were assigned by comparing retention times (coinjection with authentic samples on column C) and mass spectra with those for authentic samples (Table III). In addition, the nmr spectra of a mixture of **5** and **6** clearly showed the characteristic vinyl triplet and the bridgehead protons for bicyclo[2.2.2]octene (**6**). The nmr spectrum of a mixture of **7** and **8** clearly showed the spectra of the individual components since the spectra only overlap in one small area. The spectra agreed with those for authentic samples. The nmr spectra for **6**, **7**, and **8** are as follows: **6** (δ, CCl$_4$) 6.20 (t, J = 3 Hz, 2), 2.47 (br s, 2), 1.47 (d, J = 8 Hz, 4), 1.20 (d, J = 8 Hz, 4); **7** (δ, CCl$_4$) 1.65 (m, 9), 1.25 (d, J = 8 Hz, 2), 0.70 (m, 1); **8** (δ, CCl$_4$) 2.50 (m, 1), 1.7–2.0 (m, 5), 1.2–1.5 (m, 6).

The minor acetate products **3** and **4** were identified by comparison of retention times (coinjection with authentic samples on column

C) and by their mass spectra which were superimpossable with those of authentic samples (Table IV). Further spectral identification was thwarted by the extremely small quantities involved and by the fact that efficient separation was only attainable on capillary glc columns.

The ampoule pyrolysis products **9** and **10** were separated on column F. The nmr spectra agreed with those reported.[12,13]

Claisen Rearrangement of Cinnamyl Phenyl Ether in Isotropic and Nematic Solvents and in a Clathrate[1]

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Abstract: Claisen rearrangement of cinnamyl phenyl ether yields both ortho and para products, contrary to previous reports. In basic solvents the ortho product predominates while in acidic or neutral solvents more para product is formed. Allyl phenyl ether, on the other hand, gives exclusively *o*-allylphenol in solvents of all kinds. The rate of rearrangement of cinnamyl phenyl ether was measured in a variety of solvents including one forming a nematic phase (hydroquinone di-*p*-*n*-hexyloxybenzoate). The rate in this showed no discontinuity on passing from nematic to isotropic liquids, the activation parameters remaining unchanged ($\Delta E^{\pm}$ = 30.4 ± 0.85 kcal mol^{-1}; $\Delta H^{\pm}$ = 29.5 ± 0.85 kcal mol^{-1}; $\Delta S^{\pm}$ = −15.0 ± 1.8 cal deg^{-1} mol^{-1}). A clathrate of cinnamyl phenyl ether in 4,4'-dinitrobiphenyl was prepared. In the clathrate rearrangement of the ether was strongly inhibited.

The majority of nematic liquid crystals involve rod-shaped molecules which tend to orient themselves with their long axes parallel. If an anisotropic molecule is dissolved in such a nematic phase, it will tend to be oriented by the surrounding molecules of solvent. If then the nematic liquid crystal is oriented by, *e.g.*, a strong magnetic field, the solute molecules will adopt a corresponding and known orientation. This phenomenon has proved of practical value in several branches of spectroscopy.[2]

Consider a bimolecular reaction between two anisotropic solvents in a nematic solvent. In a "normal" solvent, three degrees of rotational freedom are lost on forming the transition state with a consequent negative contribution to the entropy of activation. The hindered rotation of solute molecules in a nematic solution should lead to a smaller loss of entropy when they combine. The entropy of activation should therefore be greater, and the rate likewise greater, for the reaction in a nematic solvent. Similar though smaller differences should be observed in the case of unimolecular reactions if the moment of inertia of the transition state differs significantly from that of the reactant.

While effects of this kind must in theory exist, no one

knows how large they are likely to be. If they were large, the use of nematic solvents could well influence polymerization reactions in a useful way.[3]

Several authors have reported effects of orientation when reactions are carried out in nematic liquid crystals instead of normal liquids, *e.g.*, the thermal decomposition of picric acid[5] and the pyrolysis of xanthates.[6] Recently it was claimed[7] that the Claisen rearrangement of allyl *p*-tolyl ether (**1a**) proceeds faster in nematic solvents; however, subsequent work[8] showed this not to be the case and similar negative results have been reported[9] for the rearrangement of 2,4,6-trimethoxy-1,3,5-triazine.

While the effects of orientation should be greater in the case of bimolecular reactions than unimolecular ones, we decided first to study a unimolecular process, the Claisen rearrangement, in view of claims[5,7] in the literature at the time this work was started. If these claims could be substantiated, one would expect rather large effects in the case of bimolecular reactions.

(1) This work was supported by the Air Force Office of Scientific Research through Contract F44620-71-C-0119 and by the Robert A. Welch Foundation through Grant F-126.

(2) See, *e.g.*, L. C. Snyder and E. W. Anderson, *J. Amer. Chem. Soc.*, **86**, 5023 (1964); E. Sackmann, *ibid.*, **90**, 3569 (1968); A. Carrington and G. R. Luckhurst, *Mol. Phys.*, **8**, 401 (1964).

(3) Some very recent papers[4] report studies of polymerization reactions in nematic solvents. The results at present seem somewhat equivocal.

(4) (a) Yu. B. Amerik, I. I. Konstantinov, and B. A. Krentsel, *J. Polym. Sci., Part C*, **23**, 231 (1968); (b) C. M. Paleos and M. M. Labes, *Mol. Crystallogr.*, **11**, 385 (1970); (c) A. Blumstein, N. Kitagawa, and R. Blumstein, *ibid.*, **12**, 215 (1971).

(5) T. Svedberg, *Kolloid-Z. Z. Polym.*, **18**, 54 (1916).

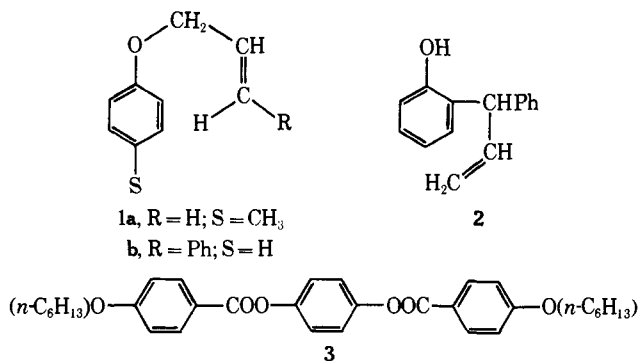(6) W. E. Barnett and W. H. Sohn, *Chem. Commun.*, 1002 (1971).

(7) W. E. Bacon and G. H. Brown, *Mol. Crystallogr.*, **6**, 155 (1969).

(8) W. E. Bacon and G. H. Brown, *Mol. Crystallogr.*, **12**, 229 (1971).

(9) W. E. Bacon and G. H. Brown, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, p 208.

1a, R = H; S = CH₃
b, R = Ph; S = H

2

$(n\text{-}C_6H_{13})O$—⟨⟩—COO—⟨⟩—OOC—⟨⟩—$O(n\text{-}C_6H_{13})$

3

The effects of orientation should be greater, the larger the reacting molecule and the greater the change in its moment of inertia on passing to the transition state. We therefore decided to study the rearrangement of cinnamyl phenyl ether (1b) which has been reported[10] to give exclusively 2-(1'-phenylallyl)phenol (2). Since we soon found that other products were also formed, we first studied the reaction in several "normal" solvents. The effect of orientation was then examined by carrying out the reaction in hydroquinone di-*p*-*n*-hexyloxybenzoate (3) over a range of temperatures including the nematic → liquid transition. Any effect of orientation should lead to a break in the corresponding Arrhenius plot at the transition temperature. We chose 3 because it is thermally stable and its nematic → liquid transition temperature[11] lies in a range where the rate of rearrangement of 1b can be followed conveniently.

As a test of the effect of extreme orientation, the rearrangement of 1b was also studied in a clathrate in a 4,4'-dinitrobiphenyl matrix.

Rearrangement of 1b in Normal Solvents

Separation by glc of the products formed by rearrangement of 1b showed that 2 was by no means the only product, large amounts of *p*-cinnamylphenol (4) being formed in most cases together with small amounts of *o*-cinnamylphenol (5), the chroman 6, and the benzopyran 7. It was shown that 6 and 7 arose by thermal cyclization of 2 and 5, respectively.

4   5

6   7
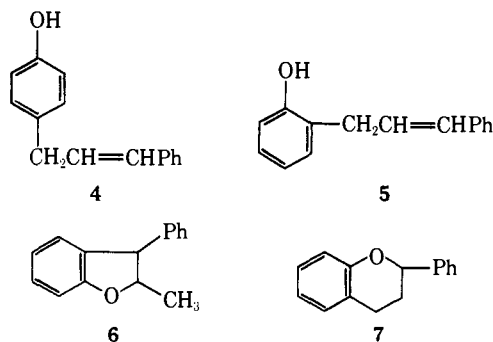
Table I shows the ratio of the ortho Claisen products (2 + 6) to the para Claisen product (4), for rearrangements in various solvents at various temperatures. It was shown that the ratio remained constant throughout each run.

(10) (a) L. Claisen and E. Tietze, *Chem. Ber.*, **58**, 275 (1925); (b) L. D. Huestis and L. J. Andrews, *J. Amer. Chem. Soc.*, **83**, 1963 (1961); (c) W. N. White and W. K. Fife, *ibid.*, **83**, 3846 (1961).
(11) M. J. S. Dewar and J. P. Schroeder, *J. Org. Chem.*, **30**, 2296 (1965); M. J. S. Dewar and R. S. Goldberg, *ibid.*, **35**, 2711 (1970).

Table I. Ratio of Ortho (2 + 6) to Para (5) Products in the Rearrangement of Cinnamyl Phenyl Ether (1b)

Solvent	144.65	164.90	175.06	Ratio (2 + 6):5, with standard deviation at temperature (°C) 185.05	194.90	204.70	214.74	224.58	245.02
Decalin		0.767 ± 0.071		0.445 ± 0.094	0.324 ± 0.043				
Diphenyl ether		3.52 ± 0.36		2.94 ± 0.53		3.20 ± 0.49		1.98 ± 0.31	2.17 ± 0.59
Dimethylaniline		>100		>100	>100				
Carbitol		30.8 ± 6.9		15.9 ± 2.0		9.8 ± 1.2			
Phenol	0.44 ± 0.17	0.57 ± 0.16	0.59 ± 0.15						
(Neat)		0.321[b]							
3		1.88 ± 0.19		1.03 ± 0.11		0.63 ± 0.10	0.49 ± 0.14		
3, 9.62 kG[a]		1.68 ± 0.34							

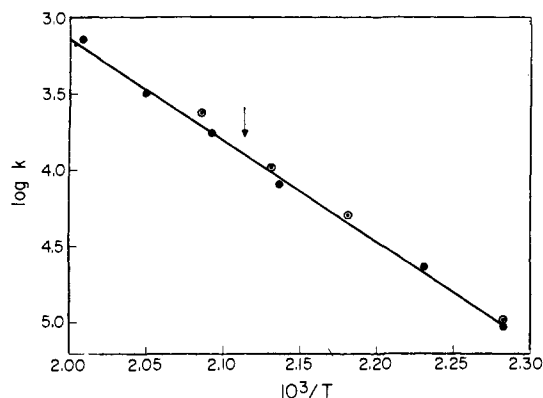*a* Magnetic field strength. *b* After 530 min.

Figure 1. Arrhenius plot for the rate of disappearance of **1b** dissolved in **3**, in the absence (●) and presence (○) of a magnetic field (9.62 kG). The nematic → isotropic transition temperature is indicated by an arrow.

While there are good analogies for the formation of chromans and benzopyrans from *o*-allylphenols, the formation of "para Claisen" products such as **5** from allyl ethers of phenol itself is unusual. Such products are usually formed only from ortho-substituted phenyl ethers where the intermediate dienone (*cf.* **9**) cannot enolize or from γ-substituted allyl ethers of meta-substituted phenols (*e.g.*, **8**) where enolization of the dienone (*e.g.*, **9**) is sterically hindered.[12] We know of only one case where a Claisen rearrangement has been reported to give significant amounts of para product from an allyl ether of phenol itself, *i.e.*, the conversion[13] of **12** to **15**. Here the. bulky *tert*-alkyl group presumably hinders enolization of the intermediate dienone **13**. While in the case of **1b** the intermediate dienone **16** is less hindered than **13**, rearrangement of **16** to **17** should be more exothermic than that of **13** to **14** since the phenyl group moves into conjugation with the double bond on forming **17**.

The only solvent in which **2** was formed exclusively was dimethylaniline. Here **16** is presumably deprotonated rapidly to a salt of **2**. High ortho/para ratios were also observed in diphenyl ether and carbitol, both of which are fairly basic. On the other hand, in decalin or phenol large amounts of **4** were formed and this was the main product when **1b** was heated alone. Apparently weak acids do not catalyze the enolization of **16**. Note also that the ortho/para ratio in each case fell with temperature, implying that the Cope rearrangement of **16** to **17** has a higher activation energy than enolization of **16** to **2**. Similar solvent effects have been observed by Schmid, *et al.*[12] These results seem to exclude formation of **4** by a competing fission into radicals (**18**) followed by recombination since the ortho/para ratio would not then have shown the observed dependence on solvent. The small amounts of the abnormal ortho product (**5**), may; however, have been formed in this way since rearrangement of **16** to **19** would be an antiaromatic pericyclic reaction violating the Woodward–Hoffmann rules.

Rearrangement of 1b in a Nematic Solvent

The rearrangement of **1b** in **3** was studied over the range 165–225°, the transition temperature of the

(12) J. Borgulya, H.-J. Jansen, R. Barner, and H. Schmid, *Helv. Chim. Acta*, 46, 2444 (1964).
(13) F. Scheinmann, R. Barner, and H. Schmid, *Helv. Chim. Acta*, 51, 1603 (1968).
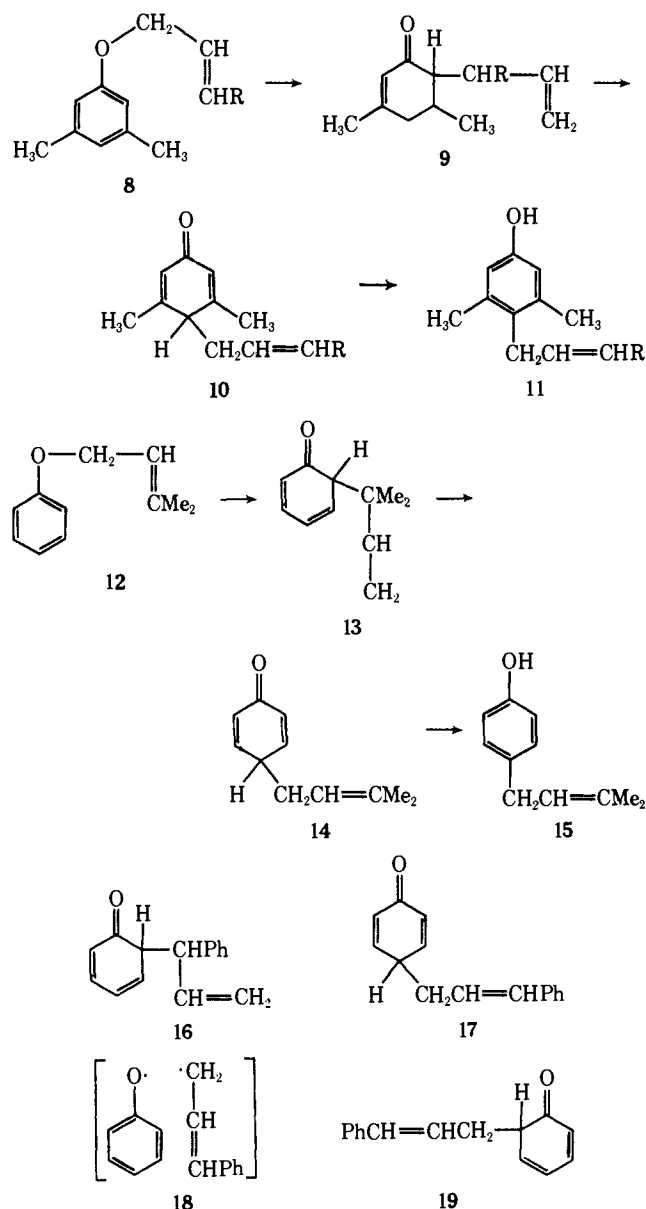
solutions used being 200°. Figure 1 shows an Arrhenius plot for the rate of disappearance of **1b** over this temperature range. It will be seen that there is no discontinuity whatsoever at the transition temperature, the points all lying, within experimental error, on a single straight line. This technique avoids the uncertainties inherent in comparisons of rates in liquid crystals and chemically different isotropic solvents. It is evident that the orientation of **1b** in nematic **3** has a negligible effect on the rate.

There was still the possibility that orientation might at least affect the products, by altering the relative rates of conversion of **16** to **2** and to **17**. However, the values of the ratios (2 + 6)/5 listed in Table I also failed to show any break at the transition temperature as is indicated by the corresponding Arrhenius plot (Figure 2). Assuming that this ratio is determined by the relative rates of conversion of **16** to **2** and to **17**, one can estimate from Figure 2 the difference in activation energy between the two processes, *i.e.*, 13.7 kcal/mol.

As a final check the experiments were repeated in a strong magnetic field (9.62 kG) where the orientation of the nematic form of **3** should have been enhanced.

Table II. Proportion of o-Cinnamylphenol (4) in the Rearrangement Product[a] from 1b

Solvent	Weight % of 4 in the product from rearrangement of 1b at temperature (°C)								
	144.65	164.90	175.06	185.05	194.90	204.70	214.74	224.85	245
Decalin		<2		5.35	5.61				
Diphenyl ether		<1		<2		2.96		7.5	14.25
Dimethylaniline		<1		<1	<1				
3		<1		<2		2.9	4.2		
Carbitol		<1		<2		<2			
Phenol									
(Neat)		14.9[a]							

[a] After 530 min.

Table III. First-Order Rate Constants for Rearrangement of 1b in Various Solvents

Solvent	First-order rate constant (sec^{-1} × 10^5) at temperature (°C)			
	144.65	164.90	175.06	185.05
Decalin		0.321 ± 0.019		1.130 ± 0.038
Diphenyl ether		0.0794 ± 0.017		3.74 ± 0.15
Dimethylaniline		0.826 ± 0.015		4.40 ± 0.11
Carbitol		4.48 ± 0.14		19.61 ± 0.31
Phenol	20.32 ± 0.63	67.9 ± 1.6	124.7 ± 2.4	
3		0.953 ± 0.043	2.35 ± 0.10	
3, 9.62 kG[a]		1.040 ± 0.083		5.06 ± 0.021[b]

Solvent	First-order rate constant (sec^{-1} × 10^5) at temperature (°C)				
	194.90	204.70	214.74	224.85	245
Decalin	2.26 ± 0.063				
Diphenyl ether		13.32 ± 0.16		36.64 ± 0.84	93.4 ± 2.0
Diphenylaniline	9.32 ± 0.14				
Carbitol		71.6 ± 2.0			
Phenol					
3	8.09 ± 0.16	17.8 ± 0.46	31.8 ± 0.086	725 ± 2.0	
3, 9.62 kG[a]	10.49 ± 0.37[c]	23.7 ± 1.58[d]			

[a] Magnetic field strength. [b] 185.39°. [c] 196.13°. [d] 205.95°.

Table IV. Activation Parameters for Rearrangement of 1b in Solvents

| Solvent	ΔE‡,[a] kcal/mol	ΔH‡, kcal/mol	ΔS‡, cal deg^{-1} mol^{-1}
Decalin	26.3 ± 1.2	±1.2	-26.2 ± 1.2
Diphenyl ether	29.5 ± 0.7 (24.9[10b])	28.5 ± 0.7	-17.3 ± 1.6 (-27.6[11b])
Dimethylaniline	33.0 ± 0.15	32.1 ± 0.15	-9.4 ± 0.33
3	30.4 ± 0.85	29.5 ± 0.85	-15.0 ± 1.8
Carbitol	29.0 ± 0.16 (30.6[10c])	28.1 ± 0.16 (29.8[10c])	-15.1 ± 0.35 (-13.1[10c])
Phenol	22.1 ± 0.43	21.2 ± 0.43	-25.4 ± 0.98

The rates, activation parameters, and products remained unchanged within the limits of experimental error.

Since no effect of orientation was observed in this very favorable case, it seems unlikely that the rates of any other unimolecular reactions will be altered significantly by carrying them out in nematic solvents.

Rates of Rearrangement of 1b in Various Solvents

The rate of disappearance of 1b in various solvents was measured by glc, the analyses being carried out at temperatures low enough for further rearrangement to be negligible. All reactions were followed to at least 95% conversion and all were of first order throughout except that in decalin. Here the rate constant began to rise after 50% conversion, apparently through catalysis by the phenols formed. Table II shows the rate constants for reaction in the various solvents at various temperatures and Table III the derived activation
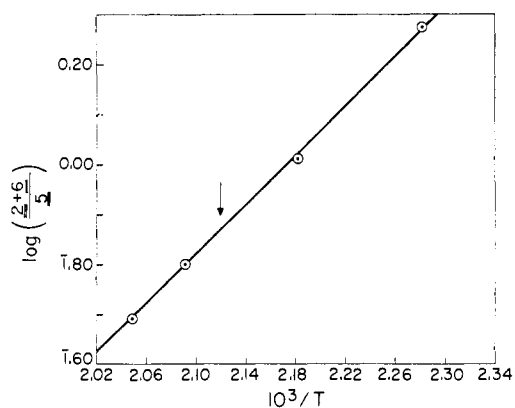
Figure 2. Arrhenius plot for the ratio (2 + 6) : 5 for rearrangement of 1b in 3. The nematic → liquid transition temperature is indicated by an arrow.

parameters. Our activation parameters (Table IV) for the reaction in carbitol agree quite well with those of White and Fife[10c] but ours in diphenyl ether differ appreciably from those of Huestis and Andrews.[10b] Since the earlier authors were unaware that products other than 2 are formed, we feel that the results reported here are more reliable.

The transition state (20) for conversion of 1b to 16 is aromatic,[14] being isoconjugate with 1-phenylnaphthalene and so analogous to 4-phenylquinoline (21). Mutual conjugation[15] between the exocyclic phenyl group and the oxygen atom in 20 should then lead to

(14) M. J. S. Dewar, Angew. Chem., Int. Ed. Engl., 10, 761 (1971).
(15) M. J. S. Dewar, J. Amer. Chem. Soc., 74, 3350 (1952).

polarization of the delocalized electrons in the peri-cyclic ring leading to polarity in the sense indicated in **20** (*cf.* **21**). The transition state (**20**) for rearrangement of **1b** should therefore be more polar than **1b** itself and the reaction should be correspondingly faster in polar solvents, particularly in protic solvents that can hydrogen bond to the negative oxygen in **20**. The rates of rearrangement in Table III follow this pattern which would be expected to occur in other pericyclic reactions where the pericyclic ring contains heteroatoms.[16] The increased positive charge on the cinnamylic phenyl group of **1b** on passing to the transition state **20** is also reflected by the effect of substituents, the rates following the Hammett equation with a small negative value (0.52)[10c] for ρ.

20   21   22
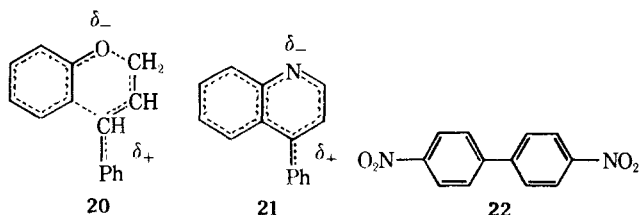
Rearrangement of 1b in a Clathrate

While the rearrangement of **1b** is apparently un-affected by orientation in an anisotropic solvent, it should obviously be possible to inhibit a reaction of this kind by using a medium able to apply a sufficiently strong constraint. Many examples are indeed known where chemical reactions of molecules are inhibited by embedding them in rigid glasses or crystals. Little use seems, however, to have been made of clathrates in this connection, although this kind of technique has been used[17] to bring about stereospecific polymerization.

Clathrates of 4,4'-dinitrobiphenyl (**22**) are known[18] to be of channel type, the crystals containing channels that run perpendicular to the axes of the rod-shaped molecules of **22**. It was established[18b] by X-ray crystallography that these channels can accommodate guest molecules and a number of such clathrates are now known[18a] that contain molecules very similar to **1b** in size and shape. In view of the restricted diameter of the channels, it seemed clear that clathrated **1b** would not be able to rearrange without disrupting the crystal and that rearrangement under these conditions should be inhibited. We were indeed able to prepare a 1:4 clathrate of **1b** in **22** and in this the rearrangement of **1b** was very strongly inhibited. Thus at 144.65° the rate of rearrangement was at least 1000-fold less than in solution (first-order rate constant 3 × 10⁻⁹), no detectable reaction having occurred after 30 days. At higher temperatures (164.9°) rearrangement did occur though still very slowly ($k < 3 \times 10^{-7}$), probably by diffusion of **12** out of the clathrate.

These results suggest that unstable species might be likewise stabilized by incorporation in suitable clath-rates or perhaps in the pores of suitable molecular sieves.

Experimental Section

Melting points are corrected. Elemental analyses were by Galbraith Laboratories.

Cinnamyl phenyl ether (1b), prepared by the method of White and Norcross[19] and purified by chromatography on alumina followed by crystallization from heptane, had mp 69.5–70.7° (lit.[10e] mp 68.0–69.7°) and was uniform (glc); nmr spectrum (δ, CCl_4) 4.62 (d, 2, J = 5 Hz, CH_2), 6.35 (m, 1, CH_2CH=), 6.63 (d, 1, J = 16 Hz, PhCH), 6.65–7.50 (m, 10, Ph).

o-Cinnamylphenol (4) was prepared by a modification of the method of Claisen, *et al.*[20] Cinnamyl chloride (61.03 g, 0.40 mol) in a little benzene was added to a slurry of phenol (37.6 g, 0.40 mol) and sodium methoxide (27.0 g, 0.50 mol) in benzene (1 l.). After 4 hr reflux, **4** (53.06 g, 63%) was isolated by the method of Claisen, *et al.*:[18] bp 143° (0.1 mm) (lit.[18] bp 208–209° (11 mm)), mp 56–57° (lit.[10] mp 55.5–56.5°); ir (KBr) 3310 (OH) and 760 (ortho substitution) cm⁻¹; nmr (δ, CCl_4) 3.50 (d, 2, J = 5 Hz, CH_2), 6.36 (m, 2, CH=CH), 7.05 (m, 10, Ph). *Anal.* Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71; O, 7.61; mol wt, 210.3. Found: C, 85.61; H, 6.72; O, 7.66; mol wt, 217 (cryoscopic in benzene).

p-Cinnamylphenol (5). Sodium methoxide (30.7 g, 0.26 mol) was added to phenol (40.5 g, 0.43 mol); the mixture was heated to 120°, cinnamyl chloride (32.84 g, 0.215 mol) was then added, and heating (120°) was continued for 4 hr. Analysis of the product (glc) showed it to be a mixture of **4** (65%) and **5** (35%).[21] Separation by glc followed by crystallization from hexane gave **5**: mp 64–65°; ir (KBr) 3230 (OH), 829 (para substitution) cm⁻¹; nmr (δ, CCl_4) 3.40 (d, 2, J = 5 Hz, CH_2), 6.14 (m, 1, CH_2CH), 6.40 (d, 1, J = 16 Hz, PhCH), 6.30–7.00 (m, 10, C_6H_5). *Anal.* Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71; O, 7.61; mol wt, 210. Found: C, 85.63; H, 6.60; O, 7.68; mol wt (cryoscopic in benzene), 220.

2-(α-Phenylallyl)phenol (2) was prepared by the procedure of Claisen and Tietze:[10a] bp 142–143° (2 mm) (lit.[10b] bp 139–140°) (2 mm)); n^{20}D 1.5978; nmr (δ, CCl_4) 4.5–5.4 (m, 4, CHCH=CH₂), 6.0–7.3 (m, 10, C_6H_5).

2-Methyl-3-phenylcumaran (6) was prepared following Claisen and Tietze,[10a] bp 166–168° (13 mm) (lit.[10b] bp 167–168° (13 mm)).

Other Materials. Phenyl benzoate (Baker), phenol (Aldrich, zone refined, 99.9%), N,N-dimethylaniline (Baker analyzed), and 4-bromobiphenyl (Eastman) were commercial samples used without further purification. Diphenyl ether was purified as recommended by Kincaid and Tarbell.[22] Carbitol and decalin were dried over $MgSO_4$ and fractionally distilled. **3** was prepared by the method of Dewar and Schroeder.[11] All solvents and materials for kinetic measurements were homogeneous to glc.

Isolation and Identification of Reaction Products. **1b** (10 g) was treated under the same conditions as the microsamples used in kinetic runs (see below). After 10 hr at 165° the product was fractionated by preparative glc, using an Autoprep Model A700 and a column (length, 10 ft; i.d., 0.25 in.) with the same packing as for the kinetic runs. Three fractions were collected as viscous oils. The first proved to be **2**. The second and third, which solidified and were recrystallized from hexane, proved to be **5** and **4** respectively.

When the reaction mixture was subjected to prolonged heating (100 half-lives of **16**), two additional glc fractions were obtained which proved to be **6** and **7**. The sums of the concentrations of **2** and **6**, and of **4** and **7**, were constant. **7** was identified by comparison of its ir spectrum with that recorded in Sadtler Standard Spectra: nmr (δ, CCl_4) 2.20 (m, 2, CH_2CHPh), 2.75 (m, 2, CCH_2-CH_2), 4.97 (m, 1, -CHPh-), 7.10 (m, 9, aromatic H).

Kinetic Measurements. A. Isotropic Solvents. Solutions of **1b** and 4-bromobiphenyl were made by dissolving weighed amounts in each solvent. Samples (2 mg) of the solution in ampoules chilled in Dry Ice-acetone were flushed three times with argon, then evacuated and sealed. The samples were heated in a thermostat (±0.05°). Temperatures were measured using standardized thermometers. The quenched samples were analyzed by glc using

(16) *Cf.* the Diels–Alder reaction of isoprene with maleic anhydride: M. J. S. Dewar and R. S. Pyron, *J. Amer. Chem. Soc.*, **92**, 3098 (1970).

(17) See V. M. Bhatnagar, *Chem. Ind.* (*London*), 717 (1965).

(18) (a) W. S. Rapson, D. H. Saunder, and E. T. Stewart, *J. Chem. Soc.*, 1110 (1946); (b) D. H. Saunder, *Proc. Roy. Soc., Ser. A*, **190**, 508 (1947).

(19) W. N. White and B. E. Norcross, *J. Amer. Chem. Soc.*, **83**, 1968 (1961).

(20) F. Kremers, F. Roth, E. Tietze, and L. Claisen, *Justus Liebigs Ann. Chem.*, **442**, 210 (1925).

(21) Heterogeneous C-alkylation of sodium phenate by alkyl halides in benzene gives mainly o-alkylphenols.[22] Under these conditions cinnamyl chloride gave mainly **4**. When the reaction was carried out under our conditions, a mixture of **4** and **5** was formed.

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

an Aerograph 1520 chromatograph with flame ionization detector and a 20% silicone elastomer (D.C. 550) on Gas-Chrom P column (7 ft × 0.05 in.). The column temperature was raised during 50 min from 185 to 225°. Under these conditions **1b** did not rearrange. The chromatograph was calibrated using pure sample with 4-bromobiphenyl as an internal standard. Reactions were followed to at least 95% conversion of **1b**. First-order rate constants were found by a least-squares fit to the individual points.

B. Nematic Solvent. A mixture (% by weight) of **1b** (2.14), phenyl benzoate (0.853) as internal standard, and **3** (97.007) was heated to 202° (*i.e.*, above the nematic → liquid transition), vigorously stirred, and then rapidly cooled. The resulting solid was pulverized and homogenized. The resulting mixture was homogeneous to glc and the nematic → liquid transition temperatures of various samples were identical (200°). The reactions were carried out as before with samples (2 mg) in evacuated ampoules. In the case of the experiments in a magnetic field, the samples were held between the pole pieces of an electromagnet in an aluminum container through which thermostated oil was circulated. The samples were dissolved in benzene for analysis by glc as before.

Clathrate of 1b in 21. The clathrate was prepared from a mixture of **1b** (0.25 g) and **22** (0.75 g) by crystallization from acetone (125 ml) forming dark yellow prisms. *Anal.* Calcd for $C_{63}H_{46}N_8O_{17}$ (*i.e.*, **1b**, (**22**)$_4$): C, 63.74; H, 3.91; N, 9.44; O, 22.91. Found: C, 63.67; H, 3.88; N, 9.35; O, 22.86. Material of the same composition crystallized from solutions of **1b** and **22** even when the ratio of the components was varied. For the kinetic experiments crystals *ca.* 3 mm in diameter were sealed in evacuated ampoules and heated in a thermostat as before. For glc analysis solutions in hot acetone were injected into the chromatograph.

Concurrent General Acid–Electrostatic Catalysis in Vinyl Ether Hydrolysis and Aspartic-52 of Lysozyme

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Abstract: The hydrolyses of various ring-substituted α-methoxystyrenes have been studied across the acidic pH region, and proceed by an initial, rate-limiting proton transfer to the vinyl ether double bond. The hydrolysis of the *p*-methoxy analog may represent an exception to this mechanism. The products of these reactions are the corresponding acetophenones, except in the case in which the ring bears an *o*-carboxyl substituent (**1a,b**). In this case, 3-methoxy-3-methylphthalide (**2**) is formed, and is, to a good approximation, an obligatory intermediate in the hydrolysis reaction at all pH values. Arguments are presented which show that the presence of the *o*-carboxyl group evidently does not alter the rate-determining process in the hydrolysis mechanism leading to **2**. Ionization of the *o*-carboxyl group accelerates the hydronium ion catalyzed reaction by a factor of only 11.6, and the formic acid catalyzed reaction by only 7.9; these numbers are shown to represent upper limits on electrostatic facilitation of general acid catalyzed α-oxycarbonium ion formation in aqueous solution *via* vinyl ether hydrolysis. These results suggest that the electrostatic role postulated for aspartic acid-52 of hen lysozyme in a very similar process is yet to be demonstrated. The trapping of the carbonium ion intermediate by the intramolecular carboxyl group, even when it is un-ionized, shows that covalent interaction of such a carboxyl with carbonium ion intermediates does not require ionization of the carboxyl group. Other roles for Asp$_{52}$ are considered.

The ready availability of hen egg-white lysozyme presents the chemist with a remarkable opportunity to study the chemical details of enzymatic catalysis. Lysozyme rapidly hydrolyzes β-1,4-linked 2-acetamido-2-deoxy-D-glucose (*N*-acetylglucosamine) polymers of five residues or greater, as well as alternating copolymers of *N*-acetylglucosamine and *N*-acetylmuramic acid, to yield smaller saccharides with β stereochemistry retained at the point of cleavage. The X-ray crystallographic structure of Phillips' group[2] and kinetic investigations in model systems have suggested at least four factors which might be crucial for catalytic activity of the enzyme.

Distortion of the saccharide ring at the point of cleavage into a half-chair conformation more like that of the transition state can result in relief of strain upon hydrolysis, and therefore a large rate acceleration. The synthesis of strained model ketals has led to small rate accelerations,[3] although it has not been possible to sort the observed effect into contributions due to altered substrate basicity and acceleration of bond breaking. The ingeniously designed transition state analog of Lienhard's group[4] has been found to bind more tightly to lysozyme than tetra-*N*-acetylglucosamine, but the actual site of binding was not proved.

There is kinetic evidence that β anomers of 2-acetamido-2-deoxyglucopyranosides are more rapidly hydrolyzed in aqueous solution than their glucose counterparts, and that this acceleration is due to nucleophilic participation of the acetamido group at the developing carbonium ion.[5] It has been shown, however, that the presence of the acetamido group in the substrate is not an absolute requirement for lysozyme-catalyzed hydrolysis.[6]

The finding of two carboxylic acid residues, aspartic acid-52 (Asp$_{52}$) and glutamic acid-35 (Glu$_{35}$), at the presumed site of cleavage of chitin oligosaccharides in the lysozyme active site suggested that these residues might be crucial for the activity of the enzyme. The carboxylic acid side chain of Glu$_{35}$ has been suggested

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