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A DRAMATIC SOLVENT EFFECT IN A $[{}_{\pi}4_s + {}_{\pi}2_s]$ CYCLOADDITION REACTION

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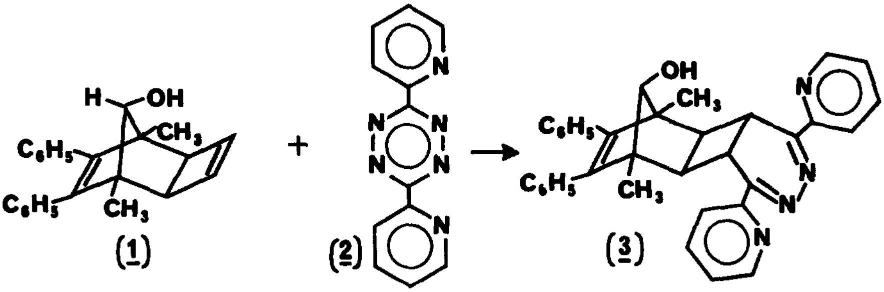
Pericyclic $[{}_{\pi}4_s + {}_{\pi}2_s]$ (Diels-Alder) reactions have been the subject of numerous mechanistic studies (*1,3*). It is generally accepted that the transition states for this class of reactions differ little in charge distribution from the initial states and may be termed isopolar (*2*). As a consequence, the activation parameters of these reactions are insensitive functions of solvent polarity. For example Sauer and his co-workers have studied (*3*) the reaction of 3,6-diphenyl-s-tetrazine with styrene and observed that the rate constant for the reaction in dimethylformamide is only 2.4 faster than that in toluene.

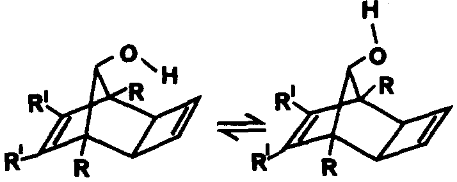
We were surprised, therefore, to observe a marked increase in the rate of reaction of the cyclobutene alcohol (1) with 3,6-di(2'-pyridyl)-s-tetrazine (2) upon change of solvent from chloroform to dimethylsulphoxide (DMSO). We present evidence to show that this solvent effect is not due to development of charge separation in the transition state, but rather to different conformational preferences of the hydroxyl group in the two solvents.



The kinetics for the reaction in each solvent were obtained spectrophotometrically by following the loss of absorbance at 550 nm due to the *s*-tetrazine (2). The bimolecular rate constants at 23.8° are: DMSO 5.62×10^{-2}; $CHCl_3$ 26.39 litre mole^{-1} second^{-1}. This represents a rate enhancement factor of 470 in favour of the reaction in DMSO*.

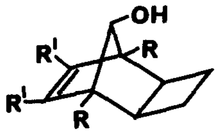
This solvent effect is peculiar to the alcohol (1), since other members of this class of dienophiles, the 9-methoxy, the 9-unsubstituted and the 9-keto compounds display normal solvent effects of 2.7, 2.1 and 1.4 respectively upon changing from $CHCl_3$ to DMSO.

An important feature of alcohol (1) is the occurrence of a *single* band in the hydroxyl stretching region of the infra red spectra in $CDCl_3$ or CCl_4 solution. The concentration independence of the position of this band and its low frequency ($\nu = 3592\ cm^{-1}$ CCl_4) compared with the saturated compound (4) ($\nu = 3645\ cm^{-1}$; $\Delta\nu = 53\ cm^{-1}$) indicates that (1) must exist almost exclusively (*4*) in the intramolecular H-bonded form (1a) in non H-bonding media. While it was not possible to examine the i.r. spectrum of (1) is DMSO due to strong solvent absorption in this region, the spectrum in di-n-butyl ether was obtained. Two bands were observed, that due to the intramolecular H-bonded form ($\nu = 3598\ cm^{-1}$) and that due to the intermolecular H-bonded form ($\nu = 3498\ cm^{-1}$). As this ether is of intermediate H-bonding capacity it would be reasonable to assume that the intramolecular H-bonded form would predominate in the strongly H-bonding DMSO solvent.



(1a) (1b)

$R' = C_6H_5$
$R = CH_3$



(4)

Further evidence that (1) existed predominantly in the intramolecular H-bonded conformation (1a) in $CDCl_3$ and CCl_4 and in the intermolecular H-bonded to solvent conformation (1b) in DMSO, was obtained from pmr spectroscopy. The coupling constant between H_9 and the OH-group is 12 Hz in $CDCl_3$ and 7.5 Hz in DMSO-d_6 in agreement with the typical coupling constants (*7*) for arrangements represented in (1a) and (1b) respectively. Upon change in solvent from $CDCl_3$ to DMSO-d_6, the OH-proton moves downfield from $\delta 3.2$ to $\delta 4.4$ ($\Delta\delta = 1.2$). This is smaller than the usual solvent shift ($\Delta\delta = 3\text{-}3.5$) (*8*) in alcohols having free

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* The product was separately isolated from each reaction and shown to be identical. The dihydropyridazine structure (3) was supported by pmr spectroscopy.

OH-groups, and reflects that here we are dealing with the differences in chemical shift of two H-bonded forms.

The solvent effect on the rate of reaction of (1) with (2) may be rationalised, making the assumption that the rotamer represented by (1b) is more reactive towards (2) than the rotamer represented by (1a) If the ratio of concentrations of (1b):(1a) is designated by K, and the rate constants for (1b) by k, then the observed constants k_o in $CHCl_3$ and DMSO are

$$k_o^{DMSO} = k^{DMSO}.K^{DMSO} \qquad k_o^{CHCl_3} = k^{CHCl_3}.K^{CHCl_3}$$

If k^{DMSO}/k^{CHCl_3} may be approximated as 2.7 (the value of the corresponding 9-methoxy compound), and since $K^{DMSO} >> K^{CHCl_3}$ it follows that $k_o^{DMSO} >> k_o^{CHCl_3}$. That the rotamer (1b) should be more reactive than the intramolecularly H-bonded rotamer (1a) towards the tetrazine (2) is probably due to two effects: a) deactivation of the cyclobutene double bond in (1a) due to the intramolecular H-bond* and b) activation of the double bond in (1b) caused by interactions between the Π MO's of the double bond and the non-bonding atomic orbitals at the oxygen atom through space, an effect which is maximised in this rotamer. This latter type of interaction if further discussed in an accompanying communication.

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* Preliminary calculations based on the INDO MO method have been carried out (9) on the interaction of methanol and ethylene. At the distances and configurations corresponding to those in compound (1a,b), these calculations suggest† that the H-bonded form (1a) is favoured over the rotamer (1b) by about 3 kcal/mole, and that charge is transferred from the double bond to the hydroxyl group. This charge transfer would naturally lessen the ease of reaction of (1a) with electron deficient dienes such as the *s*-tetrazine (2).

† Other calculations (10) on the water-water interaction have cast doubt on the validity of these semi-empirical methods (INDO and CNDO) to handle interactions involving lone pair electrons. This topic is currently under active investigation, the results of which will be published elsewhere.

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3. J. Sauer, *Angew. Chem.*, 79, 76 (1967); *Angew. Chem. Internat. Edit.*, 6, 16 (1967).
4. To our knowledge this is the first reported example of an unsaturated (ethylenic) alcohol existing almost solely in the intramolecularly hydrogen bonded form (*5*).
5. It has come to our attention that *endo*-bicyclo[2.2.1]heptan-2-ols with a 5,6-*endo*-benzo or -naphtho substituent also possess unusually strong intramolecular hydrogen bonds (*6*).
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9. A.R. Gregory, M.N. Paddon-Row and R.N. Warrener *unpublished results*.
10. A.R. Gregory and M.N. Paddon-Row, *unpublished results*.