Development Award (CA-00015).

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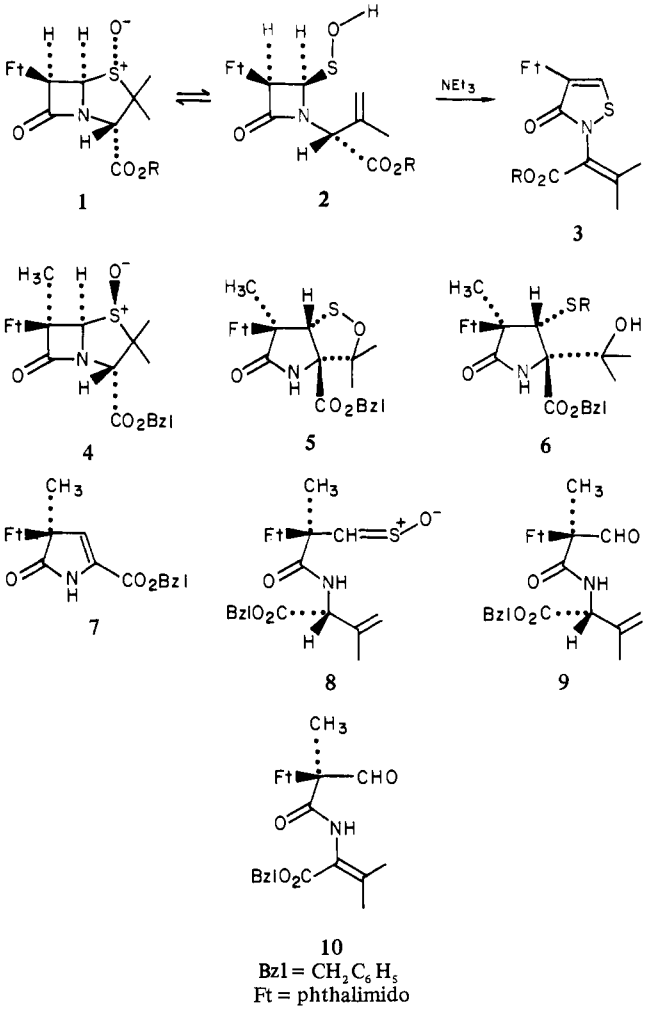
Received August 25, 1980

Rearrangement of Penicillin Sulfoxides in Base. Penicillin-Derived Sulfines

Sir:

The abnormal Pummerer rearrangement of penicillin sulfoxides (**1**) provides, under acidic catalysis, methyl-substituted penams, cephams, and cephems as well as small amounts of isothiazolone-containing products.[1] The postulated sulfenic acid

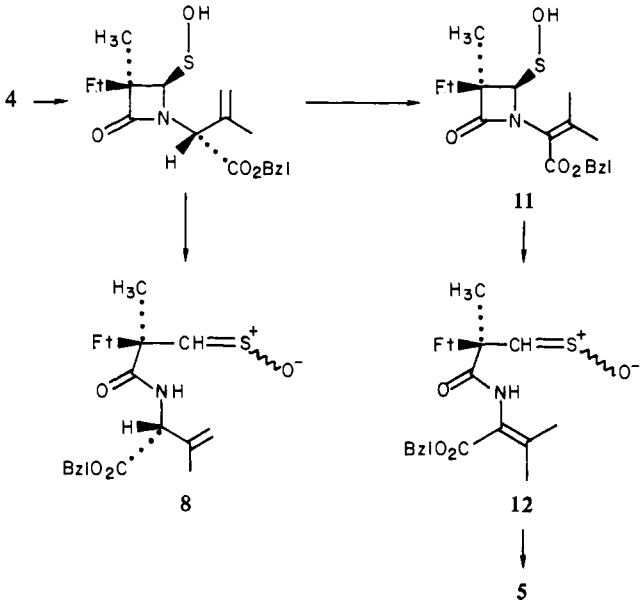


1 2 3 4 5 6 7 8 9 10

Bzl = $CH_2C_6H_5$
Ft = phthalimido

intermediate (**2**)[1] has since been isolated and shown to undergo clean base-catalyzed conversion to the isothiazolone (**3**).[2] In an attempt to determine the nature of the intermediates between **2** and **3**,[3] we have examined the pyrolysis of a 6α-methyl-substituted

Scheme I



penicillin sulfoxide in basic media. In this substance (**4**) the absence of 6α-hydrogen atom renders isothiazolone formation impossible. Thus, refluxing the β-sulfoxide **4**[4] in pyridine (40 min, argon atmosphere) gave two new substances (total yield 65%) which were separated by flash chromatography[5] (benzene/ethyl acetate 3:1, silica gel). The slower moving component (**5**), mp 166–167 °C (from toluene),[6] was isomeric with the starting material, *m/e* 466, and showed no β-lactam absorption in the IR, but along with typical phthalimido and ester peaks (1790 and 1730 cm^{-1}) exhibited a new amide absorption (1685 sh and 3430 cm^{-1}). The NMR spectrum of **5** showed three methyl groups [^1H ($CDCl_3$) δ 1.27 (s, 3 H), 1.43 (s, 3 H), and 2.08 (s, 3 H); ^{13}C ($CDCl_3$) δ 20.33, 21.89, 22.99 (q)]. The presence of a sulfenic ester moiety in **5** was demonstrated by instantaneous reaction with thiophenol to give the disulfide (**6**, R = SC_6H_5), 91%, mp 161.5–162.0 °C (from toluene), *m/e* 576, whereas triphenylphosphine gave, on subsequent hydrolysis of the first formed adduct, the hydroxy thiol (**6**, R = H), 64%, mp 205–220 °C dec (from ethyl acetate). At 230 °C this substance (**6**, R = H) lost H_2S and acetone to yield the 4-pyrrolidin-2-one **7** [IR ($CHCl_3$) 3440, 1780, 1725, 1685 (sh) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (s, 3 H), 5.27 (s, 2 H), 6.18 (d, *J* = 1.8 Hz, 1 H), 7.38 (s, 5 H), 7.51 (s, br, 1 H), 7.71–7.88 (m, 4 H); MS, *m/e* 376 (M^+), 285, 147, 104, 91]. The relative stereochemistry was proven by X-ray analysis of **5** to be that shown.[7]

The faster moving component from the sulfoxide pyrolysis (**8**), *m/e* 466, also showed no β-lactam carbonyl but showed secondary amide bands, (1685 sh and 3430 cm^{-1}) and in the NMR spectrum, the presence of an isopropenyl group adjacent to >CH-NH-CO [^1H NMR (*Z* **8**, $CDCl_3$) 1.74 (s, br, 3 H), 4.99–5.09 (m, 3 H), 7.41 (d, br, *J* = 7 Hz, 1 H)]. The sulfine hydrogen was clearly visible at 8.69 and 8.76 (*Z*/*E* ratio = 80:20). These values are essentially identical with those reported for the stereoisomeric propanethial *S*-oxides, the lachrimatory principal of onions.[8] The masked aldehyde functionality in **8** was exposed on mild acid

(1) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Am. Chem. Soc.*, **91**, 1401 (1969).

(2) T. S. Chou, J. R. Burgtorf, A. L. Ellis, S. R. Lammert, and S. P. Kukolja, *J. Am. Chem. Soc.*, **96**, 1609 (1974).

(3) Previously both sulfines and ene sulfenates have been suggested as intermediates in this transformation; cf. G. A. Koppel and S. Kukolja, *J. Chem. Soc., Chem. Commun.*, 57 (1975).

(4) J. E. Baldwin, S. R. Herchen, J. C. Clardy, K. Hirotsu, and T. S. Chou, *J. Org. Chem.*, **43**, 1342 (1978).

(5) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.* **43**, 2923 (1978).

(6) All new crystalline compounds have satisfactory analytical and spectral data.

(7) The crystallographic data for **5** were as follows: *a* = 13.088 (1) Å, *b* = 12.803 (1) Å, *c* = 16.325 (2) Å, β = 110.70 (1)°; monoclinic, space group $P2_1$, *Z* = 4. The crystal contained some disordered chloroform which severely degraded the refinement. The formula is approximately $C_{24}H_{22}N_2O_6S \cdot 0.25\ CHCl_3$. The measured density is 1.30 g cm^3. The density calculated from this formula is 1.29 g cm^3.

(8) E. Block, L. K. Revelle, and A. A. Bazzi, *Tetrahedron Lett.*, 1277 (1980).

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hydrolysis (trifluoracetic acid–water 60:40, 12 h, 25 °C) to give the aldehyde **9**. [^{1}H NMR ($CDCl_3$) δ 9.70 (s, 1 H)], which was readily isomerised by triethylamine in $CHCl_3$ (15 min, 60 °C) to **10** [IR ($CHCl_3$) 3360, 1784, 1722, 1674 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.67 (s, 3 H), 1.84 (s, 3 H), 2.14 (s, 3 H), 5.08 (s, 2 H), 7.27 (s, 5 H), 7.3–8.0 (m, 5 H), 9.62 (s, 1 H); MS *m/e* 434 (M^+), 343, 315, 147, 104].

The most reasonable explanation of these results is that the sulfenic acid derived from **4** undergoes base-catalyzed ring opening to sulfine **8** which was isolated or alternatively isomerized to **11** and, after ring opening to **12**, underwent 1,3-dipolar cycloaddition to the isolated **5** (Scheme I). Attempts to effect isomerization of 8 to 12 with various bases merely led to a generalized decomposition.

We conclude that base-catalyzed ring opening of azetidinone sulfenic acids gives sulfines, which may be isolated or intercepted as their intramolecular 1,3-dipolar adducts.

Acknowledgment. We thank the N.R.D.C. and the Cephalosporin Fund for financial support. G.S. thanks the Deutsche Forschungsgemeinschaft for a stipend, and C.P.F. thanks the University of Sheffield Research Fund for support during leave of absence.

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Received July 28, 1980

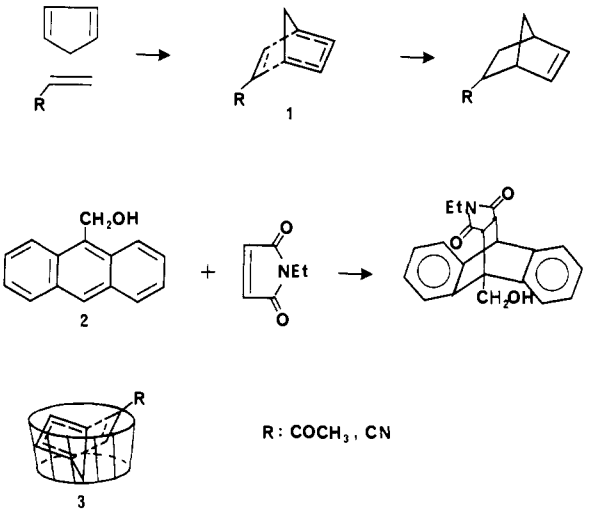
Hydrophobic Acceleration of Diels–Alder Reactions

Sir:

When substances with nonpolar regions are dissolved in water, they tend to associate so as to diminish the hydrocarbon–water interfacial area. This "hydrophobic effect"[1] is a principal contributor to substrate binding in enzymes and to the self-association of amphiphiles in micelles or membranes. Curiously, however, hydrophobic effects have not been reported, to our knowledge, for any typical bimolecular chemical reaction of small molecules in aqueous solution except for cases[2] in which long hydrocarbon chains are arbitrarily present to promote association. Since in the Diels–Alder reaction of, e.g., cyclopentadiene with butenone the transition state **1** brings together two nonpolar groups, one might expect that in water this reaction could be accelerated by hydrophobic interactions. We wish to report that this is indeed the case, both for simple hydrophobic binding and for mutual hydrophobic binding into a cyclodextrin cavity.

The reaction of cyclopentadiene (0.4 mM) with butenone (12.1 mM and 25.5 mM) was followed at 250 nm and 20.0 °C in water and showed first-order disappearance of cyclopentadiene over two half-lives. The pseudo-first-order rate constant was also first order in butenone, giving a second-order rate constant k_2 of 4.40 ± 0.07 × 10^{-2} M^{-1} s^{-1}. This rate constant is listed in Table I along with the other rate constants determined for this reaction in other media and for the other Diels–Alder reactions we have examined. As this table shows, the reaction with butenone shows more than a 700-fold acceleration in water compared with the rate in 2,2,4-trimethylpentane. The rate in methanol is intermediate, but closer to that in the hydrocarbon solvent.

Lithium chloride is a salt which increases[3] the hydrophobic effect, i.e., it "salts out" nonpolar materials dissolved in water.



As expected from this, we get an increase in the rate of the Diels–Alder reaction with 4.86 M LiCl over that in water alone. Guanidinium chloride is similar to urea in changing the water structure so that it normally decreases[3] hydrophobic interactions; i.e., it "salts in" nonpolar material. We find (Table I) that 4.86 M guanidinium chloride does not increase the Diels–Alder rate over that in water. The contrast with LiCl is as expected for a hydrophobic effect, although the absence of a rate decrease[4] with guanidinium was not expected.

The Diels–Alder reaction of cyclopentadiene with acrylonitrile (Table I) shows only a small rate increase on changing the solvent from hydrocarbon to methanol but a much larger increase with water. Again it seems likely that this large increase in water is not simply a polar effect in a reaction which shows little sensitivity to the polarity of the other two solvents but is a specific hydrophobic effect. The most striking evidence of this comes from our study (Table I) on the Diels–Alder reaction of anthracene-9-carbinol (**2**) with *N*-ethylmaleimide. This reaction is *slower* in polar solvents than it is in nonpolar hydrocarbon solution,[5] with the exception of water in which the rate is very fast. Only the hydrophobic effect seems capable of explaining this exceptional behavior of water.

Molecular models suggest that the transition states (**1**) for reaction of cyclopentadiene with butenone and acrylonitrile should be able to fit (cf. **3**) into the hydrophobic cavity of β-cyclodextrin (cycloheptaamylose) but not in the smaller cavity of α-cyclodextrin (cyclohexaamylose). The data in Table I indicate that this is correct. The two reactions are both even faster when 10 mM β-cyclodextrin is added to the water but slower with 5 or 10 mM α-cyclodextrin.[6] This inhibition by α-cyclodextrin is expected since cyclopentadiene can bind to it, but in this small cavity there is then no room for the dienophile. For the larger transition state in the anthracene-9-carbinol reaction, even β-cyclodextrin is unable to bind both diene and dienophile and is an inhibitor, not a catalyst.

The catalytic effect of β-cyclodextrin is even larger than is apparent from the data in Table I. The rates increase with increasing β-cyclodextrin concentration with no indication of kinetic saturation, so at 10 mM β-cyclodextrin we are far from V_{max}. Furthermore the hydrophobic binding of diene plus dienophile into a cyclodextrin cavity in water largely replaces the association because of hydrophobic interaction in water alone which we have already discussed earlier. Thus the catalysis of the Diels–Alder reactions of cyclopentadiene by mutual binding

(1) For reviews, see: (a) Ben-Naim, A. "Hydrophobic Interactions"; Plenum Press: New York, 1980. (b) Tanford, C. "The Hydrophobic Effect", 2nd ed.; Wiley: New York, 1980.
(2) Reference 1a, p 97, and references therein.
(3) von Hippel, P. H.; Schleich, T. *Acc. Chem. Res.* **1969**, *2*, 257.
(4) Urea at 5.38 M also gave at most a slight decrease in the rate.
(5) The decrease probably reflects hydrogen bonding between diene and dienophile in the transition state which is less effective in more polar solvents.
(6) One might in general expect some change in exo–endo product ratios for reactions which are hydrophobically accelerated by water or by cyclodextrin binding, but we have not yet seen large clear trends. Furthermore, reaction in a cyclodextrin cavity might induce chirality in the product. We do see some optical activity in the cyclopentadiene–butenone adducts, but it corresponds to only a few percent enantiomeric excess.

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