

Vibrational Activation. 2.¹ Acceleration of Bond-Making Reactions by Solvent Viscosity as a Model for Enzymic Catalysis. The Claisen Rearrangement and the Diels-Alder Reaction

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The vibrational activation theory holds that enzymes catalyze reactions in part by simply immobilizing the reactants. Typical bond-making reactions should then go faster at high viscosities. This prediction has now been verified for two different reactions. At 138 °C the Claisen rearrangement of phenyl allyl ether goes at relative rates of 1.00, 0.98, 1.13, and 1.36 in *n*-octane, isooctane, *n*-octacosane, and Nujol, whose relative viscosities at 100 °C are 1.00, 0.94, 4.92, and 11.8, respectively. The relationship is linear with slope 0.041. Addition of polyethylene to the Nujol raises the relative viscosity to 48.5 and the relative rate to 1.70. The intramolecular Diels-Alder cyclization of *N*-propargyl-9-anthraamide at 100 °C goes at relative rates 1.00, 1.16, 1.25, and 1.38 in mono-, di-, tri- and tetraglyme, whose relative viscosities at 100 °C are 1.00, 1.28, 1.54, and 1.99, respectively. The relationship is again linear, with slope 0.37. In addition, the following examples from the literature are analyzed in terms of viscosity-induced accelerations: the dimerization of cyclopentadiene, pressure-accelerated reactions where $[-\Delta V^\ddagger] > [-\Delta V]$ and liquid/gas rate ratios are >1 . A test of the theory that the liquid/gas phenomenon stems from hyperpolarizability of the transition state was made by measuring Claisen relative rates in five solvents of widely varying refractive indices. No relationship between rate and solvent polarizability was found.

Conventional kinetic theory has little to say about the effect of viscosity on reaction rates. Collision-controlled reactions should have rates independent of viscosity,² and encounter-controlled ones should, in the limiting case, have rates inversely proportional to viscosity;^{2,3} the latter are termed diffusion-controlled, or solvent-caged. Thus a typical bond-making reaction, either bimolecular or intramolecular (as contrasted with a unimolecular decomposition), should proceed independently of viscosity at ordinary viscosities, slowing down at very high viscosities, with the onset of retardation occurring sooner, the lower the activation energy.

In contrast, the vibrational-activation theory¹ predicts different behavior. It says, in essence, that a major factor in the acceleration of reactions by enzymes is that they immobilize the reactants, i.e., provide a microenvironment of high viscosity wherein the reaction takes place very rapidly, within a bulk medium of low viscosity that permits the reactants and products to come together and separate without hindrance. It has, in fact, long been recognized and speculated upon that enzymes must possess, in addition to the few amino acids at the active site, a large polypeptide chain with no apparent function other than to create a rigid cavity.⁴

A corollary, then, of the vibration-activation theory is that typical bond-making reactions ought to go faster at high viscosities. This comes about because bond-making is held to be promoted by high vibrational but low translational energy, both favored at high viscosity because translation is impeded and consequently a molecule's energy content at a given temperature is shifted from translational to vibrational modes.^{5,6} The present article

reports two successful tests of the above corollary.

It is difficult to vary the viscosity of a solvent and no other property. Even varying the degree of polymerization of most monomers will cause at least some small changes in polarity. To minimize this problem, for the first project only solvents without functional groups were chosen, i.e., saturated hydrocarbons, and a reaction whose rate is known to be independent of solvent, or almost so. This characteristic is possessed in general by thermal pericyclic reactions such as the Diels-Alder reaction,⁷⁻⁹ 1,3-dipolar cycloadditions,¹⁰ the Cope¹¹ and Claisen^{12,13} rearrangements, and the like.

Before experiments were undertaken, the literature was searched for prior art. Particularly well-studied is the Diels-Alder reaction. A possible problem with a bimolecular example such as this is that the rate *must* diminish at very high viscosities when the partners can no longer find each other, and if the postulated acceleration sets in too high on the viscosity scale, it will be unobservable. Fortunately, however, an excellent example was found that can be interpreted as viscosity-induced acceleration. It should be noted that neither the authors⁷ nor any subsequent reviewer interpreted the data in this way. In the classic study of the dimerization of cyclopentadiene by Wasserman and co-workers,⁷ the results at 35 °C in the least polar solvents contain two facts of interest: the rate in paraffin oil is twice that in CCl₄; in dicyclopentadiene it is 3.3 times the rate in monomeric cyclopentadiene; i.e., the rate constant of neat cyclopentadiene increases rapidly toward the end. However, variations in rate among highly polar solvents,^{7,8} though bearing no obvious relation to polarity, tended to obscure polarity-independent effects that might be attributed to viscosity.

Another way to alter the viscosity is to go into the gas phase. It is frequently observed that reactions go faster in nonpolar solvents than in the vapor state, and the phenomenon has not gone unremarked, but no one to our

(1) Paper 1: R. A. Firestone and B. G. Christensen, *Tetrahedron Lett.*, 389 (1973).

(2) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, 1963, pp 57 ff.

(3) E. S. Amis and J. F. Hinton, "Solvent Effects on Chemical Phenomena", Academic Press, New York, 1973, p 324.

(4) P. L. Luisi, *Naturwissenschaften* 66, 498 (1979) and references therein.

(5) Bond breaking should also be favored by high viscosity because vibrational energy is clearly needed here. In this case, however, the advantage of viscosity is less because soft collisions do not matter, as they do with bond making.¹

(6) Conventional kinetic theory, on the other hand, says that "collision is ineffective unless the kinetic energy of the reacting molecules along their line of centers equals or exceeds the activation energy".²

(7) G. A. Benford, H. Kaufmann, B. S. Khambata, and A. Wasserman, *J. Chem. Soc.*, 381 (1939).

(8) H. Kaufmann and A. Wasserman, *J. Chem. Soc.*, 870 (1939).

(9) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, 6, 16 (1967).

(10) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 2, 633 (1963).

(11) D. C. Berndt, *J. Chem. Eng. Data*, 14, 112 (1969).

(12) W. N. White and E. F. Wolfarth, *J. Org. Chem.*, 35, 2196 (1970).

(13) H. L. Goering and R. R. Jacobson, *J. Am. Chem. Soc.*, 80, 3277 (1958).

Table I. Rate of the Claisen Rearrangement of 1 vs. Solvent Viscosity

solvent	η/η_0	expt I				expt II, 233 h	
		233 h		538 h		% reacn	k/k_0
		% reacn	k/k_0	% reacn	k_0		
<i>n</i> -octane	1.00	10.0	1.00	26.4	1.00	11.4	1.00
isooctane	0.94	10.4	1.04	25.9	0.98		
<i>n</i> -octacosane	4.92	11.1	1.12	29.7	1.15		
Nujol	11.8	14.3	1.47	36.0	1.46	15.7	1.41
Nujol + polyethylene	48.5					18.6	1.70

knowledge has heretofore attributed it to viscosity. Of course, even a hydrocarbon solvent molecule has the capacity, as a polarizable body, to stabilize transient charge that vacuum does not have, but the paraffin/gas rate ratio of 4.5 for cyclopentadiene dimerization¹⁴ (at 136 °C) cannot be attributed to transient charge stabilization because the rate in acetonitrile (at 25 °C) is actually 40% slower than that in CCl₄.⁷ Also, the dimerization of butadiene and the cyclopentadiene-butadiene reaction both exhibit a small but distinctly *negative* solvent polarity effect.¹⁵ From gas to *n*-tetradecane solution (at 170 °C), the Claisen rearrangement of *p*-tolyl allyl ether¹² speeds up threefold, while a further change to di-*n*-butyl ether accelerates only another 10%.¹⁶ The 1,5 sigmatropic rearrangement of cyclopentadiene is three times faster in CCl₄ than in the vapor state, while the much more polar solvent acetone causes only 20% further acceleration.¹⁷ Many more examples could be cited.

The Cope rearrangement of 2-phenyl-1,5-hexadiene goes about four times faster in *o*-dichlorobenzene than in the gas phase, which was attributed to dispersion forces and stabilization of transient dipoles.¹⁸ Although this idea seems to be contradicted by the low solvent effects on another Cope rearrangement,¹¹ it might explain the liquid-gas phenomenon if it meant stabilization by the polarizable solvent molecules, not of charge separation in the transition state (TS) on the time scale of chemical reaction but of enhanced polarizability of the TS. Thus a molecule with little or no dipole moment could interact more favorably with other molecules if it were exceedingly polarizable than if it were not. The stabilization comes from mutual polarization by transient charge inhomogeneity on the electronic time scale, such as that which gives rise to van der Waals interactions. It is reasonable to postulate enhanced polarizability for TS's, but the magnitude of this effect is difficult to assess. Therefore an experimental test was devised (vide infra) which contraindicates this explanation for at least one reaction.¹⁹

Most bond-breaking reactions also show liquid/gas ratios >1, but this class is less interesting for our present purpose because it has long been recognized as vibrationally promoted.

Yet another way to increase the viscosity is to increase the pressure. Viscosities of liquids increase rapidly with pressure,^{20,21} and, therefore, ΔV^\ddagger , which is determined from

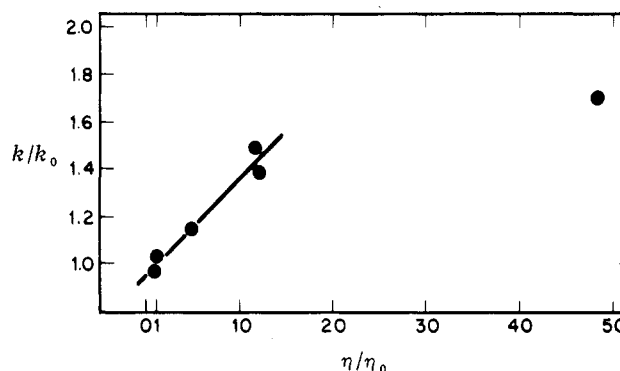


Figure 1.

the response of reaction rates to increased pressure, should always contain a $-\Delta V^\ddagger$ component from the viscosity effect. Normally, this will be added onto a much larger $-\Delta V^\ddagger$ or $+\Delta V^\ddagger$, arising from the bond changes in the reaction itself, and, therefore, not be noticed. However, it is a remarkable fact that there are many cases of reactions that are bond forming in one direction in which the *apparent volume of the transition state is smaller than that of even the smaller set of reactants*. This is commonplace with Diels-Alder reactions²² and has also been reported for the reversible electrocyclic opening of 1,2-diphenyl-3-methyl-3,4-bis(carbomethoxy)cyclobutene.²³ It is difficult to believe that a partially formed bond is smaller than a fully formed one. Consequently the calculated ΔV^\ddagger of these examples cannot measure the true volume change from reactants to TS. However, if there were a pressure-induced acceleration in *both directions* arising from the viscosity effect independently of mechanism, then correction for this might provide more reasonable values for TS volumes.

In a search for new evidence, the first reaction chosen for study was the Claisen rearrangement of phenyl allyl ether. It is a bond-making reaction,²⁴ but intramolecular,²⁵⁻²⁷ so that the two reaction partners have no need to diffuse together; its rate is first order²⁸ and almost solvent independent,^{12,13,16} barring acid catalysis; the yield is high and the product well-established; it can be easily followed

(14) G. A. Benford and A. Wasserman, *J. Chem. Soc.*, 362 (1939).

(15) K. Nakagawa, Y. Ishii, and M. Ogawa, *Chem. Lett.*, 21 (1977).

(16) Solvent effects, while small, are not negligible, however, especially for solvents carrying acidic protons; relative rates (170 °C): gas, 1; tetradecane, 3.0; dibutyl ether, 3.3; sulfolane, 10.7; octanoic acid, 24.2; *p*-chlorophenol, 303.¹² At 184.85 °C relative rates are as follows: decalin, 1.56; Ph₂CH₂, 2.12; Ph₂O, 2.08; PhAc, PhNMe₂, PhCN, and methyl salicylate, 2.41-2.49; 1-octanol, 9; phenol, 45.¹³

(17) W. R. Roth, *Tetrahedron Lett.*, 1009 (1964).

(18) M. J. S. Dewar and L. E. Wade, Jr., *J. Am. Chem. Soc.*, **99**, 4417 (1977).

(19) We thank Drs. Josef Michl and Edwin Chandross for valuable conversations on this subject.

(20) K. E. Weale, "Chemical Reactions at High Pressures", Spon, London, 1967.

(21) D. C. Munro (p 18), and W. A. Steele and W. Webb (p 163) in "High Pressure Physics and Chemistry", Vol. 1, R. S. Bradley, Ed., Academic Press, London, 1963.

(22) T. Asano and W. J. LeNoble, *Chem. Rev.*, **78**, 407 (1978).

(23) R. Mundnich and H. Plieninger, *Tetrahedron*, **34**, 887 (1978).

(24) Bond making precedes bond breaking because the allyl group inverts,²⁵ cross-over does not occur,²⁶ and the reaction is strongly pressure accelerated.²⁷

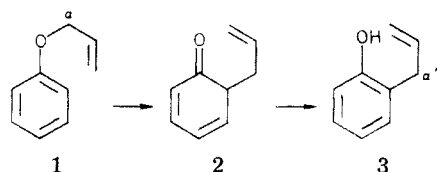
(25) L. Claisen and E. Tietze, *Chem. Ber.*, **58**, 275 (1925); J. P. Ryan and P. R. O'Connor, *J. Am. Chem. Soc.*, **74**, 5866 (1952).

(26) A. S. Fomenko, G. P. Miklukhin, and E. A. Sadovnikova, *Dokl. Akad. Nauk S.S.S.R.*, **62**, 91 (1948); *Chem. Abstr.*, **43**, 602i (1949); *Z. Obshch. Khim.*, **20**, 1898 (1950); *Chem. Abstr.*, **45**, 2895h (1951); C. D. Hurd and L. Schmerling, *J. Am. Chem. Soc.*, **59**, 107 (1937).

(27) K. R. Brower, *J. Am. Chem. Soc.*, **83**, 4370 (1961); C. Walling and M. Naiman, *ibid.*, **84**, 2628 (1962).

(28) J. F. Kincaid and D. S. Tarbell, *J. Am. Chem. Soc.*, **61**, 3085 (1939).

by NMR. The initial intermediate **2** is not normally seen, and so it is sufficient to monitor the ratio of 3:1.



The relative viscosities of the solvents employed were determined at 100 °C by the falling-sphere method, using a Teflon-encased magnet in place of the sphere for convenience. Although the shape of the magnet was not the ideal sphere, and the temperature not the ideal 138 °C the differences in viscosity that were found were so great that the small corrections that might be introduced under more perfect conditions could not significantly alter the overall conclusions.

The results of this study, summarized in Table I, fulfill the predictions of the vibrational-activation theory. The difference in viscosity between *n*-octane and isooctane is probably not significant because the falling times were so short (see Experimental Section). Although, as seen in the literature cited, there is no meaningful correlation between viscosity and rate at low viscosity, there is a meaningful correlation at higher viscosities.

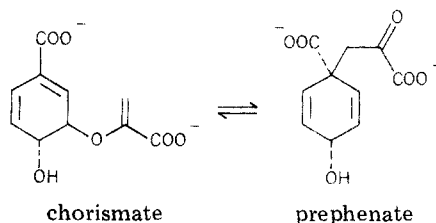
For experiment I, a plot of rate vs. viscosity is linear (Figure 1), showing that the rate increases are systematic and not random, despite their small magnitude. The relationship of rate to viscosity (by least squares) fits eq 1. If this relationship holds at very high viscosities such as those experienced by enzymic substrates, it reduces to eq 2.

$$k/k_0 = 0.95 + 0.041\eta/\eta_0 \quad (1)$$

$$\text{correlation coeff} = 0.997$$

$$k/k_0 = (4.1 \times 10^{-2})\eta/\eta_0 \quad (2)$$

It is pertinent that an enzyme exists, chorismate mutase, that catalyzes a Claisen rearrangement, chorismate \rightleftharpoons prephenate, by 2×10^6 over the uncatalyzed rate.²⁹ To account for this remarkable catalysis is difficult by conventional mechanisms of enzyme action.



Nujol and octacosane have similar molecular weights, but they differ in the extent of chain branching. The sample of Nujol used in this work had about 14% CH₃ groups by NMR, while octacosane has 7%. However, the difference in this respect between *n*-octane and isooctane (2,2,4-trimethylpentane) is even greater, and yet the rate in these two low-viscosity solvents is almost exactly the same. Therefore the degree of chain branching of the solvent is not an important factor per se.

It was desirable to obtain greater rate enhancements. Solvents were therefore needed that were more viscous than Nujol and yet still 100% saturated alkane. It was found that soft polyethylene can be dissolved in Nujol with

Table II. Rate of Claisen Rearrangement of **1** vs. Solvent Refractive Index, Experiment III

solvent	refractive index, <i>n</i>	$\frac{n^2 - 1}{n^2 + 2}$	% reacn	<i>k/k</i> ₀
CH ₃ CN	1.3442	0.212	22.6	2.14
<i>n</i> -octane	1.3974	0.241	11.3	1.00
PhCl	1.5241	0.306	19.1	1.77
PhBr	1.5597	0.323	18.2	1.68
PhI	1.6200	0.351	21.5	2.03

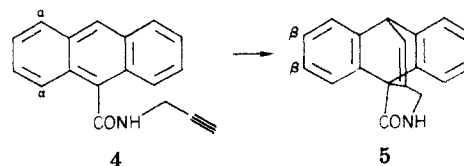
concomitant increase in viscosity.³⁰ In experiment II (Table I) this new solvent did indeed prove to cause a substantial further rate increase. The increased rate is no longer proportional to the viscosity, but this is easy to understand for two reasons. (1) For the first time, there are molecules present that are much larger than the TS, so that although the entire polyethylene molecule participates in increasing the bulk viscosity, only a portion of it influences the immediate environment of a reacting molecule³¹ if it happens to be nearby. (2) The solvent is homogeneous on a macroscopic but not a microscopic scale because it is a mixture of many small Nujol molecules and a few large polyethylene ones. Therefore the majority of reactive events take place in a purely Nujol environment, and only a few in or near polyethylene. The experimental point, then, must be an average of two different rates, one of them *very high*, and of two different microviscosities, one high and one low.

Another Claisen study was made in order to test the idea (vide supra) that high liquid/gas rate ratios (3.0 for this reaction) might be due to hyperpolarizability of the TS. An easy experimental test is to look for a dependence of rate on refractive index (*n*) of the solvent, which is related to polarizability (α) according to eq 3, in which *K* represents a group of factors that is essentially constant for all of our solvents.³²

$$\alpha = K \frac{n^2 - 1}{n^2 + 2} \quad (3)$$

The results are presented in Table II. Solvents of low viscosity but widely varying *n* were chosen. There is no systematic dependence of rate on *n*, and, therefore, the hyperpolarizability theory is not supported by these data.

A second bond-making reaction was next chosen for study. The Diels-Alder reaction shares with the Claisen rearrangement the characteristics of low solvent dependence, unrelated to polarity,⁷⁻⁹ significant liquid/gas rate ratio,⁷ and (for the example selected) intramolecularity, high yield, and easy NMR analysis of the extent of conversion. From a group reported by Ciganek,³³ the cyclization of *N*-propargylanthroamide (4 \rightarrow 5) offered the most convenience with regard to rate and analysis.



(30) We thank Dr. Raymond L. Arnett for this suggestion.

(31) In accord with this idea is the fact that activation energies of flow for long-chain polymers are almost independent of chain length. The unit of flow is a segment of approximately constant length, about 32 atoms. S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes", McGraw-Hill, New York, 1941, pp 500-501.

(32) E. U. Condon and H. Odishaw, Eds., "Handbook of Physics", 2nd ed., McGraw-Hill, New York, 1967, p 6-112.

(33) E. Ciganek, *J. Org. Chem.*, **45**, 1497 (1980). We thank Dr. Ciganek for generously providing much prepublication information.

(29) B. Davidson, E. Blackburn, and T. Dopheide, *J. Biol. Chem.*, **247**, 4441, 4447 (1972).

Table III. Rate of Diels–Alder Reaction of 4 vs. Solvent Viscosity

solvent	η/η_0	% reactn	k/k_0
glyme	1.00	34.9	1.00
diglyme	1.28	39.4	1.16
triglyme	1.54	41.5	1.25
tetraglyme	1.99	44.7	1.38

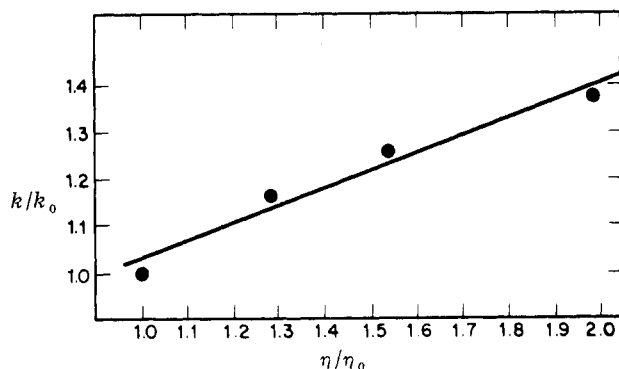


Figure 2.

Unfortunately it was insufficiently soluble in Nujol for NMR work. Consequently it was necessary to find a series of more polar solvents, and the glymes $\text{CH}_3(\text{OCH}_2\text{CH}_2)_n\text{OCH}_3$ ($n = 1, 2, 3,$ and 4) proved serviceable. Although it can no longer be said, as with the hydrocarbon series, that no polar groups whatever are present, the similarity in structure within the series and the lack of dependence on solvent polarity of typical Diels–Alder reactions assure that the study is meaningful. That there are no special peculiarities in liquid structure among the glymes is indicated by the fact that their relative viscosities are exactly the same at 25°C and at 100°C . The results are given in Table III. Once again a linear relationship between rate and viscosity was obtained (Figure 2).

The best fit to the data by least squares is eq 4, which becomes eq 5 at high viscosity. The slope is much greater than that for the Claisen rearrangement (eq 1).

$$k/k_0 = 0.66 + 0.37\eta/\eta_0 \quad (4)$$

$$\text{correlation coeff} = 0.984$$

$$k/k_0 = 0.37\eta/\eta_0 \quad (5)$$

It should be noted that in both studies, the range of actual viscosities of the reaction mixtures is compressed in comparison with those of the pure solvents because additives, including the reactants, dilute all the solvents by a constant amount. Therefore the observed slopes are undoubtedly smaller than the true ones.

The present results agree with the data cited above for the dimerization of cyclopentadiene.⁷ We therefore propose that viscosity be considered as one of the external factors—though clearly not the only one—controlling the rates of the Claisen rearrangement, the Diels–Alder reaction, and, by extension, other bond-making reactions as well.

It would be better to use microviscosity instead of macroviscosity, since the two might not always correspond. A reliable index is being sought. Also in the future are extensions to other intramolecular Diels–Alder reactions, Cope rearrangements, etc., and other solvents. Finally, molecules that confine the TS either mechanically, e.g., rings just large enough to contain TS's, or by other means such as hydrophobic or hydrogen bonding might give extra-large rate accelerations because they are part way toward approximating the situation inside the cavities or

bound complexes of enzymes.

Experimental Section

NMR spectra of the 10–14% reaction points (experiment I, Table I) were kindly run at 100 MHz by Dr. Alan Douglas, and the data reported are the averages of 5–7 machine integrations of each peak. For all other reaction points, run at 300 MHz, we are indebted to Dr. Byron Arison. The peaks of interest were spread out and integrated by planimetry; this method of integration is good to within about 2%, far more precise than machine integration. For all experiments, brand new NMR tubes were washed with dilute aqueous NaHCO_3 , water, and acetone and then thoroughly dried. Full-scale NMR spectra were run on all samples before and after reaction to guard against unexpected events. The mass spectrum of Nujol was determined by Mr. Jack Smith.

In experiments I and II, a mixture of 0.5 mL of redistilled phenyl allyl ether (NMR perfect) and 1.1 mg of diphenylamine was prepared, and 50 μL of it (49.2 mg) was pipetted into each NMR tube. Each tube was then filled to 0.50 mL with one of these five solvents: *n*-octane (Aldrich gold label); isooctane (MCB spectroquality); Nujol from a new bottle; molten octacosane (Aldrich, mp 61°C); a solution of polyethylene in Nujol (vide infra). The tubes were then sealed, with great care being taken not to heat the contents.

In experiment I, the tubes were heated together in the vapor of refluxing xylene (138°C) for 233 h. The extent of reaction was determined by 100-MHz NMR, run at 70°C . A control experiment showed negligible reaction of phenyl allyl ether after 1 week at 100°C . The $\text{O}-\text{CH}_2$ in phenyl allyl ether comes at δ 4.50 and the ArCH_2 in *o*-allylphenol at δ 3.41, so that only their ratio is necessary. Average deviations were 7–8%. The tubes were then returned to the heating bath for another 305 h. This time the peak ratios were determined on 300-MHz spectra, with the δ 4.50 and 3.41 bands spread out. The areas were measured with a planimeter. The major source of error is undoubtedly the curves themselves, but they should be reliable because the large sample sizes permitted the CW rather than FT mode to be used, eliminating relaxation time problems. The data are presented in Table I. The accuracy of the 538-h points is greater than that of the 233-h points, but there is clearly a continuity of relative rate through both heating periods.

Experiments II and III were run in the same way, both for 233 h. The results are in Tables I and II. The polyethylene-in-Nujol solvent was prepared by heating 50 mL of Nujol with several pieces of Parafilm for 5 h at 100°C and filtering as hot as possible. The NMR spectrum of the neat solution showed absolutely nothing but saturated CH. The other solvents were the best grades available from Aldrich, used as received. The full-scan NMR spectra showed no unexpected bands before or after reaction with the exception of the PhI tube, which developed some color during the experiment, and traces of impurities in the NMR. Although these impurity bands appeared not to interfere with the assay, the PhI figure must be regarded as slightly less reliable than the others.

For the Diels–Alder study, pure 4 and 5 were prepared according to the published procedure. From the NMR spectra of the pure compounds and of mixtures, the four α protons of 4 [δ 8.05 (m)] and the four β protons of 5 [δ 7.0 (m)] were selected for analysis of the reaction mixtures because they stood out most clearly from the others. Solvents were all from new bottles and peroxide-free. Glyme was distilled from LAH through a short Penn State column (perforated stainless-steel saddles (5×10 mm) obtained from Scientific Development Co., State College, PA), bp 83.5 – 84.5°C . Diglyme was distilled through the Penn State column up to the main fraction and then through a simple still, bp 161.5 – 162.0°C . Triglyme was distilled at ca. 1 mm, bp 69.5 – 71.5°C . Tetraglyme was distilled at ca. 1 mm, bp 111.0 – 112.5°C . Into 0.50 mL of each solvent were dissolved 24.9 ± 0.1 mg of 4, 1.0 mg of hydroquinone, and 0.025 mL of C_6D_6 (as an NMR lock). Samples were sealed into NMR tubes after a N_2 flush and heated for 66 h at 100°C in a steam bath. The results are given in Table III.

The relative viscosities of the solvents were determined at 100°C . A long thin-walled glass tube of i.d. 4 mm, closed at one end, containing a 10×3 mm Teflon-encased magnet, was filled with solvent to a depth of 30 cm and held vertically inside a larger tube

filled with steam to a height above the solvent level. The magnet was repeatedly raised to the top with an external magnet and dropped. Its fall to the bottom from a mark 24 cm up was timed. Terminal velocity was clearly reached well above the mark. Densities were measured at 100 °C in 5-mL volumetric flasks.

n-Octane: 1.6, 1.4, 1.6, 1.4, 1.6, 1.6, 1.6, 1.6, 1.6, s; average 1.56 ± 0.067; density 0.643.

Isooctane: 1.6, 1.4, 1.4, 1.6, 1.4, 1.4, 1.6, 1.4, 1.4 s; average 1.46 ± 0.084 s; density 0.631.

Octacosane: 8.0, 8.0, 8.0, 8.0, 8.0, 8.0, 8.0, 8.0, 8.0, 8.2 s; average 8.02 ± 0.02 s; density 0.755.

Nujol: 19.6, 19.6, 20.0, 19.8, 19.8, 20.0, 20.0, 19.4, 19.8, 19.8 s; average 19.78 ± 0.148 s; density 0.831.

Nujol-polyethylene: 81.8, 81.8, 81.8, 81.8, 82.0, 81.8, 81.8, 81.6, 81.8, 81.6 s; average 81.78 ± 0.070 s; density 0.835.

Glyme: 1.6, 1.4, 1.4, 1.6, 1.4, 1.6, 1.6, 1.4, 1.6, 1.4 s; average 1.50 ± 0.10 s; density 0.812.

Diglyme: 2.0, 2.0, 2.0, 2.0, 2.2, 1.8, 2.0, 1.8, 2.0, 2.0 s; average 1.98 ± 0.072 s; density 0.891.

Triglyme: 2.4, 2.4, 2.4, 2.4, 2.6, 2.4, 2.4, 2.4, 2.6, 2.4 s; average 2.44 ± 0.064 s; density 0.937.

Tetraglyme: 3.2, 3.2, 3.2, 3.2, 3.2, 3.2, 3.2, 3.0, 3.2 s; average 3.18 ± 0.036 s; density 0.966.

For the four glymes, falling times and densities were also determined at 25 °C, giving exactly the same relative viscosities.

The magnet used weighed 0.2176 g and occupied 0.068 ± 0.001 mL, density 3.20. The relative viscosities were calculated from eq 6 in which η = viscosity, D = density of the magnet, d = density

$$\frac{\eta}{\eta_s} = \frac{(D-d)t}{(D-d_s)t_s} \quad (6)$$

of the liquid, and t = falling time.³⁴

Registry No. 1, 1746-13-0; 4, 56948-77-7.

(34) F. Daniels, J. H. Mathews, and J. W. Williams, "Experimental Physical Chemistry", 3rd ed., McGraw-Hill, New York, 1941, p 326.

Investigation of Valency of Carbocationic Intermediates by use of Potential Energy Diagrams

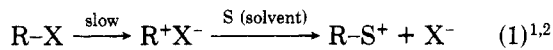
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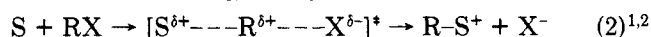
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More O'Ferrall-type potential energy diagrams are constructed for the Doering-Zeiss mechanism for nucleophilic aliphatic substitution and for the conventional mechanism in which rate-determining ionization proceeds without nucleophilic solvent assistance. These diagrams, used in conjunction with α -deuterium isotope effects and m values for benzhydryl chloride solvolyses, give predictions of structural variations in transition states that are consistent with either a Doering-Zeiss reaction mechanism or with a conventional ion-pair mechanism. The important point is that the generally ignored Doering-Zeiss mechanism is a viable alternative that should be added to the already complex mechanistic situation for solvolysis reactions.

Some 25 years ago Doering and Zeiss presented an interesting elaboration of Hughes' and Ingold's classical S_N1 (without nucleophilic assistance, eq 1)^{1,2} and S_N2 (with nucleophilic assistance, eq 2)^{1,2} mechanisms for nucleo-

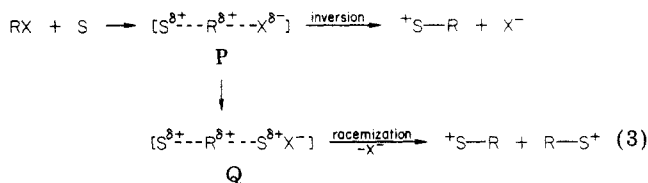


S_N1 or k_c mechanism



S_N2 or k_s mechanism

philic aliphatic substitution.³ According to Doering and Zeiss, a few substrates can react by rate-determining ionization without nucleophilic solvent assistance (i.e., according to eq 1), but most substrates, including many tertiaries, react with nucleophilic solvent assistance as shown in eq 3. According to this scheme, species P may be a transition state, as it is in a simple S_N2 reaction, or it may be an intermediate.



(1) Ingold, C. K. "Structure and Mechanism in Organic Chemistry", 2nd ed; Cornell University Press: Ithaca, New York, 1969.

(2) Schleyer, P. v. R.; Fry, J. L.; Lam, L. K. M.; Lancelot, C. J. *J. Am. Chem. Soc.* 1970, 92, 2542.

(3) Doering, W. v. E.; Zeiss, H. H. *J. Am. Chem. Soc.* 1953, 75, 4733.

Thus, Doering and Zeiss have introduced a third type of substitution pathway, which is proposed as occurring for substrates with intermediate ability to stabilize a carbocation and which involves nucleophilic solvent assistance to yield a pentavalent carbocationic intermediate. This mechanism was postulated to explain the excess inversion of configuration observed in reactions of tertiary derivatives previously thought to react without nucleophilic solvent assistance. Reference to eq 3 shows that the balance between inversion and racemization can be explained by assuming varying proportions of intermediates P and Q.

In the intervening years the Doering-Zeiss mechanism has been generally ignored, although the concept of a pentavalent intermediate has been invoked to explain the solvolysis of derivatives (e.g., secondaries) clearly reacting by a k_s mechanism.⁴⁻⁸ In only a few instances has it been suggested that nucleophilic assistance in simple tertiary substrates leads to an intermediate such as I.⁹ Bordwell

(4) Winstein, S.; Darwish, D.; Holness, N. H. *J. Am. Chem. Soc.* 1956, 78, 2915.

(5) Martin, J. C.; Basalay, R. J. *J. Am. Chem. Soc.* 1973, 99, 2972. (b) Hayami, J.-I.; Tanaka, N.; Hihara, N.; Kawai, A. *Tetrahedron Lett.* 1973, 385.

(6) (a) Harris, J. M. *Prog. Phys. Org. Chem.* 1974, 11, 89. (b) Friedberger, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* 1976, 98, 2861.

(7) (a) Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* 1977, 99, 4219. (b) Radom, L. "Modern Theoretical Chemistry"; Schaefer, H. F., III, Ed.; Plenum: New York, 1977; Vol. 4, Chapter 8. (c) Dannenberg, J. J. *J. Am. Chem. Soc.* 1976, 98, 6261.

(8) (a) Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* 1976, 98, 7658. (b) Bentley, T. W.; Bowen, C. T. *J. Chem. Soc.* 1978, 557.