Kinetics and Mechanism of the *ortho*-Claisen Rearrangement of Allyloxynaphthoquinones

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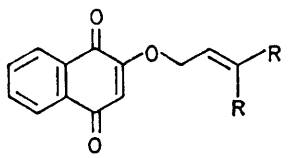
The kinetics of the Claisen rearrangements of the allyloxynaphthoquinones (1)—(3) are reported for a range of solvents, and activation parameters are calculated for rearrangements in solvents of different types. The Claisen rearrangement in protic solvents is shown to differ in mechanism from that in aprotic solvents. The relative ease of the rearrangements of (1)—(3) is discussed in relation to earlier predictions, and a transition-state model suggested on the basis of the observed solvent and structure effects. These studies are of relevance to the problem of the Claisen rearrangement in biological systems, and suggest that caution should be exercised in the design and interpretation of biosynthetic experiments in this area.

THE Claisen rearrangement of allyl phenyl or allyl vinyl ethers is a [3,3] sigmatropic process, and as such has generally been regarded as being insensitive to solvent



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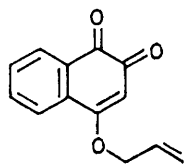

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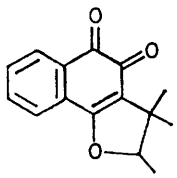

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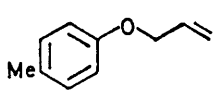

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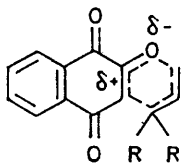

(6)

conditions, and to structural changes in the reactant.[1] Nevertheless there exist in the literature indications that changes in solvent,[2] or in structure,[2b,c, 3] can result in changes of rate constant of the order of several hundred for Claisen rearrangements. Even more striking is the recent demonstration that Claisen rearrangements can be enhanced by a factor of 10^5 when carried out in trifluoroacetic acid.[4] In this paper, we report the results of a systematic kinetic investigation of the effect of solvent on the rate of Claisen rearrangement of the allyloxynaphthoquinones (1)—(3), and discuss the implications of solvent and structural effects with regard to transition-state models of the Claisen rearrangement.

EXPERIMENTAL

Materials.—Dimethyl sulphoxide, hexamethylphosphoramide, and diethylene glycol dimethyl ether were each dried by refluxing over calcium hydride, and then distilled at 8 mmHg. Acetophenone was fractionated at atmospheric pressure.

2-Allyloxy-1,4-naphthoquinone (1),[5] 4-allyloxy-1,2-naphthoquinone (2),[5] and 2-(3,3-dimethylallyloxy)-1,4-naphthoquinone (3) [6] were synthesised by standard methods and recrystallised at least twice before use. Each ether was found to be pure by t.l.c. using both toluene–ethyl acetate (5 : 1) and toluene–ethanol (40 : 1) as solvents.

Kinetic Methods.—The Claisen rearrangement reactions

[1] For recent reviews see (*a*) S. J. Rhoads in 'Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, 1967, vol. 1, p. 655; (*b*) A. Jefferson and F. Scheinmann, *Quart. Rev.*, 1968, 391.

[2] (*a*) J. F. Kincaid and D. S. Tarbell, *J. Amer. Chem. Soc.*, 1939, **61**, 3085; (*b*) H. L. Goering and R. R. Jacobsen, *ibid.*, 1958, **80**, 3277; (*c*) W. N. White, D. Gwynn, R. Schilitt, C. Girard, and W. K. Fife, *ibid.*, p. 3271; (*d*) W. N. White and E. F. Wolfarth, *J. Org. Chem.*, 1970, **35**, 2196.

[3] (*a*) S. Marcinkiewicz, J. Green, and P. Mamailis, *Tetrahedron*, 1961, **14**, 208; (*b*) W. N. White and C. D. Slater, *J. Org. Chem.*, 1962, **27**, 2908; (*c*) W. N. White and W. K. Fife, *J. Amer. Chem. Soc.*, 1961, **83**, 3846; (*d*) W. N. White and B. E. Norcross, *ibid.*, pp. 1968, 3265; (*e*) W. N. White and E. F. Wolfarth, *J. Org. Chem.*, 1970, **35**, 3585.

[4] U. Svanholm and V. D. Parker, *Chem. Comm.*, 1972, 645.

[5] L. F. Fieser, *J. Amer. Chem. Soc.*, 1926, **48**, 3201.

[6] R. G. Cooke, *Austral. J. Sci. Res.*, 1950, **3A**, 481.

of (1)—(3) were followed by spectrophotometry using a Unicam SP 600 spectrophotometer at 484 nm, where the sodium salts of the 3-allyl-2-hydroxy-1,4-naphthoquinone products showed maximum absorption (ε 3×10^3 l mol^{-1} cm^{-1}). The reactant ethers showed less intense absorption at 484 nm (ε 2×10^2 l mol^{-1} cm^{-1}) and the ethers and their rearrangement products were found to obey Beer's Law over the concentration ranges used. Samples of the reaction mixtures were analysed by dilution with methanolic sodium methoxide solution ($2{\cdot}5 \times 10^{-2}$M) and measurement of the absorption at 484 nm against a reference containing the same concentration of methoxide in methanol. The reactions were normally followed to at least five half-lives, but accurate values for the optical density at infinite time were not normally obtained experimentally, and the first-order rate constants were therefore calculated by the method of Guggenheim,[7] using a Gugen programme on an NCR-Elliot 413a computer. Duplicate runs showed that the uncertainty in the calculated first-order rate constants is always $<5\%$ and generally $<2\%$. The values of activation parameters were calculated from the Eyring equation for unimolecular reactions.[8] At the end of each run t.l.c. in two solvent systems (above) was used to check that only products formed by Claisen rearrangement were present in addition to starting material. Trace amounts of ($<1{\cdot}0\%$) of parent phenol or of ring-closed Claisen rearrangement products are detectable by this method.

RESULTS

The Claisen rearrangements of the ethers (1)—(3) were found to give good straight line plots of $\log_e\Delta$ (optical density) *vs.* time, and were insensitive to a five-fold change in concentration. The calculated rate constants are given in Table 1. Addition of inorganic salts to the reaction of (2) generally showed no kinetic effect, although the addition of alkali metal halides to solutions of (2) in dimethyl sulphoxide resulted in predominant dealkylation. Otherwise dealkylation products were not observed.

The activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the rearrangements are given in Table 2. These were calculated for rearrangements of (1)—(3) in at least two different solvents each, in order that changes in the parameters with solvent type (non-polar, polar aprotic, and protic) could be assessed. The range of solvent was limited, partly because of solubility factors, which were especially pronounced for (3), and partly because of the sensitivity of 3,3-dimethylallyl ethers to acidic media, and of quinones to basic solvents containing nucleophilic groups (*e.g.* amines).

DISCUSSION

The ethers (1)—(3) were selected for a kinetic analysis of the Claisen rearrangement because the 3,3-dimethylallyl ether (3) was being used as part of a programme directed towards the question of the Claisen rearrangement in the biosynthesis of the plant pigment dunnione (4).[9] The kinetics of the rearrangement of allyl ethers of naphthoquinones are also of interest in view of the prediction [3a] that allyloxyquinones should have very low enthalpy of activation, *ca.* 5 kcal mol^{-1}.

Solvents Effects.—The rate data in Table 1 clearly indicate that the rate constants of the Claisen rearrangement of the ethers (1)—(3) are not greatly dependent upon solvent. For example, a factor of two covers the rate variation for 4-allyloxynaphthoquinone (2) at $90{\cdot}2 \pm 0{\cdot}1$ °C in four different solvents. Whilst

TABLE 1

First-order rate constants for the rearrangement of naphthoquinone ethers

Substrate	Solvent	10^3 Conc./M	Temp./°C	10^5k/s^{-1}	Error (%)
(1)	2-Ethoxyethanol	6·5	90·2	1·97	3·0
		6·5	113·9	11·3	1·4
		6·5	116·8	14·7	0·9
		6·5	119·4	17·3	0·5
		6·5	120·4	20·0	1·0
		6·5	130·2	36·2	1·3
	Dimethyl sulphoxide	6·5	90·1	1·55	0·5
		6·5	115·7	17·0	0·8
		6·5	121·7	30·2	0·6
		6·5	130·1	63·8	1·2
	Decalin	6·5	97·9	1·03	0·5
		6·5	115·8	5·58	1·5
		6·5	123·0	12·1	1·2
		6·5	135·1	31·5	1·6
(2)	2-Ethoxyethanol	6·5	90·1	1·58	1·7
		8·6	110·5	9·46	0·7
		15·5	110·5	9·05	1·2
		2·5	110·5	10·9	1·8
		6·5	113·9	14·1	1·8
		6·5	117·8	17·7	0·8
		3·2	120·3	25·3	0·8
		15·5	120·3	23·3	2·1
		6·5	130·2	51·2	1·8
	Acetophenone	6·5	90·3	1·13	0·5
		6·5	115·8	12·3	3·0
		6·5	130·0	42·1	0·4
	Dimethyl sulphoxide	6·5	90·1	1·95	1·2
		6·5	115·7	22·2	0·8
		6·5	130·0	71·8	3·0
	Hexamethyl-phosphoramide	6·5	90·5	1·41	3·0
		6·5	115·7	13·0	3·0
(3)	2-Ethoxyethanol	6·5	60·7	1·77	0·6
		6·5	80·1	11·2	5·0
		6·5	87·2	17·8	0·9
		6·5	90·8	25·6	0·9
		6·5	92·9	31·2	0·7
		6·5	99·3	62·5	2·0
	Dimethyl sulphoxide	6·5	60·7	1·68	1·6
		6·5	90·4	29·6	2·3
		6·5	99·3	58·6	0·8

TABLE 2

Activation parameters for the rearrangement of naphthoquinone ethers

Substrate	Solvent	Temp. range/°C	$\Delta H^{\ddagger}$/kcal mol^{-1} [a]	$\Delta S^{\ddagger}$/cal mol^{-1} [b]
(1)	2-Ethoxyethanol	90—130	20·52	−24·0
	Decalin	90—130	27·15	−8·6
	Dimethyl sulphoxide	90—130	26·27	−8·6
(2)	2-Ethoxyethanol	90—130	24·63	−13·1
	Acetophenone	90—130	25·75	−10·7
	Dimethyl sulphoxide	90—130	25·60	−9·9
(3)	2-Ethoxyethanol	60—90	21·43	−16·3
	Dimethyl sulphoxide	60—90	22·19	−14·0

[a] Error in $\Delta H^{\ddagger}$ 0·75 kcal mol^{-1}. [b] Error in $\Delta S^{\ddagger}$ 1·5 cal K^{-1} mol^{-1}.

[7] E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

[8] K. J. Laidler, 'Chemical Kinetics,' McGraw-Hill, London, 1965, p. 89.

[9] J. R. Price and R. Robinson, *J. Chem. Soc.*, 1939, 1522; 1940, 1493.

these data appear to confirm the literature generalisations about solvent effects, some recent work by White and Wolfarth indicates that the solvent effect on the rearrangement of the typical aryl ether, allyl *p*-tolyl ether (5), can be as large as 300 fold.[2d] In general, these rate enhancements appear to be associated with the presence of OH groups in the solvent, and the spectacular enhancement found in trifluoroacetic acid may be regarded as a special case of this type,[4] although it has not been disclosed whether the allyl group inverts during rearrangement, *i.e.* whether the process is in fact sigmatropic.

However, an examination of the activation data presented in Table 2 shows that the relative consistency in rate of rearrangement of the naphthoquinone ethers in different solvents is largely a consequence of the tendency of changes in $\Delta S^{\ddagger}$ to cancel the effect of changes in $\Delta H^{\ddagger}$. This is particularly true of 2-allyloxy-1,4-naphthoquinone (1), *e.g.* its rearrangement in ethoxyethanol and in dimethyl sulphoxide. Qualitatively similar trends have been commented upon by White and Wolfarth, who concluded that there was no change in the mechanism of the Claisen rearrangement when carried out in protic media, as against aprotic media.[2d] Unfortunately they used a plot of $\Delta H^{\ddagger}$ against $\Delta S^{\ddagger}$ as their criterion, in the same fashion as Leffler originally suggested for the detection of an isokinetic relationship.[10] At least two subsequent independent studies [11,12] of the isokinetic relationship have resulted in the conclusion that simple plots of $\Delta H^{\ddagger}$ against $\Delta S^{\ddagger}$ are not an adequate indication of a common mechanism in the study of reaction series, probably because they are both derived from the same kinetic data *via* the Eyring equation. Petersen [12b] has suggested that a plot of log k/T *vs.* $1/T$ would provide a much better test for a continuity of mechanism, and when this is applied to the data of White and Wolfarth on the Claisen rearrangement of allyl *p*-tolyl ether (5), as in Figure 1, it is clear that the mechanism of these reactions is not independent of solvent. Using Peterson's correlation,[12b] an isokinetic relationship should result in a common point of intersection for the plots of members of a reaction series, and clearly no such single point exists in Figure 1.

The data of Table 1 show that in general the rate of the Claisen rearrangement of naphthoquinone ethers is increased by using polar or hydroxylic solvents. White and Wolfarth have correlated [2d] a similar trend for allyl *p*-tolyl ether (5) with the *Z* factor of Kosower,[13] a measure of solvent polarity, and have shown that non-polar, polar, and protic solvents all fit this correlation. We believe that this conceals a difference between the rearrangements in protic solvents and in aprotic solvents, discussed above. The problem of correlating a bulk property, such as solvent polarity, with kinetic data from reactions in solution is a common one, but we feel that in the case of the Claisen rearrangement, a more satisfactory relationship comes from a plot of log *k* against the reciprocal of dielectric constant.[14] Although this treatment is open to the objection that the rate data and dielectric constants are not measured at the same temperature (a similar limitation on the *Z* factor correlation was also expressed by White and Wolfarth [2d]) it does permit a clear distinction between rates obtained in protic solvents and those obtained in aprotic solvents. Again the extensive data of White and Wolfarth on (5) gives a good illustration of this point, and this is presented in Figure 2. The

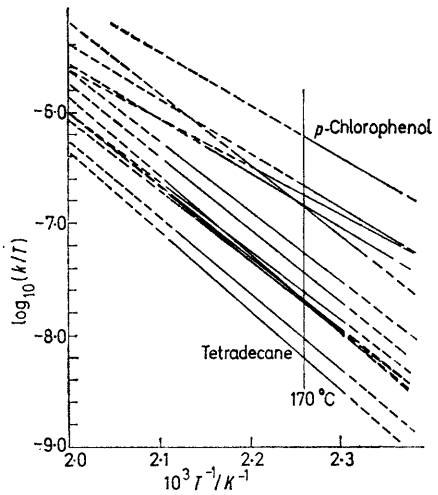

FIGURE 1 Plots of $\log_{10}(k/T)$ *vs.* $1/T$ for the solvent effect on the rearrangement of (5) (from ref. 2*d*)

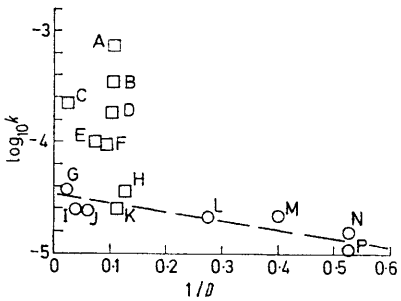

FIGURE 2 $\log_{10} k$ against $1/D$ for the rearrangement of (5) in various solvents. Rate constants were determined at 185 °C, dielectric constants at around room temperature. □, Hydroxylic solvents; ○, non-hydroxylic solvents: A, *p*-chlorophenol; B, phenol; C, *p*-cresol; D, ethylene glycol; E, benzyl alcohol; F, octan-1-ol; G, sulpholan; H, decan-1-ol; I, benzonitrile; J, acetophenone; K, methyl salicylate; L, diphenyl ether; M, diphenylmethane; N, decalin; P, tetradecane (data from refs. 2*b* and *d*)

plot of log *k* *vs.* $1/D$ shows approximate linearity for aprotic solvents, but the protic solvents all give rates in excess of expectation on the basis of their dielectric constants. Once again this indicates that an additional, favourable factor is operating in Claisen processes in protic solvents.

[10] J. E. Leffler, *J. Org. Chem.*, 1955, **20**, 1202.
[11] O. Exner, *Coll. Czech. Chem. Comm.*, 1964, **29**, 1094; 1972, **37**, 1425.
[12] (*a*) R. C. Petersen, J. H. Markgraf, and S. D. Ross, *J. Amer. Chem. Soc.*, 1961, **83**, 3819; (*b*) R. C. Petersen, *J. Org. Chem.*, 1964, **29**, 3133.
[13] E. M. Kosower, *J. Amer. Chem. Soc.*, 1958, **80**, 3253, 3261, and 3267.
[14] Ref. 8, p. 198.

Structural Effects.—It has been known for a long time that allyloxynaphthoquinones undergo a more ready Claisen rearrangement than simple allylic aryl ethers, and this trend has been quantified in terms of two parameters, the bond order and the free valence, associated with the vinyl portion of the ether.[3a] On this basis, the same authors predicted a value of 5 kcal mol^{-1} for $\Delta H^{\ddagger}$ for the rearrangement of quinone ethers, such as (1)—(3).[3a] This prediction is not confirmed by our results, shown in Table 2. It seems likely that the failure of this prediction results from the use of Hückel parameters for parent hydrocarbons, which do not necessarily parallel those of their allyloxy-derivatives. Of the two parameters used in this correlation, the free valence of substituted hydrocarbons seems to depend greatly on the nature of the substituent.[15] The π bond order of substituted hydrocarbons on the other hand

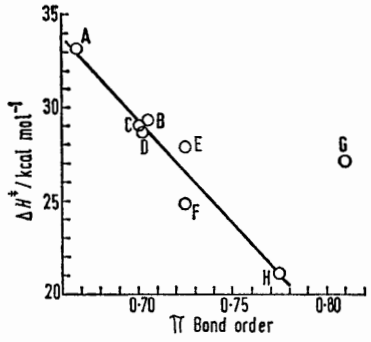

FIGURE 3 Enthalpy of activation *vs.* π bond order of parent compound for the rearrangement of allyl ethers in saturated hydrocarbon solvents: A, 4-allyloxytoluene; B, 2-allyloxyphenanthrene; C, 8-allyloxyquinoline; D, 3-allyloxyphenanthrene; E, 2-allyloxynaphthalene; F, 1-allyloxynaphthalene; G, 2-allyloxy-1,4-naphthoquinone; H, 9-allyloxyphenanthrene

is not too dependent upon the nature of the substituent, and an extrapolation from a parent hydrocarbon to an allyloxy-derivative seems to be reasonable.[15] In Figure 3 the variation of $\Delta H^{\ddagger}$ with bond order is examined for the rearrangement in saturated hydrocarbon solvents of a number of allyloxy aryl ethers, and a fair correlation is obtained. However, the correlation fails for the quinone ethers used in the present study. It is known that a linear correlation exists between π bond order and bond delocalisation energy,[16] and the relationship shown in Figure 3 therefore implies that π bond localisation has to occur before the Claisen rearrangement can occur. A similar argument has been described by Streitwieser in a discussion of the selective rearrangement of 2-allyloxynaphthalene to give 1-allyl-2-naphthol.[17]

The deviation of the naphthoquinone ethers from the linear relationship of Figure 3, implies that some other factor is operating in their rearrangement, and this will be discussed in the next section.

Transition-state Models.—While it has been recognised for some time that the transition state of the Claisen rearrangement involves a degree of charge separation,[2b,2c,3b] a generally accepted rationalisation of solvent and aromatic substituent effects has not appeared.[1a] One of the reasons for this is that a literal interpretation of Hammett-type data is difficult when the rate changes involved are small, and this point has been developed by Rhoads.[1a]

We believe that the present results are best rationalised in terms of a transition-state model in which the oxygen has accumulated charge, and the aromatic ring is electron deficient, as in (6). Thus, the rate enhancements observed in protic solvents can readily be accounted for by their ability to hydrogen bond to the electron-rich oxygen. This would be expected to cause a lowering of $\Delta H^{\ddagger}$, but would also result in a more ordered transition state, and hence an increase in $\Delta S^{\ddagger}$. Similarly, one can rationalise the fact that the ethers (1)—(3) do not rearrange as easily as would be anticipated on grounds of their π bond orders. If there is positive charge developing over the aromatic carbons in the transition state, then a quinone system, normally regarded as electron deficient, is not likely to be capable of efficient spread of this charge. In fact one might expect less charge separation in these transition states than in those derived from normal benzenoid ethers, and this could well explain the significantly decreased solvent effect observed with the quinone ethers. It will be clear, however, that other factors may also be responsible for the failure of quinone ethers to fit the correlation of Figure 3, and further investigation of this point seems desirable.

The possibility of a gradual change in Claisen rearrangement mechanism in response to solvent and structural variations has been discussed by Rhoads,[1a] and the data described here, together with the recent report of catalysis by trifluoracetic acid, serve to strengthen this viewpoint. Indeed Streitwieser has come to analogous conclusions on more theoretical grounds.[17]

Relevance to Biological Systems.—As mentioned above, one of the reasons for investigating the kinetics of the Claisen rearrangement of quinone ethers was that (3) was being used in biosynthetic studies of the plant pigment dunnione (4). Extrapolation of the present data to biological temperatures implies that the rate of spontaneous rearrangement of (3) (*i.e.* without enzymic catalysis) could be significant under the conditions of a biosynthetic experiment. Although this extrapolation is extremely crude, it indicates that the erroneous interpretation of tracer experiments is a possibility that should be guarded against.

[1/2693 *Received*, 28*th November*, 1972]

[15] C. A. Coulson and A. Streitwieser, 'Dictionary of π-Electron Calculations,' Pergamon, London, 1965.
[16] A. Pullman and B. Pullman, *Adv. Cancer Res.*, 1955, **3**, 1.
[17] A. Streitwieser, 'Molecular Orbital Theory for Organic Chemists,' Wiley, New York, 1961, pp. 445—448.