Reactions at High Pressure. Part 9. The Volume Profile for the Cycloaddition of Methyl Acrylate to a Pyridinium Betaine

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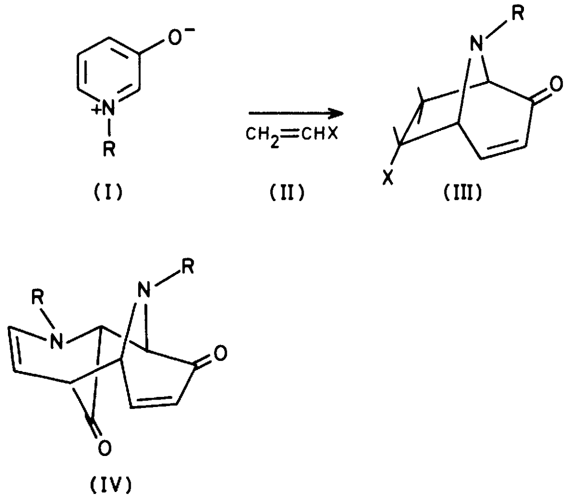
Rates of cycloaddition between *N*-(4,6-dimethylpyrimidin-2-yl)-3-hydroxypyridinium betaine and methyl acrylate in ethanol at 25° have been measured at pressures up to 1 000 bar. The volume of activation has been determined as -36 ± 2 cm^3 mol^{-1}. The volume of reaction has also been measured and found to be -37 cm^3 mol^{-1}. The characteristics of this reaction are those of a typical Diels–Alder reaction. Attempts to extend the range of dienophiles by the use of high pressure have met with only limited success.

In a series of papers, Katritzky and his co-workers[1-7] have explored the cycloadditions of 3-hydroxypyridinium betaines (I) to typical dienophiles (II). The reaction with these 2π addends occurs at the 2- and 6-positions of the pyridine ring and is regiospecific as indicated in Scheme 1 although, usually, mixtures of *exo*- and *endo*-isomers were obtained. The products (III) are tropane derivatives with potential biological activity capable of transformation to tropolones or tropones. The structural requirements of the betaine are fairly flexible; the nitrogen substituent may be alkyl or aryl and the ring may be annellated. The dienophile, on the other hand, needs an electron-withdrawing substituent which precludes the synthesis of adducts (III; X = alkyl). Cycloadditions in general are promoted by the use of high pressures. Numerous ' difficult ' Diels–Alder reactions have been accomplished by the expedient of working at 8—15 kbar [8,9] and it seemed certain that the reactions described above would respond similarly so that this approach might be profitably used to widen the scope of the reaction. The large and negative volume of activation typical of a Diels–Alder reaction (*ca.* -30 cm^3 mol^{-1}) is deemed to be characteristic of the synchronous formation of two bonds in a neutral reaction. Betaine cycloadditions, however, also contain a dipolar element in that the charges on nitrogen and oxygen are removed during product formation and this might be expected to be accompanied by electrostrictive release of solvent resulting in a volume of activation substantially less negative than this value. We therefore decided to measure the volume of activation, ΔV‡, for a typical betaine cycloaddition before embarking upon synthetic studies and for this purpose chose the reaction between (I; R = 4,6-dimethylpyrimidin-2-yl) and methyl acrylate which has previously been shown to be well behaved and to occur at a convenient rate with second-order kinetics. This betaine is readily prepared and purified and may be stored as the dimer (IV), from which monomer may be obtained by warming as required.[10,11]



Scheme 1

EXPERIMENTAL

N-(4,6-Dimethylpyrimidin-2-yl)-3-hydroxypyridinium betaine (I; R = 4,6-dimethylpyrimidin-2-yl) was prepared according to published procedures [10,11] and was initially obtained as the dimer (IV). Methyl acrylate was purified by fractional distillation prior to use and solvent ethanol was AnalaR quality (Burrough), the same batch being used for all measurements.

A solution of (IV) (2.5×10^{-4}M) in ethanol was prepared and heated to 80° for 2 min in order to dissociate the dimer (IV) to (I). This solution was then stable towards dimerisation. The reaction mixture consisted of 3.0 ml of this solution and methyl acrylate (2.0 ml), the large excess of the latter giving convenient rates at 25° and pseudo-first-order kinetics. The reaction was followed by observing the decay of the absorbance at 366 nm at $25 \pm 0.1°$. The kinetic runs at elevated pressure were carried out in a similar manner in a Nova Swiss high-pressure optical cell as described previously.[12] First-order rate constants were obtained by a Guggenheim or Swinbourne procedure [13] from absorbance measurements spanning *ca.* 70% reaction, the slopes being obtained by a least-squares fit. Values of ln *k* as a function of pressure were fitted by a least-squares procedure to a quadratic function [equation (1)]. Since

$$\ln k = A + Bp + Cp^2 \quad (1)$$

$$\Delta V^{\ddagger} = -RT\left(\frac{\partial(\ln k)}{\partial p}\right)_{p\to 0} \quad (2)$$

$$\Delta V^{\ddagger} = -BRT \quad (3)$$

equations (2) and (3) hold, the volume of activation was obtained. The results are given in Table 1 and the Figure.

The volume of reaction, $\Delta\bar{V}$, is useful in the interpretation of $\Delta V^{\ddagger}$ in terms of the progress of the reaction at the

TABLE 1

Rate constants as a function of pressure for the reaction between *N*-(4,6-dimethylpyrimidin-2-yl)-3-hydroxypyridinium betaine and methyl acrylate in ethanol at 25° [a]

p/bar	$10^{-4}\,k_1$/s^{-1}
1	4.34
100	4.85
175	5.36
300	6.11
370	6.75
510	7.93
750	8.33
1 000	9.02

[a] Uncertainty in p ±10 bar; reproducibility of k_1 *ca.* 4%; standard deviation of each individual rate constant *ca.* 1%. Constants of equation (1): A −7.775, B 0.001 493, C -8×10^{-7}. Volume of activation −36.0 cm^3 mol^{-1}.

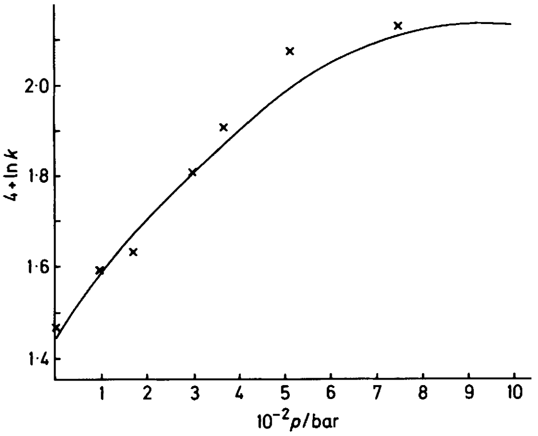


FIGURE Rate data for the reaction between (I; R = 4,6-dimethylpyrimidin-2-yl) and methyl acrylate in ethanol at 25° as a function of pressure. The line is that of the equation, $\ln k = -7.775 + 0.001\,493p - 8 \times 10^{-7}p^2$. It should be noted that the fit to this arbitrary function is not good at the high-pressure end, but at low pressure fits sufficiently well to yield a value of $\mathrm{d}\ln k/\mathrm{d}p(p \rightarrow 0)$

transition state This was measured by determining separately the partial molar volumes of reagents and product by means of density measurements of the solutions as previously described.[12] Results are given in Table 2.

TABLE 2

Partial molar volumes, $\bar{V}$, and volume of reaction, $\Delta\bar{V}$, in ethanol

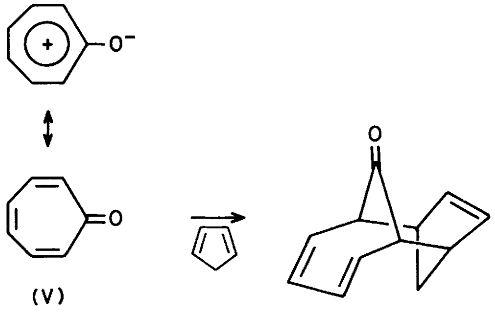
	$\bar{V}$/ cm^3 mol^{-1}
N-(4,6-Dimethylpyrimidin-2-yl)-3-hydroxypyridinium betaine	171.7
Methyl acrylate	92.2
Adduct (III; R = 4,6-dimethylpyrimidin-2-yl)	227.0
Volume of reaction	−37.0

Preparative high-pressure reactions were carried out in a piston and cylinder device hydraulically powered and capable of maintaining 14 kbar at up to 100°. All such reactions were conducted within a capsule of Teflon.

DISCUSSION

The cycloaddition reactions described appear to take place by a concerted process as judged by the entropy of activation ($\Delta S^{\ddagger}$ −36 ± 2 cal mol^{-1} K^{-1}) [8] and the insensitivity of the rate towards a change of solvent ($k_{\mathrm{CHCl_3}}/k_{\mathrm{H_2O}}$ 2.3),[1] characteristics which are typical of a normal Diels–Alder reaction. Furthermore, the application of perturbation theory to the rates of addition of compounds (I) with varying R appeared to produce a correlation with the frontier orbital term, a further characteristic of a pericyclic reaction.[14]

Our volume measurements are in agreement with this conclusion. The volume of activation, −36 cm^3 mol^{-1}, lies within the range of values characteristically exhibited by Diels–Alder reactions.[15] This may be taken as between −30 and −50 cm^3 mol^{-1}, usually only slightly solvent dependent. Such large, negative values are a consequence of the synchronous formation of two bonds. A further feature of these reactions is the similarity in the values of the volumes of activation and reaction. Indeed, the latter are often slightly less negative than the former by 1—2 cm^3 mol^{-1}. That is to say, there are a number of cases recorded of a Diels–Alder transition state which apparently occupies a smaller volume than does the product.[16] A highly compact transition state close to product is indicated with additional attractive interactions between remote parts of the two molecules. The same appears to be the case in our measurements for which $\Delta\bar{V} - \Delta V^{\ddagger} \sim -1$ cm^3 mol^{-1}. The cycloadditions of pyridinium betaines therefore appear to behave as normal Diels–Alder reactions and are evidently greatly accelerated by pressure. This contrasts sharply with the behaviour of tropone (V) which, acting as dienophile in a (4π + 6π) cycloaddition to cyclopentadiene (Scheme 2) shows only a small volume change, ($\Delta\bar{V}$ −4.3, $\Delta V^{\ddagger}$ −7.5 cm^3 mol^{-1}).[17] This was interpreted as being due to the positive component of volume change due to release of electrostricted solvent as the dipole of tropone is reduced. A similar possibility exists in the present case. The betaine undoubtedly posesses a large dipole, absent in the product, yet no such relaxation of sovent is apparent. The reason for the difference between these two cases is not apparent. The difference in solvent (the tropone reaction was carried out in dioxan) would not alone seem to account for such a large difference although it would tend to increase the electrostrictive term compared with ethanol which posesses a higher dielectric constant.



SCHEME 2

Unfortunately it is difficult to measure $\Delta V^{\ddagger}$ for our reactions in non-polar solvents since dimerisation intervenes.

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