Kinetics of the Reaction of 1-*p*-Tolylsulphonylazocyclohexene with Maleic Anhydride

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In the presence of maleic anhydride in aprotic solvents, 1-*p*-tolylsulphonylazocyclohexene undergoes in part a spontaneous transformation by a process in which free radicals are not formed as intermediates and in part enters into a cycloaddition reaction with formation of 3a,4,6,6a-tetrahydro-4,6-dioxo-3*H*-furo[3,4-*c*]pyrazole-3-spiro-cyclohex-2′-yl *p*-tolyl sulphone (II). The cycloaddition process takes place by two independent mechanisms, one first order and the other second order. In the first mechanism the formation of the ion pair (III) is rate determining: this species reacts immediately with maleic anhydride to form the adduct (II) by a [3 + 2 ⟶ 5] cycloaddition. The second mechanism is characterized by a low solvent effect, relatively high entropy of activation and activation energy, and moderate sensitivity to steric effects.

As described earlier,[1] 1-*p*-tolylsulphonylazocyclohexene (I) enters into [3 + 2 ⟶ 5] cycloadditions[2] with maleic anhydride and a number of other dipolarophiles in benzene at room temperature to form the corresponding Δ^1-pyrazolines. The structures assumed for these products were established by chemical and spectrographic methods,[1] and confirmed in one case by *X*-ray crystallographic analysis.[3]

It is also known that (I) undergoes base-catalysed isomerization in aprotic solvents to form the corresponding hydrazo-derivative, which is thermodynamically more stable.[4]

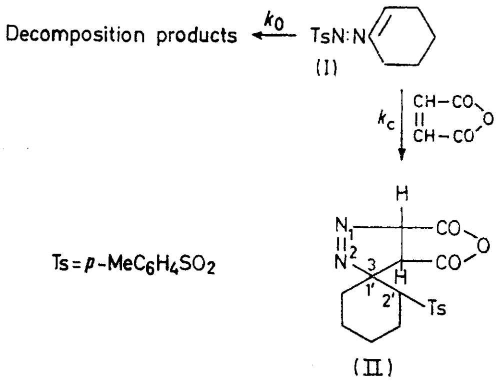
The analogous phenylazocyclohexene,[5] on the other hand, does not isomerize under the same conditions, but it enters into [4 + 2 ⟶ 6] cycloadditions[2] with formation of tetrahydropyridazines.

To help to clarify the mechanistic aspects involved in the diverse behaviour of these azoalkenes we have investigated the kinetics of the cycloaddition of (I) with maleic anhydride in various aprotic solvents; for comparison, we also examined the reactions with some other dipolarophiles in benzene.

RESULTS

Since (I) reacts spontaneously in aprotic solvents, it is necessary to consider the ' spontaneous ' reaction alongside the cycloaddition, as indicated in Scheme 1.

The constant k_0 was found[4] at three different temperatures in benzene, dioxan, chlorobenzene, and anisole, and have also been measured by us in chloroform.



SCHEME 1

The presence of free radicals as intermediates in this type of reactions has been demonstrated[6a,b] by the use of the stable free radical α,γ-bis(biphenylene)-β-phenylallyl (Koelsch's radical[7]) as a scavenger; the rate of disappearance of this radical can be conveniently measured spectrophotometrically (see Kice and Gabrielsen[6a] and references cited). When (I) was allowed to decompose in deaerated or undeaerated benzene at 25 °C in the presence of Koelsch's radical as a scavenger and in concentrations similar to those earlier,[6a] no evidence for free radicals was found. A slight

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[1] W. Barbieri, L. Bernardi, P. Masi, L. Caglioti, and G. Rosini, *Tetrahedron Letters*, 1970, 1343.

[2] R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 565.

[3] L. Caglioti, E. Foresti, and L. Riva di Sanseverino, *Tetrahedron Letters*, 1970, 1347.

[4] A. Dondoni, G. Rosini, G. Mossa, and L. Caglioti, *J. Chem. Soc.* (*B*), 1968, 1404.

[5] L. Caglioti, G. Rosini, P. Tundo, and A. Vigevani, *Tetrahedron Letters*, 1970, 2349.

[6] (*a*) J. L. Kice and R. S. Gabrielsen, *J. Org. Chem.*, 1970, **35**, 1004; (*b*) 1010.

[7] C. F. Koelsch, *J. Amer. Chem. Soc.*, 1957, **79**, 4439.

diminution in the concentration of Koelsch's radical (11% in six hours) in undeaerated benzene is probably due to dimerisation of the material.

Use of diphenyl-2-picrylhydrazyl (DPPH) as scavenger similarly indicates the absence of radical intermediates in the decomposition of (I). Thus any influence on the cycloaddition by free radicals arising from the decomposition of (I) is precluded. The decomposition of *p*-tolylsulphonylazoalkenes is being further investigated in our laboratory.

In the kinetic experiments carried out in the presence of maleic anhydride, the dipolarophile was always used in a large excess over (I). In every case the reaction is found to be first order in (I); the experimental rate constants are denoted by k_{expt}. The corresponding constant k_0 for the 'spontaneous' process is subtracted from k_{expt} to obtain the pseudo-first-order constants k_c for the cycloaddition. k_c Is a linear function of the concentration of the dipolarophile, and satisfies an equation of the type (1).

$$k_c = k_1 + k_2[\text{dipolarophile}] \qquad (1)$$

TABLE 1

Rate constants for the reaction of (I) with maleic anhydride in benzene at different temperatures

$\frac{t}{°\text{C}}$	$\frac{[\text{Maleic anhydride}]}{\text{M}}$	$\frac{10^4 k_o}{\text{s}^{-1}}$	$\frac{10^4 k_{\text{expt}}}{\text{s}^{-1}}$	$\frac{10^4 k_c}{\text{s}^{-1}}$	$\frac{10^4 (k_c)_{\text{calc.}}\,^c}{\text{s}^{-1}}$	$\frac{10^4 k_1}{\text{s}^{-1}}$	$\frac{10^4 k_2}{\text{l mol}^{-1}\,\text{s}^{-1}}$
15	0·224	0·112 [a]	0·246	0·134	0·110	0·050	0·269
	0·448		0·279	0·163	0·170		
	0·672		0·329	0·217	0·231		
	1·210		0·494	0·382	0·375		
	1·694		0·603	0·491	0·505		
25	0·040	0·404 [a]	0·554	0·150	0·142	0·100	1·06
	0·171		0·672	0·268	0·281		
	0·220		0·691	0·287	0·333		
	0·659		1·21	0·806	0·798		
	1·098		1·62	1·22	1·26		
	1·537		2·24	1·83	1·73		
	1·757		2·36	1·95	1·96		
30	0·207	0·740 [b]	1·50	0·760	0·754	0·400	1·71
	0·622		2·19	1·45	1·46		
	1·037		2·90	2·16	2·17		
	1·451		3·29	2·55	2·88		
	1·660		4·61	3·87	3·24		
35	0·171	1·25 [a]	2·46	1·21	1·36	0·800	3·30
	0·279		3·04	1·79	1·72		
	0·372		3·22	1·97	2·03		
	0·428		3·57	2·32	2·21		
	0·558		3·86	2·61	2·64		
	0·652		4·20	2·95	2·95		

[a] See ref. 4. [b] Average from four experiments at different concentrations of (I). [c] Calculated from equation (1).

We verified separately that the zero-order constant k_1 with respect to maleic anhydride does in fact lead to the required quantity of cycloaddition product by isolating the product (II) in experiments with higher molar ratios of (I) to [maleic anhydride] than those used in the kinetic experiments.

k_1 and k_2 were found as the intercept and the slope, respectively, of a graph of k_c against the molar concentration of the dipolarophile. The results for the reaction of (I) with maleic anhydride in benzene at various temperatures are shown in Table 1.

The activation parameters, obtained in the usual way,[8] are: $E = 22{\cdot}1 \pm 0{\cdot}5$ kcal mol^{-1}, $\Delta S^{\ddagger} = -4{\cdot}7 \pm 1{\cdot}5$ cal mol^{-1} K^{-1}, $\Delta G^{\ddagger} = 22{\cdot}9$ kcal mol^{-1} (at 25 °C).

To investigate the effect of the solvent on the rate of cycloaddition, we carried out experiments in dioxan, anisole, chlorobenzene, and chloroform as well as in benzene. Chloroform was used in addition to the other solvents for which the k_0 values were known[4] because this solvent, unlike the others examined, does not give charge transfer complexes with maleic anhydride.[9]

The k_0 value found in chloroform is higher by a factor of 5—10 than those found in the other solvents;[4] this shows that the decomposition is not so insensitive to variation of the solvent as was formerly thought.[4] To avoid the possibility of acid catalysis, the chloroform used was rigorously purified, and an experiment carried out in the presence of suspended calcium oxide gave the same value for k_0, within the limits of experimental error. Table 2 shows the results obtained at 25 °C in various solvents.

To obtain an indication of the influence of steric factors on the rate of addition to geometrically isomeric alkenes, we allowed (I) to react with dimethylmaleic anhydride, diethyl maleate, and diethyl fumarate in benzene at 25 and 35 °C. The results are shown in Table 3.

k_1 Values have little significance since the straight line plots and hence the intercepts are based on too few data points and since the low reactivity made it necessary to use very high concentrations of the dipolarophiles, so that the solvent cannot be considered as simply 'benzene'; we were nevertheless able to establish a scale of reactivity (k_2) for the dipolarophiles examined: maleic anhydride > dimethylmaleic anhydride > diethyl maleate > diethyl fumarate. However, the differences in the rates are not large (the range is covered by a factor of 15).

The cycloaddition products were characterized chemically and are described in the Experimental section for maleic

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[8] S. Glasstone, K. J. Laidler, and H. Eyring, 'Theory of Rate Processes,' McGraw-Hill, New York, 1941.

[9] L. J. Andrews and R. M. Keefer, *J. Amer. Chem. Soc.*, 1953, **75**, 3776.

TABLE 2

Rate constants for the reaction of (I) with maleic anhydride in various solvents at 25 °C

Solvent	[Maleic anhydride] M	10^4k_0 s^{-1}	10^4k_{expt} s^{-1}	10^4k_c s^{-1}	$10^4(k_c)_{calc.}$ [d] s^{-1}	10^4k_1 s^{-1}	10^4k_2 $l\ mol^{-1}\ s^{-1}$
Dioxan	0·196	0·545 [a]	0·737	0·192	0·182	0·025	0·790
	0·393		0·912	0·376	0·335		
	0·590		1·06	0·520	0·491		
	0·789		1·16	0·620	0·648		
	1·179		1·52	0·977	0·956		
	1·572		1·74	1·19	1·27		
Benzene [b]						0·100	1·06
Anisole	0·193	0·889 [a]	1·09	0·200	0·197	0·020	0·915
	0·386		1·32	0·430	0·373		
	0·409		1·24	0·350	0·394		
	0·772		1·66	0·770	0·726		
	1·115		1·86	0·980	1·04		
	1·300		2·05	1·16	1·21		
	1·740		2·47	1·58	1·61		
Chloroform	0·168	3·91 [c]	5·09	1·18	1·18	0·800	2·25
	0·173		5·11	1·20	1·19		
	0·346		5·62	1·71	1·58		
	0·420		5·42	1·51	1·74		
	0·589		6·20	2·29	2·12		
	0·778		6·34	2·43	2·55		
Chlorobenzene	0·103	0·670 [a]	0·828	0·158	0·149	0·020	1·25
	0·206		0·946	0·276	0·277		
	0·310		1·08	0·410	0·411		
	0·401		1·25	0·580	0·521		
	0·413		1·15	0·480	0·536		
	0·619		1·38	0·710	0·794		
	0·801		1·73	1·06	1·02		
	0·826		1·64	0·97	1·05		
	1·202		2·24	1·57	1·52		

[a] See ref. 4. [b] From Table 1. [c] Average from four experiments at different concentrations of (I). [d] Calculated from equation (1).

TABLE 3

Rate constants for the reaction of (I) with some dipolarophiles in benzene at 25 and 35 °C

Dipolarophile	t °C	[Dipolarophile] M	10^4k_{expt} s^{-1}	10^4k_c s^{-1}	$10^4(k_c)_{calc.}$ [a] s^{-1}	10^4k_2 $l\ mol^{-1}\ s^{-1}$
Dimethylmaleic anhydride	25	0·137	0·469	0·065	0·0647	0·472
		0·412	0·605	0·201	0·194	
		0·687	0·720	0·316	0·324	
	35	0·101	1·51	0·256	0·248	1·22
		0·203	1·58	0·327	0·373	
		0·520	1·84	0·590	0·515	
		0·609	2·04	0·784	0·868	
		0·800	2·37	1·12	1·10	
Diethyl maleate	25	0·348	0·452	0·048	0·037	0·107
		0·525	0·471	0·069	0·056	
		0·871	0·490	0·087	0·093	
		1·114	0·502	0·098	0·119	
		1·67	0·605	0·201	0·179	
	35	0·348	1·32	0·025	0·094	0·27
		0·871	1·46	0·21	0·235	
		1·22	1·60	0·35	0·329	
Diethyl fumarate	25	0·450	0·447	0·043	0·041	0·0687
		0·750	0·457	0·053	0·061	
		1·05	0·488	0·084	0·081	
	35	0·300	1·57	0·320	0·308	0·143
		0·871	1·64	0·390	0·418	
		1·16	1·73	0·480	0·474	

[a] Calculated from equation (1).

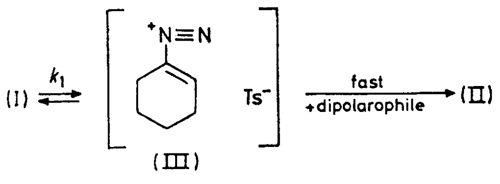
anhydride and diethyl fumarate. For the other two dipolarophiles we have assumed that apart from the spontaneous decomposition, the disappearance of (I) occurs exclusively by cycloaddition.

DISCUSSION

We conclude from the above results that the cycloaddition of (I) proceeds by two concurrent and independent mechanisms. The first, which particularly at high dipolarophile concentrations, makes the smaller contribution to the total cycloaddition, is first order and the rate constants for this mechanism are denoted by k_1. The second, whose rate constants are denoted by k_2, is second order.

It is known [10] that the dissociation equilibrium of the diazo-sulphones is almost completely displaced to the left, even in a polar protic solvent such as methanol.

It is thus reasonable to believe that the cycloadduct is formed by the interaction of the maleic anhydride with the ion pair intermediate (III),[11] whose formation (k_1) is the rate-determining step of the reaction.



SCHEME 2

Since ionic species are involved in this unimolecular mechanisms, k_1 should be sensitive to variation of the solvent, whereas it should be insensitive to variation of the dipolarophile, which participates in the fast step of the process. Though only the order of magnitude of k_1 is significant with maleic anhydride as the dipolarophile, while k_1 is of practically no significance for the other dipolarophiles, the results seem to confirm this supposition. In particular, on going from dioxan to chloroform, k_1 varies by a factor of >30, whereas k_2 varies by a factor of <3.

The bimolecular mechanism, which predominates under our conditions, is unusual in comparison with the typical [11] $[3 + 2 \longrightarrow 5]$ cycloaddition to which it formally corresponds. This is obvious on comparison of the slightly negative value found for $\Delta S^\ddagger$ with the characteristic values,[11] which are generally strongly negative ($\Delta S^\ddagger \leqslant -25$ cal mol^{-1} K^{-1}), and also in view of the high activation energy of the reaction in relation to the value expected [11] for a concerted process. The rate of addition of (I) to maleic anhydride does not appear to be influenced by whether the latter is free, as in chloroform, or held [9] in a charge transfer complex as in the other solvents examined.

The values of k_2 for the other dipolarophiles show that the reaction is only slightly influenced by steric effects, whereas it is known [11] that the rates of concerted processes are often dramatically affected by these factors. Moreover, the geometric isomers, fumaric and maleic esters, give a k_{trans}/k_{cis} value of approximately 0·7, which is small and opposite to the values found [11] in $[3 + 2 \longrightarrow 5]$ cycloadditions.

EXPERIMENTAL

Instruments.—^{1}H N.m.r. spectra were recorded with a JEOLCO C-60 HL machine, with tetramethylsilane as an internal standard. I.r. spectra were recorded with a Perkin-Elmer model 337 spectrophotometer.

Materials.—Chloroform was passed through an alumina column and then through 4 A molecular sieves and was distilled under nitrogen. Analytical grade solvents were purified by standard methods [12] and distilled through a Vigreux column (2 m) under nitrogen. Koelsch's radical was synthesized as described [7] and DPPH was commercial.

Dipolarophiles.—Maleic anhydride was purified by dissolution of commercial product (20 g) in anhydrous benzene (100 ml). After filtration, the filtrate was evaporated to dryness. Evaporation was repeated twice to eliminate traces of maleic acid present. The product was crystallized from anhydrous chloroform. This procedure was followed for dimethylmaleic anhydride. Commercial diethyl maleate and diethyl fumarate were purified by vacuum distillation.

1-p-*Tolylsulphonylazocyclohexene* (I).—This was prepared as described.[13] It was further purified by dissolution of 1·0 g in ether (50 ml) and a few drops of benzene. The yellow solution was rapidly filtered, and n-hexane was added until crystals formed which were then filtered off and dried under vacuum, m.p. 59—61 °C (decomp.).

Cycloaddition of 1-p-*Tolylsulphonylazocyclohexene and Maleic Anhydride in Benzene.*—Compound (I) (0·527 g) was dissolved in anhydrous benzene (25 ml) and maleic anhydride (1·5 g) was added. The mixture was left in a thermostatically controlled bath at 35 ± 0·1 °C for 1 day. After concentration on a Rotavapor, the crystalline precipitate which formed was filtered off, washed with benzene and then with ether, and dried. 3a,4,6,6a-*Tetrahydro*-4,6-*dioxo*-3H-*furo*[3,4-c]*pyrazole*-3-*spirocyclohex*-2′-*yl* p-*tolyl sulphone* (II) (0·386 g) was obtained. The product was crystallized from dichloromethane–hexane, m.p. 161—162 °C, $\lambda_{max.}$ (EtOH) 290 nm (ε 10,000), $\nu_{max.}$ (KBr) 1850, 1775 (five membered anhydride), 1300, 1150 (sulphone), and 820 (p C_6H_4) cm^{-1}. δ [$(CD_3)_2SO$] 7·4 (4H, q, AA′BB′, J_{AB} 9 Hz, p-C_6H_4), 6·29 (1H, d, J 9 Hz), 4·49 (1H, d, J 9 Hz), 4·30 (1H, m, J_{aa} 12, J_{ae} 4 Hz, C*H*Ts), 2·35 (3H, s, ArCH_3), and 1·2—2·2 (8H, m, 4 × CH_2) (Found: C, 56·45; H, 5·5; N, 7·6. $C_{17}H_{18}N_2O_5S$ requires C, 56·35; H, 5·0; N, 7·75%).

Cycloaddition of 1-p-*Tolylsulphonylazocyclohexene and Diethyl Fumarate in Benzene.*—Compound (I) (2·028 g) was added to freshly distilled diethyl fumarate (2·682 g) dissolved in anhydrous benzene (10 ml). After stirring for 5 h, the mixture was eluted with cyclohexane–ethyl acetate (1 : 1 v/v) through a silica gel (0·05—0·2 mm) column. Two fractions were collected; a pure cycloaddition product was obtained from the former and two isomers were isolated by recrystallization (cyclohexane–ethyl

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[10] C. D. Ritchie, J. D. Saltiel, and E. S. Lewis, *J. Amer. Chem. Soc.*, 1961, **63**, 4601.

[11] R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 633.

[12] A. Weissberger, ' Technique of Organic Chemistry,' Interscience, New York, 1955, vol. VII.

[13] L. Caglioti, P. Grasselli, F. Morlacchi, and G. Rosini, *Chem. and Ind.*, 1968, 25.

acetate) from the latter. The structures of these isomers are still under investigation.

Kinetics.—The reactions were carried out in the cells of Unicam SP 800 or Unicam SP 700 spectrophotometers thermostatically maintained at the desired temperature ±0·15 °C. The disappearance of *ca.* $1{\cdot}5 \times 10^{-2}$M-(I) was recorded at the wavelength of maximum absorption in the visible region. In anisole, to compensate for the strong absorption due to the charge transfer complex[9] between the solvent and maleic anhydride, maleic anhydride was introduced into the reference cell in a concentration equal to that used in the other cell. The optical density at the end of the reaction was very close to zero, and the rate constants were calculated from the slope of the straight-line plot of log $(D_t - D_\infty)$ against t as described earlier.[4]

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