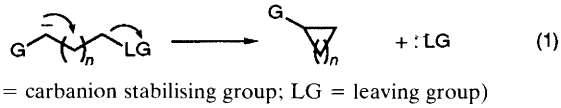
Strain-induced Mechanism Change: the Limit of Strain Tolerance in Intramolecular Nucleophilic Substitution?

Stephen M. Jeffery, Stefan Niedoba (in part) and Charles J. M. Stirling*

Department of Chemistry, The University of Sheffield, Sheffield S3 7HF, UK

The limit of strain energy differential for intramolecular nucleophilic substitution *via* a sulfonyl-stabilised carbanion to give cyclopropane analogues in hydroxylic solvents is around 160 kJ mol^{-1}; above this level, concerted, albeit unactivated, 1,2-elimination is preferred.

The effect of strain on reactivity has been subjected to much recent examination and a body of quantitative data bearing on this matter is now available.[1] In the case of intramolecular nucleophilic substitution by carbanions [eqn. (1)] it has been found[2] that the enthalpies of activation for cyclisation are insensitive to the excess enthalpy[1a,3] of the ring system being formed, at least in the region spanning 0–113 kJ mol^{-1}. Gaoni[4] has shown, however, that the inherent strain of a cyclic system does not prevent its formation by the reaction of eqn. (1) even if this strain, as in the case of bicyclobutanes, is large (excess enthalpy of bicyclobutane = 276 kJ mol^{-1}). In a previous communication[5] we reported that subjection of the mesylate **5** to strongly basic conditions generated, in competition, two highly strained products **7** and **6** resulting from 1,2- and 1,3-elimination respectively. These observations raised the general question of the response of strained systems to the excess enthalpy differential (EED)† between starting material and products as shown in the activation parameters. We have now addressed this question using a number of systems in which the excess enthalpies of the product skeletons are known, and we have examined not only the feasibility of the reactions, but have also looked for any correlations between EED values and ΔH.‡

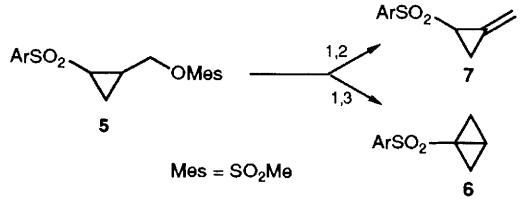


(1)

(G = carbanion stabilising group; LG = leaving group)

The systems studied are in Scheme 1 and kinetic and activation data in Table 1.

A number of striking conclusions emerge from these data. First, there *is* restraint, *cf.* **3** to **4**, on the formation of very



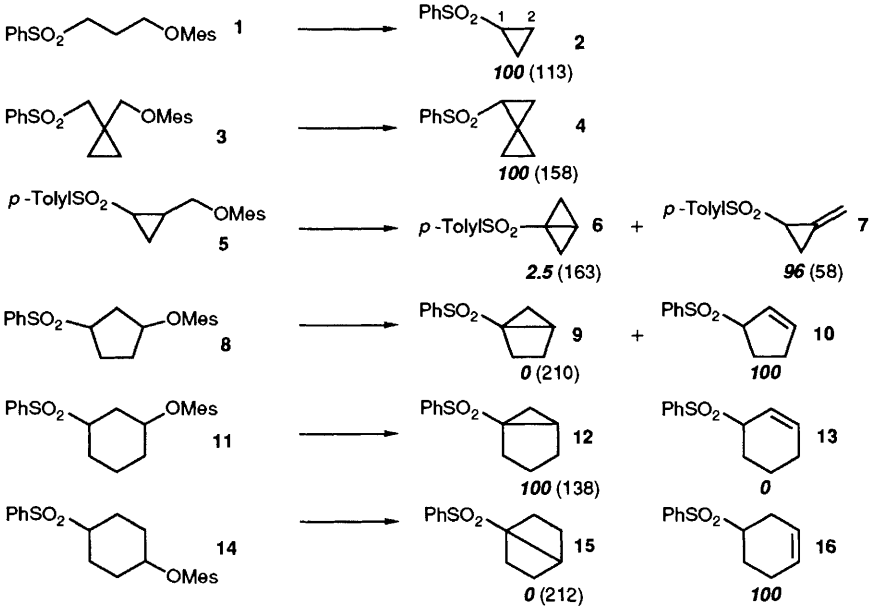
† *E.g.* for **5** → **6** the excess enthalpy difference between methylenecyclopropane (171 kJ mol^{-1}) and cyclopropane (113 kJ mol^{-1}). The assumption is made, in the absence of combustion data, that excess enthalpies are independent of ring substituent.

‡ In this connection, we have found that for substrate **1** in reactions with Bu^{t}OK–Bu^{t}OD, there was incorporation of deuterium α- to the phenylsulfonyl group in the starting material and in the mesyloxy group of the starting material. In the product, deuterium was incorporated adjacent to the sulfonyl group but not at C-2, ruling out a carbene insertion mechanism for cyclisation. The thermodynamic acidities of **1**, **3** and **5** are comparable notwithstanding the structural differences [pK_a (Me_2SO) for $PhSO_2Et$, 31; $PhSO_2$-cyclopropyl 31.8; $PhSO_2CH_2$-cyclopropyl probably very similar to $PhSO_2Et$]; *cf.* M. J. Perkins, N. B. Peynircioglu and B. V. Smith, *J. Chem. Soc., Perkin Trans. 2*, 1978, 1025. Substrates **1**, **5** and **14** show $k_{H/D}$ exchange ≫ elimination and **8** and **11** epimerise from pure isomers faster than they eliminate.

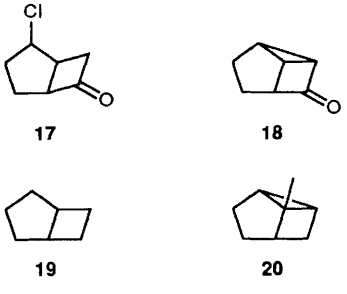
Table 1 Cyclisation *versus* elimination in sulfone mesylates

Mesylate	Product	$k^{a,b}$ (cyclisation)	$k^{a,b}$ (elimination)	$\Delta H^{\ddagger c}$	$\Delta S^{\ddagger d}$	EED[c]
1	**2**	97	—	65	−46	113
3	**4**	2.4	—	92	+13	158
5	**6** and **7**	0.003[e]	0.08[f]	—	—	163
8[g]	**10**	—	6.4[h]	—	—	210
11[i]	**12**	0.87	—	97	+21	138
14	**16**	—	0.15[j]	—	—	210

[a] × 10^3 dm^3 mol^{-1} s^{-1} for reactions with Bu^{t}OK–Bu^{t}OH. [b] At 25 °C. [c] kJ mol^{-1} for cyclisation. [d] J K^{-1} mol^{-1}. [e] Value for 2% of reaction flux. [f] At 27.9 °C. [g] Identical results with 9:1 *cis–trans*-mixture as for pure *cis* indicating rapid equilibration of configurations at carbon bearing the phenylsulfonyl group. [h] At 28.5 °C. [i] Identical results with 3:1 *cis–trans*-mixture as with pure *cis*. [j] At 26.6 °C.



Scheme 1 Cyclisation *versus* elimination in sulfone mesylates. All reactions with Bu^{t}OK–Bu^{t}OH. Yields of products (%) in bold italics; EED in parentheses.



strained products by intramolecular nucleophilic substitution. The parameters respond to the additional strain; the rate constant is depressed by a factor of 40 *versus* the 'unstrained' analogue **1** → **2** but this factor disguises the increase in $\Delta H^{\ddagger}$ which nearly matches the strain differential. The positive entropy of activation is reminiscent of earlier work on formation of cyclopropanes[2] where again this was manifest.

An analogous situation is seen in the conversion of **11** to **12**. The EED is comparable, as are the activation parameters. The reactivity ratio **1** : **11** is similar to that for **1** : **3**. An odd feature which emerged from the comparison of these three reactions is the change from negative to positive entropies of activation on going from the less strained **1** to the more strained systems **3** and **11**. The latter pair are, of course, considerably more rigid and the appropriate transition structures for the required trajectories are inherently more favourable.

When the EED for cyclisation is 163 kJ mol^{-1} as for substrate **5**, cyclisation is a very small fraction of the reaction flux. Further increase in the EED (substrates **8** and **14**) prevents cyclisation under the protic solvent conditions we have used here. Unactivated 1,2-elimination supervenes. What is being observed, therefore, is the balance between the *stepwise*, carbanion-mediated cyclisations (1,3-elimination)‡ on the one hand and the *concerted* 1,2-elimination on the other. In earlier work,[5] we showed that for substrate **5** there was no pick-up of deuterium from Bu^{t}OD–Bu^{t}OH at carbon β to the leaving group. The balance between the two processes is evidently held by the strain differential; the rate constants for the concerted reactions are of the same order of magnitude as the stepwise reactions, and this is a remarkable example of strain-induced mechanism change. Even though the methylenecyclopropane **7** is some 58 kJ mol^{-1} more strained than its precursor, the rate of 1,2-elimination to form it is very similar to that for the cyclohexane system **14** in which the EED value for 1,2-elimination is close to zero.

Finally, it should be stressed that an EED of even 210 kJ mol^{-1} is not an absolute barrier to cyclisation; substrate **5** gives[4] **6** (55–60%) on treatment with butyllithium in tetrahydrofuran (THF) and in this work we have found that **8** gives **9** (95%) under the same conditions. Evidently cyclisation proceeds when the conversion to carbanion is nearly complete. Formation of tricyclic ketone **18** from ketone **17** apparently occurs rapidly with methanolic potassium hydroxide.[6] The ketone **17** is much more acidic than the sulfones used in this work and the EED can be estimated at 136 kJ mol^{-1}

from the strain energies of **19**[3] and **20**.[7] For **14** however, none of **15** is obtained even with BuLi–THF and starting material is recovered on quenching. Concerted 1,2-elimination from the α-sulfonyl carbanion is, unsurprisingly, suppressed and no cyclisation is observed even under forcing conditions. This is yet another manifestation of the very large ratio between rate constants for 1,3- and 1,4-eliminations.[1]

We thank the SERC for support and Professor G. M. Blackburn for useful discussions.

Received, 16th January 1992; Com. 2/00239F

References

1 (*a*) C. J. M. Stirling, *Tetrahedron*, 1985, **41**, 1613; (*b*) C. J. M. Stirling, in *Strain and Its Implications in Organic Chemistry*, Kluwer, Dordrecht, 1989.
2 F. Benedetti and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1986, 605.
3 A. Greenberg and J. F. Liebman, *Strained Organic Molecules*, Academic Press, New York, 1978.
4 Y. Gaoni, *J. Org. Chem.*, 1982, **47**, 2564.
5 S. W. Roberts and C. J. M. Stirling, *J. Chem. Soc., Chem. Commun.*, 1991, 170.
6 J. T. Lumb and G. H. Whitham, *Chem. Commun.*, 1966, 400.
7 P. Gund and T. M. Gund, *J. Am. Chem. Soc.*, 1981, **103**, 4458.