IC/IR/2005/007
INTERNAL REPORT
(Limited Distribution)

United Nations Educational Scientific and Cultural Organization
and
International Atomic Energy Agency

THE ABDUS SALAM INTERNATIONAL CENTRE FOR THEORETICAL PHYSICS

SOLVENT EFFECTS IN THE ACID-CATALYSED REARRANGEMENTS OF 1, 2-OXAZINES

Ahmed K. Yagoub[1]
College of Applied and Industrial Science, University of Juba,
Khartoum, P.O.B., 794, Omdurman, Sudan
and
The Abdus Salam International Centre for Theoretical Physics, Trieste, Italy

John A. Ogur and Adam K. Wanekaya
University of Nairobi, Kenya.

Abstract

The rates of acid-catalyzed rearrangements of 6-ethoxy-5,6-dihydro-3-phenyl-*4H*-1,2-oxazines have been investigated in H_2SO_4 / methanol, MeCN and Me_2SO by means of spectrophotometric methods. Pseudo first order rate constants were obtained in each case. Results in methanol supported an A1 type mechanism. Also investigated were the correlation of reaction rates with Hammet acidity function ($H_\circ$) by application of the Bunnet criterion where a slope of -0.67 was obtained. Further, the solvent effect was considered from two points of mechanistic views: the thermodynamic transfer functions of MeOH to MeCN and Me_2SO where the rate was found fast in MeCN and slow in Me_2SO and the Kirkwood-Buff preferential solvation with aqueous MeOH, MeCN and Me_2SO. The techniques supported the proposed transition state structure.

MIRAMARE – TRIESTE
December 2005

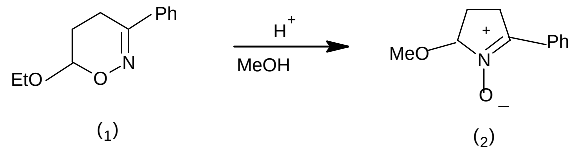
---

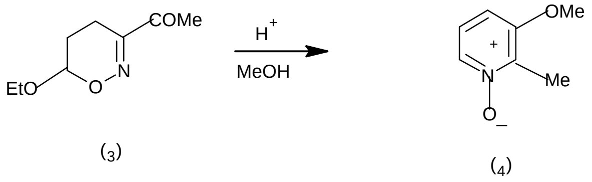
[1] Senior Associate of ICTP.

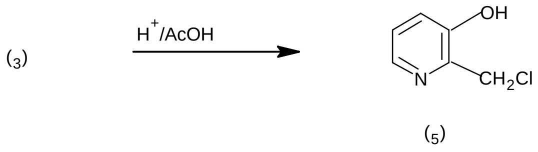
1. Introduction

1.1 The reaction

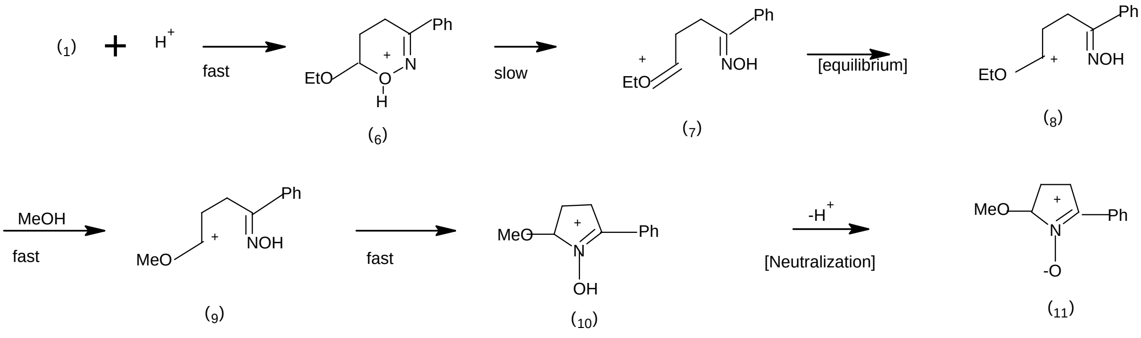
It is known that 6-ethoxy-5,6-dihydro-3-phenyl-*4H*-1,2-oxazine (1) undergoes an acid catalysed rearrangement in methanol to give 3,4-dihydro-2-methoxy-5-phenyl-*2H*-pyrrol-1-oxide [1,2]. (2) (Scheme 1). We also note that the 3-acetyl substituted oxazine (3) gave 3-methoxy-2-methyl pyridine-1-oxide (4) while HCl acidified Acetic acid gave chloromethylpyridines. These reactions are general and have high synthetic potential however, the transformation is very interesting and challenging as a mechanistic problem







The reaction of (3) with acid proceeds via 2-acetyl-substituted nitrone (5) which cannot be isolated as it is thought is to open and recyclise fast to (4) [1]. Hence, a preliminary mechanistic study of these reactions is rational with a kinetic study of the phenyl oxazines because its rearrangement product the 5-phenylpyrrole-1-oxides (2) is stable and have been isolated. A tentative mechanism is shown in scheme 1.



Scheme 1

1.2 Acid Catalysis

1.2.1 Catalysis in Sulphuric Acid

The sulphuric acid system contains a complex milieu of species in equilibrium.[3,4,5] The nature and concentration of the species present are dependent on the acid region under consideration.[5] In the dilute acid region the important species beside H_2O are $H(H_2O)_n^+$, HSO_4^- and to a lesser extent SO_4^{2-}. The actual hydronium ion, H_3O^+, reaches maximum concentration at 85% H_2SO_4. In the region 85-100% H_2SO_4, the H_3O^+, HSO_4^- and SO_4^{2-} species (as well as H_2O) rapidly decrease in concentration. Simultaneously, undissociated H_2SO_4 increases in concentration and becomes the principal species present. In the 100% H_2SO_4 region and through the dilute oleum region, the acidic species present are H_2SO_4, $H_2S_2O_7$, SO_3 and $H_3SO_4^+$ while the basic species are HSO_4^-, $HS_2O_7^-$ (and H_2SO_4).

1.2.2 The H$_\circ$ acidity function

The H$_\circ$ is a quantitative measure of acidity derived from ionization equilibria of a particular class of indicators, those behaving in the Bronsted-Lowery sense as uncharged bases.

$$B \quad + \quad H^+ \quad \longrightarrow \quad BH^+$$

It is defined by [6,7,8] .

$$H_\circ = pK_{BH^+} - \log \frac{C_{BH^+}}{C_B}$$

where $\frac{C_{BH^+}}{C_B}$ is the ratio of the concentration of an indicator in its acid and basic forms and it is directly measurable for a given solution by means of spectrophotometer. K_{BH^+} is the thermodynamic ionization constant of the conjugate acid, $= \frac{C_{BH^+}}{C_B}$. Thus

$$H_\circ = -\log \frac{(a_{H^+} f_B)}{f_{BH^+}} = -\log h_\circ$$

where a_{H^+} represents hydrogen-ion activity and f_B and f_{BH^+} are molar concentration activity coefficients. By convention the f_B and f_{BH^+} are taken to be unity in ideal dilute aqueous solutions while a_{H^+} under this condition is identified with conventional hydrogen ion concentration [8]. In the limiting case of the ideal dilute aqueous solution, h$_\circ$ becomes equal to hydrogen-ion concentration while H$_\circ$ become equal to *p*H.

The H$_\circ$ function serves specifically as a measure by the tendency for the solution in question to transfer a proton to an uncharged base molecule. The H$_\circ$ acidity scale has turned out to be useful for the measurement of the base strength of very weak bases and also for the interpretation of the kinetics of certain classes of acid catalyzed reactions. One of the more important properties of the acidity function is that it can be utilized in non-aqueous solutions and the resulting acidities are referred to the dilute aqueous reference automatically.

It is also applicable to very concentrated solutions. However, there are some limitations to some non aqueous or mixed solvents, particularly those solvents with low dielectric constant. [9,10]

One of the ideas underlying the original development of the $H_\circ$ indicator acidity scale by Hammett and Deyrup was its possible bearing on acid catalysis. In the subsequent years there have been many applications of this function to the kinetics of acid catalyzed reactions, and a number of correlations between reaction rates and indicator acidity have been discovered.

This has evolved through many attempts: Zucker-Hammett[11,12,13] , Bunnett[14] and the modified treatment of Olsen and Bunnett[14a] :

$$\text{Log } k + H_\circ = \varphi\,(H_\circ + \log C_{HX}) + \text{constant}$$

where φ is a hydration parameter reflecting the involvement of water in a reaction. For $\varphi < 0$ the reaction is A1 type, 0.22 to 0.56 for A2 type with nucleophilic attack on H_2O and > 0.58 A2 with H_2O proton acceptor.

1.3 Solvent effect on reaction rates

The sophisticated analysis of solvent effects on transition states has superceded the earlier correlations of log k with solvent parameters[14b] . With the advent of transition state theory it became possible to dissect solvent effects on reaction rates into initial-state and transition-state contributions. Although the necessary theory has been worked out and applied to the solvolysis of t-butyl chloride [15], only since the work of Winstein and Fainberg [16] has progress on these lines been made. In principle, the solvent effect on any activation parameter (e.g. $G^{\neq}$, $H^{\neq}$, $S^{\neq}$, $V^{\neq}$, free energy, enthalpy, entropy and molar volume respectively) may be dissected into the initial state and transition state contributions, but it is the free energy function that is related directly to the rate constants.

The specific rate of a chemical reaction depends on the standard free energy difference between reactants and transition state. Therefore, the problem of the influence of the solvent on reaction rate reduces to an easier one of determination of free energies of solvation of the reactants and of transition states. [17,18]

Any consideration of solvent effects on rate or equilibria must start from solvent activity coefficients ${}^{\circ}\tau_i^s$ for reactants, transition states or products[18,19]. Once solvent activity coefficients are available or can be predicted, it is highly probable that an enormous amount of information on the kinetics of reaction in solution properties can be reduced to a relatively small number of constants. This include solubility, acid-base strength and kinetics of reaction in different solvents[19,20].

Solvent activity coefficients are defined such that ${}^{\circ}\tau_i^s$ reflects the change in the standard chemical potential μ_i of a solute i, (hypothetically ideal to Henry's Law, unimolar solution), on transfer from an arbitrary chosen reference solvent (i.e. the standard state) to another solvent, s. The superscripts o and s denote the reference solvent and the other solvent, respectively. Hence

$$\mu_i^s = \mu_i^\circ + RT \ln {}^{\circ}\tau_i^s$$

Solvent activity coefficients are applied to reaction rates in terms of the Absolute Rate Theory, which assume an equilibrium between reactants and transition states, $X^{\neq}$. If the transmission coefficient is unity, the rate of reaction is given by the product of a frequency factor kT/h and the concentration, $[X^{\neq}]$, of the transition state.

$$rate = \frac{kT}{h}\left[X^{\neq}\right]$$

For a bimolecular reaction:

$$A \;+\; B \longrightarrow X^{\neq} \longrightarrow P$$

In solvent, s, $[X^{\neq}]$ is given by the following equation where $K^{\#}$ is the thermodynamic equilibrium constant between transition state and reactants.

$$\left[X^{\neq}\right] = K^{\neq}[A][B]\;\frac{{}^{\circ}\tau_A^s\;{}^{\circ}\tau_B^s}{{}^{\circ}\tau_{X^{\neq}}^s}$$

Hence,

$$rate = [A][B]K^{\neq}\frac{kT}{h}\;\frac{{}^{\circ}\tau_A^s\;{}^{\circ}\tau_B^s}{{}^{\circ}\tau_{X^{\neq}}^s}$$

and the specific rate constant in solvent s is given by the equation:

$$k^s = K^{\neq}\frac{kT}{h}\;\frac{{}^{\circ}\tau_A^s\;{}^{\circ}\tau_B^s}{{}^{\circ}\tau_{X^{\neq}}^s}$$

In the standard solvent, ${}^{\circ}\tau_i^s$ is, by definition, unity, so that

$$k^{\circ} = \frac{kTK^{\neq}}{h}$$

and rate constants in different solvents are related by the following equation which allows a quantitative prediction of solvent effects on rates of reactions if ${}^{\circ}\tau_i^s$ for the solutes and solvent are known or can be estimated.

$$k^s = k^{\circ}\;\frac{{}^{\circ}\tau_A^s\;{}^{\circ}\tau_B^s}{{}^{\circ}\tau_{X^{\neq}}^s}$$

1.3.1 Thermodynamic Transfer Functions

In the recent past, there has been a great increase in the use of thermodynamics transfer functions by organic chemists. Their use to elucidate transition state behavior started in the 1960's, on one hand with Arnet [17] who aimed to explain the serpentine variation of the hydrolysis of t-butyl chloride in alcohol-water mixtures and on the other with Parker's studies of bimolecular nucleophilic substitution reactions in dipolar aprotic solvents. The latter were found to have very large rate-enhancing properties in many instances as compared with hydroxylic solvents.[21]

The thermodynamics transfer function approach of medium changes is highly informative concerning transition state structure enabling one to deduce subtle effects of charge distribution and the correlation between medium effects and structure reactivity relationships.

If $\delta\delta G$ is the change in standard free energy that accompanies the transfer of solvent to another, it can be obtained (for neutral molecules) from relative solubility or from the distribution coefficients relative to a third mutually immiscible solvent.[22] For single ions the calculations are less reliable, as one cannot dissolve a cation without taking the accompanying anion into solution as well. A reliable assumption is to assume that the charge plays an insignificant role in salvation if it is embedded deep inside the hydrocarbon part of a large polarisable organic molecule. Thus for the salt $(Ph_4As^+)(Ph_4B^-)$ the observed $\delta\delta G$ is divided into equal contributions from each ion. One can then obtain $\delta\delta G$ values for any other ion say X- , by subtracting the value for Ph4As+ from the measured value for $Ph_4As^+X^-$.

Finally, the reaction can be measured in each solvent to obtain $G^{\neq}$ values, hence $\delta\delta G^{\neq}$, the free energy of solvent transfer to the transition state is obtained by completing the cycle in fig 1 below. Alexander[23] carried out similar work on S_N2 reactions e.g. $MeI + Cl^-$ and $Me_3S^+ + SCN^-$.

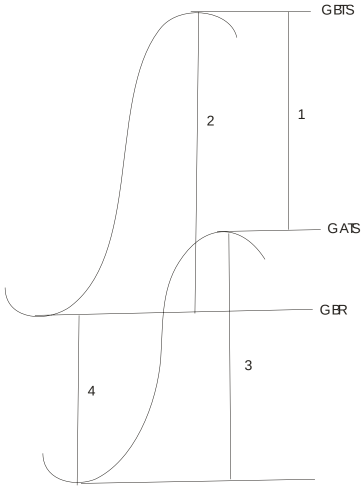


Fig. (1) Calculation of the free energy of transition state from solvent A to solvent B.
GBTS = Free energy of TS in B GATS = Free energy of TS in A
GBR = Free energy of reactants in B GAR = Free energy of reactants in A
1 = $\delta\delta G_B^{A\neq}$; change in standard free energy of transfer of transition state from solvent A to B.
2 = $\Delta G_B^{\neq}$; change in free energy of activation of solvent B.
3 = $\Delta G_A^{\neq}$; change in free energy of activation of solvent A.
4 = $\Sigma\delta\delta G_B^{A\theta}$; summation for all solutes of change in standard free energy of transfer of a solute from solvent A to B.

$$-RT\ln\left(\frac{k_B}{k_A}\right) = \Delta G_B^{\neq} - \Delta G_A^{\neq}$$

$$\delta\delta G_B^{A\neq} = \Sigma\delta\delta G_B^{A\theta} + \Delta G_B^{\neq} - \Delta G_A^{\neq}$$

1.3.2 Kirkwood-Buff Treatment of Preferential Solvation

It has been observed that by changing the composition of aqueous systems it is possible to control, speed up or slow down a given chemical reaction[24]. Aqueous mixtures have been classified into typically aqueous and typically non aqueous mixtures. The mixtures are classified as typically non-aqueous mixtures if excess molar enthalpies of mixing $\left(H_m^E\right)$ are larger than the excess molar entropies-temperature product i.e. $\left(H_m^E\right) > TS_m^E$.

The Kirkwood-Buff treatment of liquid systems was originally aimed at showing how the thermodynamic properties of a mixture could be classified from knowledge of angle-averaged Pair-correlations functions, g_{12} (R), g_{22} (R) and g_{11} (R) where R is the scalar distance. The link between this function and the thermodynamic properties is established through the integral functions G_{11}, G_{22} and G_{12}. Thus for the integral function G_{12},

$$G_{12} = \int [g_{12}(R) - 1] 4\Pi R^2 .dR$$

The function G_{12} measures the tendency of molecules of liquid 1 towards the molecules of liquid 2. The inverse Kirkwood-Buff developed by Ben-Naim [25] uses the thermodynamic data of a given mixture to calculate the integral functions G_{11}, G_{22} and G_{12}. For ethanol (2) and water (1), the functions G_{11}, G_{22} and G_{12} have been calculated using excess molar Gipps free energies G_m^E, molar volumes, V_m and isothermal compressabilities, κ_T at 298.2K.

The integral functions G_{j1} expresses the affinity of solute j for solvent 1 in its cosphere. [25,26]

The analysis of the rates of reaction in aqueous solvents in the whole mole fraction ranges and their comparison with molar excess thermodynamic functions and Kirkwood-Buff integral functions may yield valuable mechanistic information regarding the transition state.

These observations have been known to point out an interesting link extending from kinetics through equilibrium thermodynamic properties of solutions and liquid mixtures to statistical thermodynamics treatment of liquid systems.

2. Experimental

I.R. spectra were recorded in KBr disc on a Beckmann Acculab 2 Infrared Spectrometer. ^{1}H nmr spectra were recorded on a Joel spectrometer operating at 90 MHz. and a Brucker spectrometer operating at 270 Mhz. Mass spectra were recorded on a VG 12-250 organic mass spectrometer. Melting points were uncorrected. Methanol was first distilled normally and then dried by refluxing it over magnesium metal and iodine for one hour followed by redistillation and storage over 3A molecular sieve. H_2SO_4 concentration was determined potentiometrically.

Kinetics

Kinetics measurement were made on an SP8-150 Pye Unicam spectrometer using thermostated 4 cm. Cells at 25°C. all runs were followed by recording the absorbance at appropriate wavelengths within regular intervals up to infinite absorbance.

The Guggenheim method eliminates the uncertainty surrounding infinite absorbance because of instrumental drift at long intervals, side reactions and temperature fluctuations. Secondly the error is applied to $\ln(A - A_\infty)$ rather to the observed quantity A where A is the absorbance.

The pseudo-first order rate constants were calculated using the Guggenheim method [27] from the slope of

$\ln (\in_{NIT} - \in_{OX})/(\in_{NIT} - \in_t)$ against time where:

$\in_{NIT}$ = Extinction coefficient of nitrone at kinetics wave length.

$\in_{OX}$ = Extinction coefficient of oxazine at kinetics wave length.

$\in_t$ = Extinction coefficient at time t.

All runs were followed up to the end of the fourth half life. Oxazine solutions were prepared prior to kinetics measurement. Kinetics wave length were 270 nm (1) and 360 nm (2).

Known concentration of the oxazine and methanol (containing a known concentration of the acid) were equilibrated in volumetric flasks placed in a constant temperature bath (25 ± 0.01 °C). Pseudo first order conditions were employed with the acid being in considerable excess. The spectrophotometer was zeroed using acidic solvents. The cells were thoroughly washed and a fresh portion of the acidic solvent was half filled in the sample and reference cells. The oxazine solution was finally introduced into the sample cell such that the concentration of sulphuric acid in the two cells is the same and the concentration of the oxazine in the sample cell is accurately known. Sulphuric acid concentration was varied from 1.83% to 27.9%. The same procedure was used for other solvents and aqueous solvents. The reactions were followed at wave lengths; 270 nm, for the oxazine and 280 nm for the nitrone.

A *p*H meter 22 Radiometer was used to follow the potentiometric titration of sulphuric acid against standardized sodium hydroxide in order to know the exact concentration of the acid.

Solubility

The solubility of the oxazine in MeOH, MeCN and Me_2SO were determined spectrophotometerically. The solutions were equilibrated by mechanical shaking a considerable excess of the finely grounded oxazine for several hours in 10 ml volumetric flask in thermostated water bath (25 ± 0.01 °C). Samples were drawn out, their specific gravities determined and the necessary dilutions done before their respective absorbance were read. The solubility were calculated from their molar absorptivity constants and the dilutions using Beer-Lambert law. These solubility values were converted to the mole fraction scale by using the predetermined specific gravities of the solution. Activity coefficients were obtained from freezing point depression data for the oxazine in Me_2SO and boiling point elevation for MeOH and MeCN solvents.

This was done by an improved method due to Beckmann [28], using ordinary freezing point depression apparatus. The activity a_{Me_2SO} was obtained from the equation:

$$a_{Me_2SO} \quad = \quad \exp\left(\frac{-H_{f,Me_2SO}\Delta T_f}{RT_f^2}\right)$$

where;

T_f = Freezing point of Me_2SO = 12.6 °C = 295.6 K.

H_{f,Me_2SO} = Molar heat of fusion of Me_2SO = 6.527 kj mol^{-1} [29]

ΔT_f = Freezing point depression.

and the activity coefficient of the solvent dimethylsulphoxide τ_{Me_2SO} was obtained from the equation;

$$\tau_{Me_2SO} = \frac{a_{Me_2SO}}{X_{Me_2SO}}$$

where X_{Me_2SO} is the mole fraction of Me_2SO in the various solutions. Finally a plot of

$\left(\frac{X_{Me_2SO}}{X_{oxa}}\right) vs \ln \tau_{Me_2SO}$ where X_{oxa} is the mole fraction of the oxazine in solution.

The plot curve is extrapolated and the area under the curve is determined. The activity coefficient is given by;

$\tau_{Me_2SO} = -\exp(-Area)$

From the boiling point elevation data the activity and activity coefficient were similarly calculated for methanol and acetonitrile.

Synthesis

6-Ethoxy-5,6-dihydro-3-para-chloro-phenyl-4*H*-1,2-oxazine[1,2] (1):

3,4-Dihydro-2-methoxy-5-phenyl-2*H*-pyrrole-1-oxide [1,2] (2):

3. Results and Discussion

MeOH was considered to be the standard solvent for the acid rearrangement in this work. The H_2SO_4 acid concentration varied from 1.83 to 27.9 % H_2SO_4 in MeOH. The rates of reaction in MeCN and Me_2SO were measured at 5% H_2SO_4 and compared with those of MeOH in an attempt to investigate solvent effects on the rate of reaction.

3.1. Acidity function

A least square fit to ($\log k_{obs} + H_o$) vs. ($\log[H_2SO_4] + H_o$) (Table 1) is linear with slope of (-0.67 ; linear correlation, r = 0.933). This supports an A1 according to the Bunnett criterion [30]. That is the protonated species (7) undergoes reaction in a unimolecular step. The negative slope also rules out the involvement of water in the rate determining step. Such a negative slope is typical of acetal hydrolysis. Alkoxy 1,2-oxazines are analogous to acetals.

Table 1: Observed rate costant in the MeOH/H_2SO_4 reaction.

%H_2SO_4	-H_o	$k_{obs} * 10^3 (min^{-1})$
1.83	-0.60	10.79
2.26	-0.48	11.72
3.73	-0.29	19.47
4.92	-0.13	20.41
6.12	0.04	17.84
7.29	0.15	21.28
9.02	0.27	17.75
11.60	0.33	16.33
14.92	0.55	16.69
17.5	0.75	15.42
20.01	1.01	11.06
27.9	1.55	12.52

The nonlinear behavior of (k_{obs}) against (-H_o) in high acid concentration could rationalize a change in mechanism. The rate increases steadily with increase in acid concentration up to about 7.3% H_2SO_4 (H_o = 0.15) after which a gradual decrease sets in. This is similar to what Wiig [31] got in the decomposition of citric acid in sulphuric acid [32] and the well known oxime and semicarbazones acid catalyzed addition to carbonyl compounds. The likely explanation is that at higher acidities the reactant is being converted into some species of much lower reactivity [33]. In the reaction above there is a likelihood of protonation of the nitrogen in (7) (scheme 1) at high acid concentration to give (11). This protonation decreases the concentration of (7) and hence the rate of the reaction. The decreased concentration of (7) makes the intramolecular attack by nitrogen the rate determining step.

3.2. Thermodynamic transfer functions

Differential solvation of initial and transition states is an important tool in mechanistic studies. The solvent effects on the rate of reaction were investigated by changing the solvent from MeOH to Me_2SO and MeCN at 5% H_2SO4.

3.2.1 MeOH to MeCN

Comparison of the rate constants in table 2 shows that the reaction in MeCN is almost twice as fast as the one in

MeOH. A look at table 3 reveals the initial state the (oxazine) is slightly stabilized ($\delta\delta G_{MeOH}^{MeCN^{\theta}}$ = -0.66 kjmol^{1}) on transfer from MeOH to MeCN.

The reason for this stabilization is that MeCN can much more readily accommodate polar solutes within its structure than protic solvents like MeOH. The standard chemical potential of polar molecules in protic solvents, is normally greater than the one in dipolar aprotic solvents and hence molecules are less soluble in protic solvents which lower their free energy.[34]

Similarly, the transition state is also stabilized on transfer from MeOH to MeCN ($\Delta G_{MeCN}^{\neq} - \Delta G_{MeOH}^{\neq} = -1.43 Kj.mol^{-1}$). The above stabilization is greater in magnitude as compared to the ground state stabilization ($\delta\delta G_{MeOH}^{MeCN^{\theta}} = -0.66 Kj.mol^{-1}$). This is a strong indication of substantial localization of charge on an electronegative atom in the transition state [35] which is in accord with the postulated transition state structure (7). Further more it is generally accepted that reactions passing through a positively charged transition state have their transition states more solvated by dipolar aprotic solvents than by protic solvents. [36] This observation had earlier been cited by Alexander and his group [37] who concluded that positive centers are generally more solvated by dipolar aprotic solvents than by MeOH. The negative end of MeCN dipole is significantly less diffuse than the positive end. As a result MeCN solvates positively charged centers better than negatively charged centers. In addition, MeCN has very weak basic properties as has been known for a long time from spectroscopic work. Thus, MeCN solvates not by accepting hydrogen bond from protic donors but essentially through ion-dipole, dipole-dipole and charge dispersion interactions. It is therefore clear from the argument above that although both the initial and transition state are stabilized in this transfer, the transition state stabilization surpasses the initial state stabilization and this results in an overall increase in reaction rate.

Another point worth mentioning is the reactivity of the solvated proton in MeCN. Being a weakly basic solvent, dissolving an acid in MeCN establishes a double acid base equilibrium. In H_2SO_4, for example is:

$$H_2SO_4 + MeCN \longrightarrow MeCN^{+}H + HSO_4^{-}$$

The reactivity of the solvated proton could be another reason for the enhanced reaction rate in MeCN as compared to MeOH. In fact solvated proton reactivity is high in MeCN and this prompted some authers to regard the protonated MeCN as a “super acid”. [38]

Table 2: Rate constants, activity coefficients and solubility of the oxazine in MeOH and MeCN (mole fraction).

Parameter	MeOH	MeCN
Rate constant(k, min^{-1}) x 10^3	20.41	35.48
Solubility $X_{solvent}$	0.50	0.67
Activity coefficient $\tau_{solvent}$	0.15	0.15

Table 3: Thermodynamic analysis of differential salvation from MeOH to MeCN at 25°C (G in kj mol^{-1})

k_{MeCN}/k_{MeOH}	1.74
$\delta\delta G_{MeOH}^{MeCN\theta}$	-0.66
$\Delta G_{MwCN}^{\neq} - \Delta G_{MeOH}^{\neq}$	-1.43
$\delta\delta G_{MeOH}^{MeCN\neq}$	-2.09

3.2.2 MeOH to Me$_2$SO

Transfer from MeOH to Me$_2$SO in 5% H_2SO_4 presents a very different picture. Table 4 shows that there is almost an 80-fold decrease in the rate of reaction on this transfer (k_{MeOH}/k_{Me2SO} = 78). Table 5 reveals that the initial state is destabilized ($\delta\delta G_{MeOH}^{Me_2SO\theta}$ = 5.0 kj.mol^{-1}). However the transition state destabilization ($\Delta G_{Me_2SO}^{\neq} - \Delta G_{MeOH}^{\neq}$ = 10.80 kj.mol^{-1}) is greater than the initial state destabilization. This results in an overall decrease in reaction rate. Ground state destabilization could be due to the fact that Me$_2$SO is slightly ordered solvent as shown by its abnormally large Trouton's constant [36] (29.6 cal.deg^{-1}.mol^{-1}; cf 25cal.deg^{-1}.mol^{-1} for MeOH and 20 cal.deg^{-1}.mol^{-1} for MeCN). This may cause some problems in the salvation of some solutes due to the difficulty in breaking the solvent structure.

Table 4: Rate constant, Activity coefficients and solubility of the oxazine in MeOH and Me$_2$SO (in mole fraction).

Parameter	MeOH	Me$_2$SO
Rate Constant (k, min^{-1}) x 10^3	20.41	0.26
Solubility $X_{solvent}$	0.50	0.48
Activity Coefficient $\tau_{solvent}$	0.15	0.02

Table 5: Thermodynamic analysis of differential salvation at 25°C from MeOH to Me$_2$SO (G in kj.mol^{-1}).

k_{MeOH}/k_{Me2SO}	78.00
$\delta\delta G_{MeOH}^{Me_2SO}$	5.00
$\Delta G_{M_2SO}^{\neq} - \Delta G_{MeOH}^{\neq}$	10.80
$\delta\delta G_{MeOH}^{Me_2SO\neq}$	15.80

Another factor which may explain the tremendous decrease in rate of reaction in Me_2SO as compared to MeOH is the fact that Me_2SO is 100 times more basic than methanol.[39] Hence the proton activity is 100 times lower in Me_2SO due to this tremendous difference in basicity.

3.3 Aqueous Organic Solvent Effects

The reaction was further investigated in aqueous MeOH, MeCN and Me_2SO in 5% H_2SO_4. The results are listed in Tables 6,7,8.

Table 6: Rate constants in aqueous MeOH.

X_{MeOH}	k x 10^3	Log k_{obs}
1.00	20.4	-1.69
0.69	1.8	-2.75
0.57	1.2	-2.92
0.27	1.7	-2.77
0.12	2.3	-2.64

Table 7: Rate constants in aqueous MeCN.

X_{MeCN}	k x 10^3	Log k_{obs}
1.00	35.5	-1.8
0.64	15.7	-1.99
0.40	10.3	-2.15
0.22	7.1	-1.94
0.10	11.6	-1.45

Table 8: Rate constants in aqueous Me_2SO.

X_{Me2SO}	k x 10^3	Log k_{obs}
1.00	0.3	-3.52
0.79	2.4	-2.62
0.71	4.4	-2.35
0.48	14.9	-1.83
0.34	38.9	-1.41
0.24	19.1	-1.72

The plot of log k_{obs} vs. mole fraction for the reaction in aqueous MeOH and aqueous MeCN showed a minimum at $X_{MeOH} = 0.60$ and $X_{MeCN} = 0.2$ respectively where X denotes the mole fraction. A similar plot of the reaction in aq. Me_2SO showed a maximum at $X_{Me2SO} = 0.3$. Attempts to carry out the reactions at 100% H_2O were fruitless because of solubility problems.

3.3.1 Me_2SO – H_2O Binary System

There was an increase in the rate of reaction when water was added to the Me_2SO-reaction system reaching a maximum at $X_{Me2SO} = 0.3$. Below $X_{Me2SO} = 0.2$, the oxazine did not dissolve appreciably and hence it could not be quantified accurately. The increase in the rate of reaction could be explained by the fact that there is considerable interaction between Me_2SO and the water molecules. The increase of rate on addition of water is an indication that the transition state is stabilized and the ground state destabilized or less stabilized by these interactions. The order in Me_2SO is disrupted by strong S=O…..H_2O interactions. This is evident by increase in viscosity when water is mixed with Me_2SO. In fact it has been observed that a mixture of H_2O and Me_2SO at $X_{Me2SO} = 0.34$ does not freeze till it reaches liquid nitrogen temperature. [40].

3.3.2 MeCN - H_2O Binary System

The of reaction decreases when water is added to MeCN reaching a minimum at $X_{MeCN} = 0.2$ followed by a substantial increase. This decrease in reaction rate could be attributed to the lack of interaction between MeCN and water molecules. Consequently it seems as if the transition state prefer the MeCN domain to the water domain. Therefore, the postulated transition state, which is charged and has hydrophobic property should be highly destabilized when H_2O is added to MeCN and this is what was observed from the reduced rate. On the other hand the ground state is stabilized as the uncharged oxazine will prefer water addition as opposed to its charged counterpart. This development occurs due to lack of mutual interaction between MeCN-H_2O molecules similar to the one evidenced earlier with H_2O and Me_2SO.

MeCN(2) – H_2O(2) mixtures differ significantly in terms of thermodynamics properties from Me_2SO-H_2O mixtures for example $G^E_M > 0$ [41,42] but $|H^E_M| > |TS^E_M|$. Therefore like the Me_2SO-H_2O system the MeCN-H_2O system is also classified as typically non aqueous but unlike the Me_2SO-H_2O system there is no interaction between MeCN and H_2O molecules.

Evidence for this is further obtained from the Kirkwood-Buff integral functions. The maximum in G_{11} and G_{22} show that the probability of finding H_2O in close proximity to H_2O molecules and MeCN molecules in close proximity to MeCN molecules are high. On the other hand the minimum in G_{12} shows that the probability of finding a MeCN molecule near a H_2O molecule is very low. That is MeCN cluster in MeCN rich domains and H_2O cluster in H_2O rich domains.

3.3.3 MeOH – H_2O Binary System

There is a decrease in rate of reaction when water is added to MeOH reaching a maximum at $X_{MeOH} = 0.55$ followed by a slight increase in reaction rate. Since the reaction involved the transformation of a non-electrolyte (the oxazine) to a charged transition state (22), the addition of H_2O to MeOH results in the ground state being relatively stabilized or less destabilized than the transition state which is highly destabilized. This results in an overall decrease in reaction rate.

The maxima in the integral functions G_{11} and G_{22} mean that the probability of finding H_2O molecules in close proximity to H_2O molecules and similarly for alcohol are very high. The minimum in G_{12} likewise indicate the low probability of getting the likes together. Ben-Naim[25] attributed the maximum for MeOH(2)-H_2O(1) mixtures at low X_{MeOH} to strong hydrophobic bonding between MeOH molecules.

3.3.4 Addendum

In a separate work a Hammett plot for the reaction (for a set of Cl, Br, Me and NO_2) [43] gave a ρ value of (-0.33, r = -0.99). This indicate that the reaction is decelerated by electron withdrawing groups and vise versa. The negative ρ obtained is in agreement with that obtained in many acetal hydrolysis reactions [3,4]. Substituent effects are felt most after ring opening. The substituents then influence the intramolecular attack by nitrogen, which results in the formation of a five-membered nitrone.

The ρ value of -0.33 is consistent with and supports the rate determining oxonium/carbenium ion formation since the electron donation from polar substituents will both favor pre-equilibrium protonation and stabilize the carbonium ion developing in the transition state. Further more the negative ρ value is also an indication of substantial development of positive charge in the transition state, which is enhanced by electron donating groups. This in agreement with proposed transition state structure (7).

4. Conclusion

Pre-equilibrium protonation is the first step in the acid catalyzed rearrangements of 1,2-oxazines.

This is followed by the unimolecular decomposition of the protonated oxazine in an A1 type reaction. The second step is intramolecular attack by nitrogen to form the five membered nitrone compounds. At concentrations more than 7.3% H_2SO_4 there is further protonation on the nitrogen slowing the cyclization, step and probably making it rate determining. This conclusion have been strongly supported by the negative slope of -0.63 in the Bunnett plot. An A2 type reaction in which water could have been involved in the rate-determining step as either a base or a nucleophile is automatically ruled out.

Thermodynamic functions of transfer from MeOH to MeCN have shown that the transition state is stabilized. This is strong indication of substantial localization of charge on an electronegative atom in the transition state. The stabilization of the transition state on this transfer is in accord with an observation that positively charged transition states are more solvated by dipolar aprotic solvents than by protic solvents.

The postulated transition state structure is further supported by the Kirkwood-Buff treatment of preferential salvation. Lack of interaction between MeCN and water highly destabilize the transition state which is charged and hydrophobic properties. The same argument applied to MeOH and water system where addition of water to the oxazine (non-electrolyte) results in the oxazine being stabilized or less destabilized than the charged transition state which is highly destabilized. Unlike these the Me_2SO water system has a totally opposite effect on the transition state as evidenced by the increased rate of reaction on addition of water to Me_2SO due to mutual interaction between water and Me_2SO molecules.

Generally one cannot prove a reaction mechanism in an absolute sense. The chemist can often reject conceivable mechanisms on the basis of experimental evidence and thereby narrow the field of possibilities perhaps till only one mechanism remains which stimulate further work and yet new ideas.

Acknowledgments. This work was done within the framework of the Associateship Scheme of the Abdus Salam International Centre for Theoretical Physics, Trieste, Italy.

5. References

1. Gilchrist, T. L. and Yagoub, A. K.; *J. Chem. Soc. Perkin 1*, (1985), 2769.
2. Gilchrist, T, L., Iskander, G. M. and Yagoub, A. K.; *J. Chem. Soc. Chem. Commun*., (1981), 696.
3. Hammett, L. P.; **Physical Organic Chemistry**, 2nd ed. McGraw-Hill, New York, 1970.
4. Deno, N. C. and Taft, R. W.; *J. Am. Chem. Soc*., (1954) 78, 244.
5. Cox, R. A.; *J. Am. Chem. Soc*., (1974), 96, 1059.
6. Hammett, L. P. and Deyrup, A. J.; *J. Am. Chem. Soc*., (1932), 54, 2721.
7. Hammett, L. P.; *Chem. Revs*., (1935), 35, 67.
8. Paul, M. A. and Long, F. A.; *Chem. Revs*., (1957), 57, 1.
9. Gutbezahl, B. and Grunwald, E.; *J. Am. Chem. Soc*., (1953),75, 559.
10. Gutbezahl, B. and Grunwald, E.; *J. Am. Chem. Soc*., (1953),75, 565.
11. Zucker, L. and Hammett, L. P.; *J. Am. Chem. Soc*., (1939), 61, 2791.
12. Yates, A and Mclelland,R. A.; *J. Am. Chem. Soc*., (1967), 89, 2686.
13. Long, F. A. and Paul, M. A.; *Chem. Revs*. (1957), 57, 935.
14. Bunnett, J. F.; *J. Am. Chem. Soc*. (1961), 83, 4956., *ibid*, 4968, 4973,4978.
15. Grunwald, E. and Winstein, S.; *J. Am. Chem. Soc*., (1948), 70, 846.
16. Winstein, S. and Fainberg, S.; *J. Am. Chem. Soc*., (1957), 79, 5937.
17. Arnett, E. M., Bentrude, W. G., Burke, J. J. and McDuggleby, P.; *J. Am. Chem. Soc*. (1965), 87, 1544.
18. Wiberg, K. B.; **Physical Organic Chemistry,** Wiley, New York, 1964.
19. Parker, A. J.; *J. Chem. Soc. A,* (1966), 220.

20. Parker, A. J.; Avances in Organic Chemistry, (1969), vol 5, Ed. Raphael Taylor and Wynberg, Interscience, New York.
21. Delpuech ,J. J.; (1966), *Bull. Soc. Chem. Fr.*, 1624.
22. Abraham, M. H.; (1974), Prog. Phys. Org. Chem. 11, 2.
23. Alexander, R., Ko, E. C. F., Parker, A. J., and Broxton, T. J.; *J. Am. Chem. Soc.* (1968), 90, 5049.
24. Blandamer, M. J., Burgess, J., Horn, I. M., Engberts, J. B. F. N, and Warwick Jr., P.; *Colloids and Surfaces*, (1990), 48, 139.
25. Ben-Naim, A.,; *J. Chem. Phys.*, (1977), 67, 4884.
26. Blandamer, M. J., Burgess, J., Horn, I. M., Engberts, J. B. F. N and Blundell, J.; *J. Chem. Soc. Chem. Commun.*, (1989), 1233.
27. Guggenheim, H. A.; *Phil. Mag.*, (1926), 7, 2, 428.
28. Findlay, A. **Practical Physical Chemistry**, ed. Kitchener, J. A., Longmans, 8th ed. 1962.
29. Lange, N. A., **Lange's Handbook of Chemistry**, Dean, J. A., Ed., McGraw Hill, 12th ed. 1979.
30. Bunnett, J. F. and Olsen, F. P.; *Can. J. Chem.*, (1966), 1899.
31. Wiig, E. O., *J. Am. Chem. Soc.*, (1930), 52, 4729.
32. Ref. 7.
33. Zucker, L. and Hammett, L. P.; *J. Am. Chem. Soc.*, (1939), 61, 2779, 2785.
34. Parker, A. J.; (1967), Adv. Phy. Org. Chem., 5, 173.
35. Buncel, E. and Wilson, H.; (1977), Adv. Phy. Org. Chem., 14, 133.
36. Parker, A. J.; *Chem. Revs.*, (1967), 67, 1.
37. Alexander, R., Ko, E. C. F., Parker, A. J., and Broxton, T. J.; *J. Am. Chem. Soc.* (1968), 90, 5049.
38. Kolthoff, I. M. and Coetzee, J. F.; *J. Am. Chem. Soc.,* (1957), 79, 6110.
39. Arnett, E. M., (1963), Prog. Phys. Org. Chem., 1, 223.
40 Blandamer, M. J., Burgess, J., Horn, I. M., Cowles, J. and Blundell, N. J.; *J. Chem. Soc. Faraday Trans.*, (1990), 86(2), 277.
41. French, H. F., (1987), *J. Chem. Thermodyn.*, 19, 115.
42. Villamanan, M. A. and Van Ness, H. C.; *J. Chem. Eng. Data.*, (1985), 30, 445.
43. Author's Unpublished work.