The effect of strain on reactivity: poor leaving groups increase strain-induced inhibition of alkene-forming elimination

Luca Volta and Charles J. M. Stirling*

Department of Chemistry, The University, Sheffield, UK S3 7HF. E-mail: c.stirling@sheffield.ac.uk

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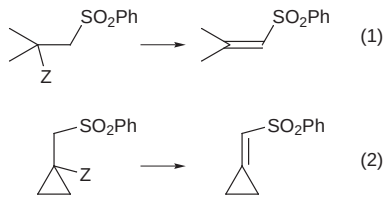
Elimination to form a carbon–carbon double bond exocyclic to a cyclopropane ring is inhibited by factors which increase from 1.4 to $10^{4.5}$ as the leaving group becomes poorer; strain induced in the transition structure can amount to some 50% of the enthalpy difference between strained and unstrained products.

The effect of strain on reactivity is a very familiar phenomenon, but one which has only rarely been quantified.[1] In order to quantify the effects of strain on reactivity properly, systems of known and defined strain energy are required (not always a simple matter) and reactions of unambiguous mechanism are also needed (not always a simple matter either). In this connection, earlier work from these laboratories has examined acceleration of 1,2-elimination by incorporation of the leaving group in a strained ring.[2–4] In such cases acceleration results from the release of strain, effectively lowering the energy of the transition structure relative to the starting material. We have also examined the effect of strain in the inhibition of higher order eliminations leading to strained ring products in which the effects of strain are remarkably variable.[5,6] Both situations have been examined theoretically[7,8] and the correlation between theory and practice is good.

We now report on the kinetics of formation of methylenecyclopropanes in activated 1,2-eliminations which reveal the impact of strain as the transition structure changes. The systems we have examined, involving five different leaving groups (Z) are in Table 1, giving rate constants for the unstrained [eqn. (1)] and strained reactions [eqn. (2)] respectively. Making the



assumption that strain energies are unaffected by substituents, the strain energy difference between substrate and product for the methylenecyclopropane systems of eqn. (2) amounts to 50 kJ mol^{-1}. This is the strain energy difference between cyclopropane and methylenecyclopropane[9] although its origin is under discussion.[10]

The open-chain halides **1** were obtained by homolytic addition of sulfonyl halides to 2-methylpropene.[11] Addition of thiophenol to the alkenyl sulfone **2** gave sulfide **3** which on oxidation gave the bis-sulfone **4** The cyclopropanes were obtained by the routes of Scheme 1. Reactions were run in ethanolic sodium ethoxide to allow direct comparisons with earlier results; the product from the open-chain substrates was the conjugated alkene **2** and non-conjugated alkene **2a**,[12] while the cyclopropanes gave the ethoxy adduct **10** from slow elimination followed by rapid addition to the electrophilic methylenecyclopropane **7**. The unlikely alternative course of direct substitution was ruled out by the piperidine test in which, for example, the bis-sulfone **9** failed to react with piperidine in ethanol (too weakly basic) but reacted rapidly with piperidine in ethanolic sodium ethoxide to give the piperidino derivative **11** (piperidine more nucleophilic than ethoxide).

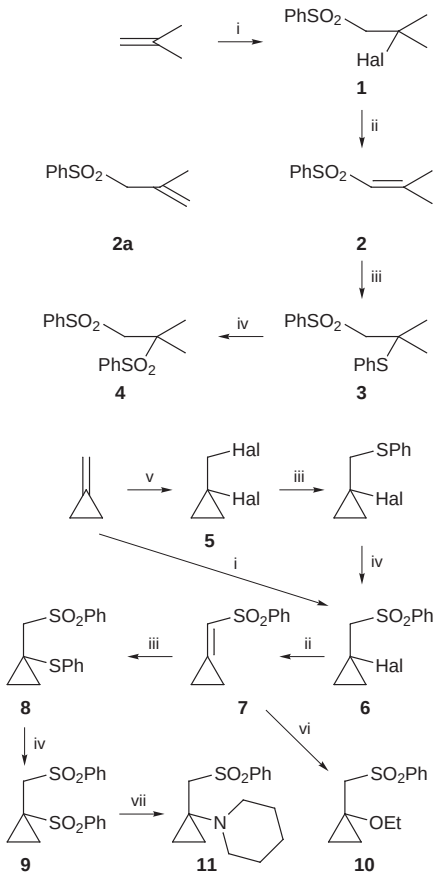
Reactions were followed by UV spectroscopy for reactions in which the product alkene was detectable and otherwise by GC. Reactions were first order in substrate and first order in base.

Before comment on the impact of strain differentials can be made, it is crucial to be certain of the mechanism of the reactions in each case. Two methods to throw light on the mechanisms have been adopted; the observed rate constants have been compared with the rates of ionisation obtained by interpolation on a Taft plot[13] of $k_{ionisation}$ in ethanolic sodium ethoxide *versus* the inductive constant σ^*. It can be seen that for the leaving groups SO_2Ph, SPh and OMe, the rate constant for ionisation is greater than the elimination rate constant. This points for each case to the $(E1cB)_R$ mechanism, in which a pre-equilibrium with the carbanion is established with the base–solvent system. The rate-determining step in each case, therefore, is the expulsion of the leaving group from the intermediate carbanion. The second procedure was to carry out reactions in EtOD and to examine by ^2H NMR spectroscopy recovered starting material for deuterium incorporation. In all of these cases, starting material had exchanged considerably with the solvent, confirming the conclusions from interpolation. By contrast, with the halogen leaving groups, the observed rate constants in all cases are close to or greater than the interpolated ionisation rate constants and no incorporation of deuterium occurred in exchange experiments. These observations point

Table 1 Elimination to form unstrained and strained alkenes

	Rate constants/mol^{-1} dm^3 s^{-1}				
	Open chain		Cyclopropane		
Z	k_{EtO^-} [a]	$k_{ion.}$ [a,b]	k_{EtO^-} [a]	$k_{ion.}$ [a,b]	k_{rel} unstrained:strained
Br	2.3×10^2	2.3×10^1	3.2×10^2	3.2×10^1	0.7
Cl	7.8×10^1	4.1×10^1	5.5×10^1	5.7×10^1	1.4
SO_2Ph	3.44	8.8×10^2	1.5×10^{-2}	1.2×10^3	230
SPh	6.6×10^{-2}	4.8×10^{-1}	1.0×10^{-5}	6.7×10^{-1}	6000
OMe	4.3×10^{-5} [c]	3.1	1.5×10^{-9} [d]	5.3×10^{-1}	29 000

[a] For reactions in EtONa–EtOH at 25 °C. [b] See text. [c] See ref. 13; [d] By extrapolation from an Arrhenius plot.



Scheme 1 *Reagents and conditions*: i, $PhSO_2Hal$, AIBN, benzene, 90 °C, 72 h; ii, Et_3N, PhMe; iii, PhSNa, EtOH; iv, H_2O_2, AcOH; v, Hal_2, THF; vi, EtONa, EtOH; vii, EtONa, EtOH, piperidine.

either to the E2 mechanism, in which departure of the leaving group is concerted with β-proton removal, or to the $(E1cB)_I$ mechanism, in which it is not. For the latter mechanism, a close similarity between k_{EtO^-} and $k_{ionisation}$ is to be expected. This is true for the chlorides, but the comparison for the bromides suggests concerted mechanisms.

For 1,2-eliminations, it can reasonably be concluded that the more difficult the leaving group is to expel, the greater is the degree of double-bond character in the transition structure required to expel it. In earlier work[14] we were able to compare accurately the leaving abilities of a series of groups placed β to a sulfonyl-stabilised carbanion. These groups included SO_2Ph, SPh and OMe in descending order of nucleofugality. Nucleofugalities of halide leaving groups could not be assigned because, as in the present work, the reactions did not follow the $(E1cB)_R$ mechanism. Our observation of probable E2 and/or $(E1cB)_I$ mechanisms for the halides mentioned above, suggests higher nucleofugalities for the halogens, as would be expected.

The results of Table 1 show that as the nucleofugality of the leaving group decreases, so the ratio of the reactivities of the unstrained to the strained substrates increases. This reveals a consistent picture in which as the nucleofugality of the leaving group decreases, so the degree of double bond character in the transition structure increases and the additional strain of the double bond exocyclic to the cyclopropane ring is increasingly felt.

This leaves the important question of the extent of strain inhibition in these reactions. In the system with the largest unstrained to strained reactivity ratio, *i.e.* with Z = OMe, the inhibition amounts to a factor of some 29,000 or about 26 kJ mol^{-1} in $\Delta G^{\ddagger}$. This amounts to about 50% of the strain energy difference between strained and unstrained products. When the leaving group is halogen, the unstrained and strained substrates have almost identical reactivities and there appears to be so little double bond character in the transition structure that reactions are little inhibited by formation of a strained alkene product.

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