 (C-6), 21.66 and 22.90 (5-Me_2 and 6-Me_2); −58 °C, 101.95 (C-3), 24.98, 26.28, 26.34, 33.36, 36.19 (C-3-'cyclohexyl'), 74.58 (C-5), 81.52 (C-6), 21.05, 21.90, 22.45 and 22.94 (5-Me_2 and 6-Me_2). **1d**, +25 °C, 103.89 (C-3), 26.80, 27.41, 33.83, 33.91, 36.07, 37.33 (C-3-'adamantyl'), 74.89 (C-5), 81.39 (C-6), 21.69 and 25.69 (5-Me_2 and 6-Me_2); −58 °C, 103.81 (C-3), 26.26, 26.86, 33.28, 33.37, 33.44, 33.80, 36.78, 36.90, 37.13 (C-3-'adamantyl'), 74.68 (C-5), 81.32 (C-6), 21.11, 21.95, 24.59 and 26.39 (5-Me_2 and 6-Me_2).

δ_C(50 MHz). **2i**, −140 °C, 98.28 (C-2), 77.42 (C-4), 67.79 (C-6), 34.38 (C-5), 21.80, 19.99 (5-Me_2), 23.59, 30.81 (2-Me_2) and 25.18 (4-Me_2).

Acknowledgements

We thank the SERC for a Research Studentship (to A. S.).

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Paper 3/01925J
Received 5*th April* 1993
Accepted 30*th June* 1993