Ionic Effects on the Stereoselectivities of Diels−Alder Reactions: The Cyclopentadiene−Methyl Acrylate Reaction in Aqueous LiCl, NaCl, NaBr, $CaCl_2$, $LiClO_4$, and Guanidinium Chloride

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The variations in the endo- and exo-stereoselectivities for the reaction of cyclopentadiene (CP) with methyl acrylate (MA) have been investigated in salt−solvent reaction media (SSRM) at different concentrations of salts. The SSRM employed in the reaction include aqueous solutions of LiCl, NaCl, NaBr, $CaCl_2$, guanidinium chloride, and $LiClO_4$. The endo/exo (N/X) ratios have been noted to be sensitive to the ionic concentrations. Salts such as LiCl, NaCl, NaBr, and $CaCl_2$ enhance the N/X ratios, while the solutions of guanidinium chloride and $LiClO_4$ decrease them. The results have been analyzed in light of the salting-out and -in coefficients. The scaled particle theory has also been employed to calculate the contributions from the cavitation and solvation effects. The correlations of the N/X ratios with the surface tension of the SSRM are presented, which bring out clearly the impact of the surface tension of reaction media on the stereoselectivities of the above reaction. An attempt has also been made to interpret the results in terms of internal pressure of the SSRM in conjunction with the activation parameters. With the help of internal pressure, it is possible to suggest a division of zones to describe the salting-out and -in effects by different SSRM for the CP + MA reaction.

Introduction

The Diels−Alder reaction is considered as a power tool resulting in highly stereoselective six-membered systems.[1] Different aspects such as mechanism, solvent effects, uses, etc. of the Diels −Alder reactions have been described by many workers.[1a,d] Due to isopolar activated complexes in the Diels−Alder reactions, it can be considered that these reactions should not be sensitive to the changes in the solvents acting as reaction media.[2] A careful survey of the literature shows that the solvents exhibit appreciable influence on the kinetics of the Diels−Alder reactions. Three distinct categories of these effective solvent media can be (i) water and its mixtures with other organic solvents, (ii) water with ionic species, e.g., aqueous salt solutions, and (iii) nonaqueous solvents and their salt solutions. As a matter of fact, Breslow and his school[3a,b] showed that the kinetic profiles of the Diels−Alder reactions could be greatly altered by using water and its salt solutions as solvent media. Breslow[3c] has summarized the relationship between hydrophobic effects arising out of water, reactants, and salts. Engberts and co-workers[4] are the first who have systematically investigated the effects of water and its mixtures with other organic solvents on the reaction kinetics of the Diels−Alder reactions and explained their results in terms of the enforced hydrophobic interactions. The third category involving the solution of a salt in a nonaqueous or organic solvent acting as a reaction medium has brought a revolutionary change in the progress of work on these reactions. Grieco, Nunes, and Gaul[5] in their classic work demonstrated that several-fold increases in reaction rates could be achieved by the use of $LiClO_4$−diethyl ether (abbreviated as LPDE) as the solvent medium. Cantheridin earlier achieved[6] at an ultrahigh pressure of about 15 kbar (1 bar = 103 125 N) could be synthesized in LPDE under ambient conditions thus obviating high-

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(1) (a) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741. (b) Fringuelli, F.; Tatichi, A. *Dienes in the Diels−Alder reactions*; Wiley: New York, 1990 and references cited therein. (c) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990; see also references cited therein. (d) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis*, **1994**, 741.

(2) Sauer, J. Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779

(3) (a) Rideout, D.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901. (c) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159 and references cited therein. (d) Breslow, R.; Guo, T. *J. Am. Chem. Soc.* **1988**, *110*, 5613. (e) Breslow, R.; Connors, R. V., *J. Am. Chem. Soc.* **1995**, *117*, 6601: Breslow has used attractive terminology for calling LiCl type salts, calling them prohydrophobic agents, while he calls salts such as GnCl and $LiClO_4$ antihydrophobic ones.

(4) For example see: (a) Blokzijl, W.; Engberts, J. B. F. N.; Blandamer, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4241. (b) Blokzijl, W.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1992**, *114*, 5440. (c) Mersbergen, D.; van Wijnen, J. W.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, *63*, 8801. (d) Meijer, A.; Otto, S.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, *63*, 8989 and references cited therein for their earlier contributions. also see: (e) Schneider, H.; Sangwan, N. K. *J. Chem. Soc., Chem. Commun.* **1986**, 1787. (f) Schneider, H.; Sangwan, N. K. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 8976. Other important references: (h) Cativiela, C.; Mayroral, J. A.; Avenoza, A.; Peregrina, J. M.; Roy, M. A. *J. Phys. Org. Chem.* **1990**, *3*, 414. (i) Cativiela, C.; Garcia, J. I.; Royo, A. J.; Salvatella, L.; Assefeld, Y.; Urz-Lopez, M. F. *J. Phys. Org. Chem.* **1992**, *5*, 230. (j) Cativiela, C.; Garcia, J. I.; Mayrol, J. A.; Salvatella, L. *J. Chem. Soc., Perkin Trans. 2* **1994**, 847 and references cited therein. (k) See for an informative review: Cativiela, C.; Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *Chem. Soc. Rev.* **1996**, 209.

(5) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595. See for a comprehensive review: Grieco, P. A. *Aldrichim. Acta* **1991**, *24*, 159.

(6) Dauben, W. G.; Kessal, C. R.; Takemura, K. H. *J. Am. Chem. Soc.* **1980**, *102*, 6893

(7) (a) Casaschi, A.; Desimoni, G.; Faita, G.; Ivernizzi, A. G.; Lanati, S.; Righetti, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 8002 and references from the same school. (b) Pagni, R. M.; Kabalka, G. W.; Bains, S.; Plesco, M.; Wilson, J.; Bartmess, J. *J. Org. Chem.* **1993**, *58*, 3130. (c) Saraswathy, V. G.; Sankararaman, S. *J. Org. Chem.* **1994**, *59*, 4665.

10.1021/jo990583z CCC: $18.00

pressure requirements. Later, efforts were made to conduct many reactions in LPDE to enhance their reaction rates.[7]

The above-mentioned developments in this direction have prompted investigators to quantify the origin of forces responsible for such impressive effects of salt–solvent reaction media (SSRM). Lewis-acid catalysis, hydrogen-bonding, solvent polarity, hydrophobic hydration, aggregation, etc. are a few examples of some parameters studied in this regard. In this direction, our efforts have been prompted toward the possible application of the solution properties of SSRM for explaining the rate enhancement of Diels–Alder reactions. This property, namely, internal pressure P_i, of SSRM caused by the ion–solvent interactions was shown to be an alternative explanation for describing the rate enhancements in both aqueous[8] and nonaqueous[9] ionic media.

Besides the reaction rates, diastereoselectivities have been reported to be solvent dependent, but no systematic studies on this aspect are available. Breslow and Guo[3c,d] pointed out that the SSRM-like LiCl–water increases the endo/exo (henceforth abbreviated as N/X) ratios in a Diels–Alder reaction, while guanidinium chloride (GnCl)–water acts in the opposite manner.

To gain deeper insight into the forces and factors responsible for variation of the N/X ratios in the presence of ionic species, we in this investigation undertake a systematic study on the effects of SSRM on a simple Diels–Alder reaction. Selection of a simple reaction, i.e., cyclopentadiene (CP) with methyl acrylate (MA), was made as several other physicochemical parameters that might be needed in understanding the changes in the N/X ratios were available. Reaction of CP with MA has been investigated previously by a few workers[4j,10] in the presence of pure organic solvents and their mixtures in water. The variations in the N/X ratios with the use of different solvents have been correlated with polarizability, Brownstein and Kosower solvophobicity parameters, etc.[4k]

Inspired by the scope of using SSRM in the Diels–Alder reactions and the work of Breslow[3] and of Grieco,[5] we have investigated the effects of several aqueous salts solutions, such as LiCl, NaCl, NaBr, $CaCl_2$, GnCl, and $LiClO_4$, on the N/X ratios of the CP + MA reaction. In this investigation we attempt to answer two major questions: (i) What is the relationship between the N/X ratios of the above reaction and the varying salt concentrations of SSRM? and (ii) What are the possible factors responsible for such variations in light of physicochemical parameters of SSRM?

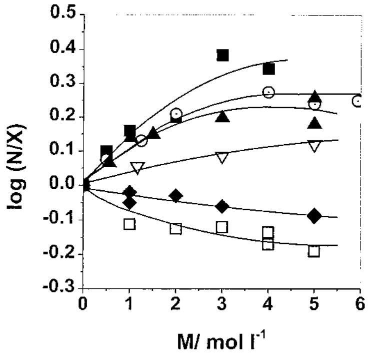

Figure 1. log(N/X) and the salt concentrations, *M*, of aqueous LiCl (■), NaCl (○), NaBr (▲), $CaCl_2$ (▽), GnCl (◆) and $LiClO_4$ (□) for the cyclopentadiene + methyl acrylate reaction.

Table 1. Adjustable Parameters *a* and *b* in Eq 1 for Correlating log(N/X) and Concentrations, *M*, of Different SSRM for the CP + MA Reaction

SSRM	*a*	*b*	std dev of fit
LiCl	0.168	−0.0194	0.04
NaCl	0.128	−0.0151	0.02
NaBr	0.120	−0.0145	0.02
$CaCl_2$	0.043	−0.004	0.01
GnCl	−0.025	0.0016	0.02
$LiClO_4$	−0.072	0.0076	0.02

Results and Discussion

Reaction of CP with MA was carried out in different SSRM. These SSRM include aqueous LiCl, NaCl, NaBr, $CaCl_2$, GnCl, and $LiClO_4$. Reactions were conducted in different salt concentrations ranging up to 6 M. The results obtained in the investigation are plotted in Figure 1 in the form of log(N/X) as a function of the concentration (*M*) of SSRM. An examination of Figure 1 shows two distinctly opposite trends in the variations of log(N/X) values with respect to the concentrations of SSRM. One group of SSRM comprising of LiCl, NaCl, NaBr, and $CaCl_2$ increase the N/X ratios, while another group of salts, namely, $LiClO_4$ and GnCl, reduce these ratios. It is interesting to note from Figure 1 that both the increase and decrease in log(N/X) are the distinct function of the salt concentrations. However, with increasing salt concentration, the log(N/X) versus *M* curves begin to taper at high salt concentrations. The variations of log(N/X) with the concentrations of SSRM can be expressed by

$$\log(\mathrm{N/X}) = aM + bM^2 \qquad (1)$$

The values of adjustable coefficients, i.e., *a* and *b*, obtained from the least-squares fit are recorded in Table 1. The standard deviations of fits as shown in Table 1 are within the uncertainties of the N/X ratios obtained from the NMR data. Rideout and Breslow[3a] have noted that the butenone reaction is accelerated in the presence of LiCl, while GnCl suppresses the reaction rates. From the above, it is apparent that the effects of aqueous ionic species are powerful in altering the kinetic profiles of the Diels–Alder reactions. Salts such as LiCl, NaCl, etc., which increase the N/X ratios, also increase the hydrophobic effects, while the reverse action can be thought to occur in $LiClO_4$ and GnCl solutions. This increase or decrease in the hydrophobic effects can also be described in terms of salting-out and -in properties. Accordingly, the solubilities of reactants decrease in aqueous LiCl, NaCl, NaBr, etc., causing the salting-out of the components. Interactions of Gn^+ and $ClO^-{}_4$ with water increase the solubilities of the above reactants in the solutions. Thus, the rates are related to the relative changes in the solubilities of the diene and dienophile in aqueous salt solutions. It will, therefore, be of interest to compute their solubilities in the above SSRM. For this purpose we employed the well-established universal functional group contribution model (abbreviated as UNIFAC).[11] Since the

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(8) (a) Kumar, A. *J. Org. Chem.* **1994**, *59*, 230. (b) *J. Org. Chem.* **1994**, *59*, 4612.

(9) Kumar, A. *J. Phys. Org. Chem.* **1996**, *9*, 287

(10) (a) Berson, J. A., Hamlet, Z, Mueller, W. A., *J. Am. Chem. Soc.* **1962**, *84*, 297 (b) Cativiela, C.; Garcia, J. I.; Mayroral, J. A.; Avenoza, A.; Peregrina, J. M.; Roy, M. A. *J. Phys. Org. Chem.* **1991**, *4*, 48.

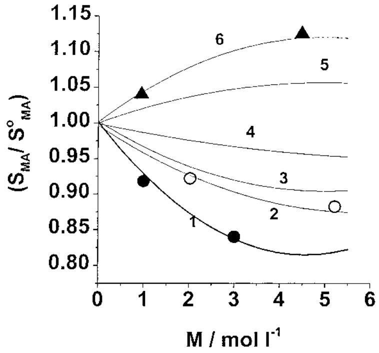

Figure 2. Computed relative solubilities of MA, (S_{MA}/S^0_{MA}) as a function of the concentration of salt, *M*, for different aqueous salt solutions for the CP + MA reaction: (1) LiCl, (2) NaCl, (3) NaBr, (4) $CaCl_2$, (5) GnCl, (6) $LiClO_4$.

solubility of CP in water is highly limited, it was thought worthwhile to compute the relative solubilities of MA, i.e., S_{MA}/S^0_{MA}, as an example. Thus, the computed S_{MA}/S^0_{MA} of MA S_{MA}/S^0_{MA}) are plotted in Figure 2 as a function of the concentration *M* of different SSRM.[12] The solubility of MA in the salt solution is indicated by *S*, while a superscript 0 denotes that in pure water. A survey of Figure 2 reveals that SSRM, such as LiCl, NaCl, NaBr, and $CaCl_2$, decrease the solubilities of MA to a greater extent. On the other hand, an increase in the solubilities of MA is noted on the addition of salts such as GnCl and $LiClO_4$. The agreement of the computed S_{MA}/S^0_{MA} with the experimental values[12] lends confidence to our calculation procedure. It is important to note that the solubilities tend to taper at high salt concentrations. The correlations of log(N/X) with S_{MA}/S^0_{MA} for MA in the case of each SSRM are demonstrated in Figure 3, pointing out the impact of the solubilities on the stereoselectivity ratios. In terms of Debye−McAulay theory,[13] $\log(S°/S) = \log f$, where *f* is the molar activity coefficient of a nonelectrolyte in the salt solution. Thus, the values plotted in Figure 3 are the log of the inverse of S/S^0 in different SSRM. If one calculates the salting-out and -in parameters from the above theory, one obtains the correct sign of the salting-out and -in coefficients. The order in which the salt solutions vary the solubilities of MA is in full agreement with the trends observed for the log(N/X) values. The nearly invariant solubility−concentration gradient at higher salt concentrations is also reflected in the log(N/X) versus *M* plots given in Figure 1.

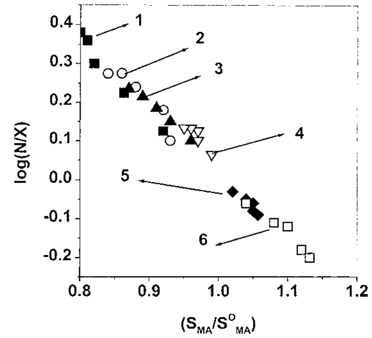

Figure 3. Variation of log(N/X) with respect to the relative solubilities of MA (S_{MA}/S^0_{MA}) for the CP + MA reaction. Symbols are as in Figure 2.

Since the salting-out and -in phenomena can be criteria to investigate the rate enhancement or decrease, it is useful to compute their values in the present context. An effective method to calculate the salting-out and -in coefficients involves the scaled particle theory (SPT).[14] The SPT is based on two components: (a) work required in creating a cavity large enough to accommodate a nonelectrolyte molecule and (b) the energy of interactions of the solute with the surrounding solvent. We opt for SPT in the present context in view of its successful applications to the predictions of several solution properties, including solubilities.[14b,15] In addition, the input parameters in using SPT are readily available molecular properties.

In the present case, we follow the equations and methodology of computations described by Shoor and Gubins.[16] Accordingly, the salting-out or -in coefficient is given by

$$\kappa_S = \kappa_a + \kappa_b + \kappa_c \qquad (2)$$

where κ_a and κ_b account for the contributions due to the cavity formation and introduction of nonelectrolyte to the cavity, respectively. The number density of solution species is given by κ_c. The diameters of water, cation, and anion together with the apparent molal volume at infinite dilution of a salt in a given solution are the input parameters for computing κ_a. Similarly, the calculations of κ_b require energy parameters and polarizibility of nonelectroyte molecules. The κ_c component is linearly related to the apparent molal volume of a salt at infinite dilution, ϕ^0. The mixing rule employed in the calculations was taken from Pierotti.[14d] In Table 2 are summarized the computed values of κ_a, κ_b, κ_c, and κ_S in different SSRM. The input parameters for the computational work were taken from the literature.[4i],An examination of Table 2 reveals that positive values of κ_S are noted for LiCl, NaCl, NaBr, and $CaCl_2$ in decreasing order. Negative values of κ_S, however, are recorded for GnCl and $LiClO_4$. The positive and negative κ_S values signify the salting-out and -in properties, respectively. Let us now comment

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(11) (a) Several versions of UNIFAC are available and have been modified according to the requirements. For a summary see: (b) Kumar, A. *Sep. Sci. Technol.* **1993**, *28*, 1799. In the present case, a calculation procedure described in (c) Kikic, I.; Fermegha, M.; Rasmussen, P. *Chem. Eng. Sci.* **1991**, *46*, 2775 was followed. In this method, a modified Debye−Huckel term (for ions) is added with a concentration-independent UNIFAC term. This term accounts for the interactions between ions and solvent. (d) For computation see: Hirata, M.; Ohe, S.; Nagayama, K. *Computer Aided Data Book of Vapor Liquid Equilibria*; Kodansha Ltd., Elsevier Science Publishing Co.: Tokyo, 1975. (e) for extensive tabulations see: *Models for Thermodynamic and Phase Equilibrium Calculations*; Sandler, S. I., Ed.; Marcel Dekker: New York, 1993; Chapter 4. (f) There is a continuous addition of UNIFAC parameters in Data Bank.

(12) A few experiments were conducted to determine the solubilities of MA in the salt solutions. In the case of MA, optical densities of a solution saturated with MA in both pure water and salt solutions were measured with a Lambda 15 UV spectrophotometer (Perkin-Elmer) at 196 nm. See: Closson, W. D.; Brady, S. F.; Orenski, P. J. *J. Org. Chem.* **1965**, *30*, 4026. The changes in the ionic concentrations produced negligible changes in the absorptivity of MA.

(13) Debye, P.; McAulay, *J. Phys. Z.* **1925**, *26*, 22.

(14) (a) Reiss, H.; Frisch, H. L.; Lebowitz, J. L. *J. Chem. Phys.* **1959**, *31*, 369. (b) Reiss, H. *J. Phys. Chem.* **1992**, *96*, 4736. Also see: (c) Masterton, W. L.; Lee, T. P. *J. Phys. Chem.* **1970**, *74*, 1776. (d) Pierotti, R. A. *Chem. Rev.* **1976**, *76*, 717 and references cited therein. (e) For application to mixture containing components of varied sizes see: Kumar, A. *J. Am. Chem. Soc.* **1993**, *115*, 9243.

(15) Though UNIFAC can be used to calculate the solubilities, we have employed the scaled particle theory as it differentiates the solution phenomena into cavity formation and solvation effects. These effects play significant roles in the salting-out and -in phenomena.

(16) Shoor, S. K.; Gubbins, K. E. *J. Phys. Chem.* **1969**, *73*, 498.

Table 2. Contributions of κ_a, κ_b, and κ_c to the Total κ_S from the SPT Calculations for the CP + MA Reaction in Different SSRM

SSRM	κ_a	κ_b	κ_c	κ_S
LiCl	0.546	−0.062	0.010	0.494
NaCl	0.447	−0.058	0.008	0.397
NaBr	0.423	−0.055	0.006	0.374
$CaCl_2$	0.242	−0.043	0.004	0.203
GnCl	0.091	−0.323	−0.032	−0.264
$LiClO_4$	0.060	−0.462	−0.067	−0.469

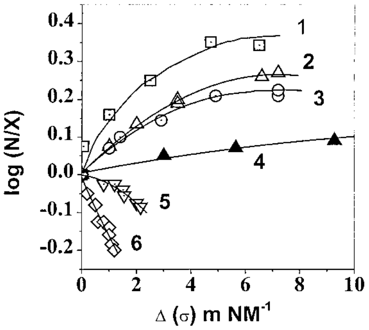

Figure 4. log(N/X) and the changes in the surface tension of water upon the addition of salts, Δ(σ), for the CP + MA reaction. Symbols are the same as in Figure 2.

on the significance of individual terms and their overall impact on the determination of the total κ_S. For LiCl, NaCl, NaBr, and $CaCl_2$, the κ_a values are high and positive. These values manifest the positive change in the Gibbs free energy of cavitation. This implies that the cavitation in such a type of SSRM is a difficult phenomenon. On the other hand, small positive κ_a values for GnCl and $LiClO_4$ suggest the possibilities of easier cavitation as compared to LiCl, NaCl, etc. One notes a regular decrease in κ_a from LiCl to $LiClO_4$. The κ_b values for the rate-enhancing SSRM are negative though small in magnitude. Higher negative κ_b values for GnCl and $LiClO_4$ can be attributed to strong solute−solvent interactions. It, thus, appears that the salting-in effects of GnCl and $LiClO_4$ are governed by the solvation of hydrocarbons. The solute−solvent interactions in the system are favored by higher negative κ_b values.[14d] The κ_b values for GnCl and $LiClO_4$ dominate over κ_a, thereby causing the solute−solvent interactions to play an important role in the salting-in effects. Small values of κ_c are noted in general. However, for the salts with a large size cation or anion, the κ_c appears to be significant. This is due to the fact that κ_c is calculated from ϕ^0 values of the salt, which are larger for GnCl and $LiClO_4$. The prediction of κ_S is, therefore, a product of the competitive contributions of both the cavitation and solvation terms. In short, it can be stated that the salting coefficients vary in the same order, as do the log(N/X) values. The SPT predicts that the salting coefficients decrease with the increase in the ionic sizes, which has also been shown to be true for the current reaction.

Since the arrangement of water molecules due to the presence of ions is greatly influenced, it is reflected in the physicochemical properties of the salt solutions. One of such properties is the variation in the surface tension of water with salt concentrations. In Figure 4 we plot the log(N/X) values as a function of Δ(σ), an increment in the surface tension on the addition of a given salt.[18]

Table 3. Adjustable Parameters of Eq 3 for Correlating log(N/X) with Δ(σ) of SSRM for the CP + MA Reaction

SSRM	q_1	q_2	q_3	std dev of fit
LiCl	0.139 ± 0.019	−0.013 ± 0.003	0	0.04
NaCl	0.075 ± 0.002	−0.005 ± 0.0005	0	0.01
NaBr	0.069 ± 0.003	−0.005 ± 0.0001	0	0.01
$CaCl_2$	0.015 ± 0.001	−0.0005 ± 0.0001	0	0.02
GnCl	−0.011 ± 0.003	−0.013 ± 0.002	0	0.02
$LiClO_4$	−0.312 ± 0.050	0.336 ± 0.015	−0.179 ± 0.009	0.02

First it is important to note that the surface tension of water increases sharply when a salt, such as LiCl, NaCl, NaBr, $CaCl_2$, etc., is added to pure water. In the cases of aqueous GnCl and $LiClO_4$, this increase in surface tension is relatively weak. The curves shown in Figure 4 demonstrate good correlations between log(N/X) and Δ(σ) in different SSRM for the CP + MA reaction. From these data, it is easy to write the expression for the above correlation as

$$\log(\mathrm{N/X}) = q_1\Delta(\sigma) + q_2(\Delta(\sigma))^2 + q_3(\Delta(\sigma))^3 \qquad (3)$$

The values of the adjustable parameters q_1, q_2, and q_3 are listed in Table 3. The strong correlations as shown in Figure 4 suggest the significant role of surface tension in the CP + MA reaction. The values of derivatives, $\partial(\log(\mathrm{N/X}))/\partial(\Delta(\sigma))$ for example, at 1 M in the present case are calculated as 0.113, 0.076, 0.060, 0.014, −0.037, and −0.173 for LiCl, NaCl, NaBr, $CaCl_2$, GnCl, and $LiClO_4$, respectively. These derivatives show clearly the remarkable effect of the surface tension of SSRM on the stereoselectivity ratios of the CP + MA reaction.[19]

Considering the surface tension studies, it is important to examine the cavity formation and solvation terms in relation to the stereoselectivity ratios. The changes in the surface tension of water in GnCl and $LiClO_4$ are smaller and positive.[20] This indicates that the formation of cavities in these solutions is not favored, as the surface tension of water does not decrease with the concentrations of GnCl and $LiClO_4$ unlike in the case of water−tetrabutylammonium salt. Thus, the effect should originate from the solvation of the species in the liquid phase. Breslow and Guo[20] suggested the competitive roles of the Gibbs free energies of cavitation and solvation while describing the salting effects on the organic reactions. The Gibbs free energies of cavitation and solvation are altered by a salt, which can be written as

$$\delta(\Delta G^\circ)_{\mathrm{soln}} = \delta(\Delta G^\circ)_{\mathrm{cavn}} + \delta(\Delta G^\circ)_{\mathrm{solvn}} \qquad (4)$$

In the above equation, $\delta(\Delta G^\circ)_{\mathrm{soln}}$ is the relative change in the Gibbs free energy on the addition of a salt, while $\delta(\Delta G^\circ)_{\mathrm{cavn}}$ and $\delta(\Delta G^\circ)_{\mathrm{solvn}}$ refer to that involved in cavitation and solvation, respectively. Employing the computation technique,[15c,21,22] we calculated both the components on the right-hand side of eq 4. Since the effect of a salt is expected to be on the cavitation and solvation energetics, it is interesting to estimate the relative contributions to the overall $\delta(\Delta G^\circ)_{\mathrm{soln}}$. For the purpose of illustration are

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[17] Marcus, Y. *Ion Solvation*; Wiley: New York, 1986.

[18] Horvath, A. L. *Handbook of Aqueous Electrolyte Solutions*; John Wiley: Chichester, 1985.

[19] The role of other solution properties in this connection is not disregarded. The role of surface tension is also pointed out in ref 1d.

[20] (a) Breslow, R.; Guo, T. *Proc. Natl. Acad. Sci.* **1990**, *87*, 167. (b) Breslow, R.; Halfon, S. *Proc. Natl. Acad. Sci.* **1992**, *89*, 6916.

[21] Sen, U. *J. Am. Chem. Soc.* **1979**, *101*, 2531.

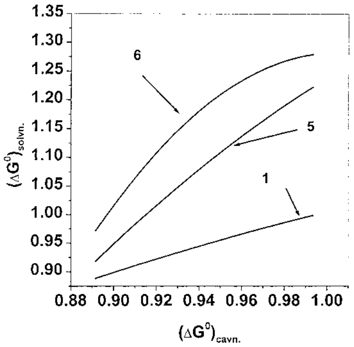

Figure 5. Plots of $\delta(\Delta G°)_{solvn}$ against $\delta(\Delta G°)_{cavn}$ for LiCl, GnCl, and $LiClO_4$ in the CP + MA reaction. For symbols, refer to Figure 2.

plotted in Figure 5 the $\delta(\Delta G°)_{solvn}$ against $\delta(\Delta G°)_{cavn}$ for LiCl, GnCl, and $LiClO_4$. For the GnCl and $LiClO_4$ salts, which act as salting-in agents, the $\delta(\Delta G°)_{solvn}$ is a larger term as compared to $\delta(\Delta G°)_{cavn}$. This would emphasize the greater role of these salts originating from the solute−solvent interactions. This effect increases with the salt concentrations. In the case of LiCl type salts, no such effect is witnessed. As a matter of fact, the degree of electrostriction (see later part for details) is high in LiCl, NaCl, NaBr, and $CaCl_2$. Due to electrostriction, less empty space is available for accommodating the hydrocarbons. Thus, cavitation in the presence of the above salts is more difficult as compared to GnCl and $LiClO_4$. An easier cavitation in GnCl and $LiClO_4$ solutions is reflected in the changes in the surface tension of water, when a salt is added. The surface tension data as mentioned above exhibit a a positive steep slope of $(\partial(\sigma)/\partial(M_i))$ for the LiCl type of salts. The gradient however is positive but quite weak. The above $\partial(\Delta(G°))$ calculations also confirm that the surface tension of SSRM is an effective criterion to quantify the N/X ratios in these SSRM.

Not disagreeing with the existing explanations to describe the kinetic profiles of these reactions, we had proposed an alternate concept to quantify the correlation between the rate enhancement and internal pressure of SSRM.[8,9,23,24] Internal pressure of an ionic solution varies due to the electrostriction process.[25]

The calculated internal pressures, P_i, of SSRM by the technique described before[8] and using volumetric data can be described as a function of the salt concentration, M, by the expression

Table 4. Values of the Parameters of Eq 5 for Correlating Internal Pressures of SSRM ($P_{i,w}$ = 166.4 MPa)

SSRM	s_1	s_2	s_3	s_4
LiCl	108.33	−32.26	35.15	−3.03
NaCl	83.72	−32.38	30.82	−2.78
NaBr	11.95	26.31	12.42	−1.27
$CaCl_2$	1.94	25.61	8.56	−1.10
GnCl	−7.58	1.48	−0.12	0
$LiClO_4$	−13.26	1.97	−0.122	0

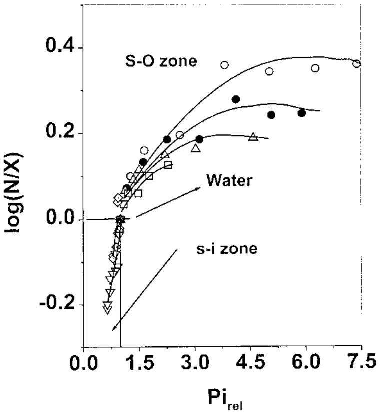

Figure 6. Division of salting-out and -in zones as obtained from the plots of log(N/X) versus $P_{i,rel}$ for the CP + MA reaction in different SSRM.

$$P_i = P_{i,w} + s_1M + s_2M^2 + s_3M^3 + s_4M^4 \qquad (5)$$

with the adjustable parameters s_1, s_2, and s_3 listed in Table 4.

It is clear that internal pressures increase with an increase in the salt concentration of LiCl, NaCl, NaBr, and $CaCl_2$. This considerable increase in the internal pressure of these salt solutions is due to electrostriction phenomena. Correlation of any pressure term with the rates requires knowledge of the activation volume, $\Delta V^{\#}$ of a reaction, which is in general negative[26] for the Diels−Alder reactions. For this reaction, the estimated $\Delta V^{\#}$ is reported[4k] to be −30.1 cm^3 mol^{-1}, which is in good agreement with our value (−27.54 cm^3 mol^{-1}) calculated from the use of reaction rates and internal pressures.[9] Thus, the increased internal pressure of SSRM, when coupled with a negative activation volume, will enhance the reaction rates. Both the diene and dienophile due to their dislike for water come close enough to react. This hydrophobic effect is further enhanced by the presence of salts, such as LiCl, NaCl, etc. On the other hand, $LiClO_4$ and GnCl decrease the internal pressure of water. But since the $\Delta V^{\#}$ is negative, the decrease in the internal pressure retards the rates of the Diels−Alder reaction. The decrease in the internal pressure is due to "anti-electrostriction phenomena" produced by ClO_4^- and Gn^+ ions.

Further, we construct a plot (Figure 6) from the log(N/X) and $P_{i,rel}$ (where $P_{i,rel} = P_i/P_{i,w}$) for each SSRM employed in this reaction. On both the axes, $P_{i,rel} = 1 \rightarrow \log(N/X) = 0$ describes the reaction conditions involving pure water alone. Two clear zones can be drawn out of such a plot, where the rate-enhancing and -reducing effects of SSRM are evident. In other words, the upper

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[22] In view of approximate calculations of $(\Delta G°)_{soln}$, which are performed to establish the importance of eq 4, we define $\delta(\Delta G°) = \delta(\Delta G°)_{salt-water}/\delta(\Delta G°)_{water}$ rather than a difference property. Breslow used the term "relative" in place of "difference". The "difference" = $\delta(\Delta G°)_{salt-water} - \delta(\Delta G°)_{water}$. Examination of "relative" as followed by us is justified, as we intend to observe the changes in the ratios with respect to the concentrations of SSRM.

[23] (a) Hildebrand, J. H.; Scott, R. L. *Regular Solution Theory*; Prentice Hall: Englewood Cliffs, NJ, 1962. (b) Thermodynamically speaking, a liquid undergoing a small, isothermal volume expansion does work against the cohesive forces, which causes a change in the internal energy, U. The function $(\partial(U)/\partial(V))_T$ is called the internal pressure of a liquid. According to Hildebrand and Scott, the definition of internal pressure for a nonpolar liquid can be transformed into that for a polar liquid by a specific factor, indicating the polarity of a solvent. (c) For a detailed definition of internal pressure see: Dack, M. R. *J. Chem. Soc. Rev.* **1975**, *4*, 211. (d) Some authors have expressed their doubt about the role of the internal pressure of water due to hydrogen-bonding; see: ref 1d.

[24] Ouette, R. J.; Williams, S. H. *J. Am. Chem. Soc.* **1971**, *93*, 466.

[25] For details see: Kumar, A. *Biochemistry* **1995**, *34*, 12921.

[26] (a) Van Aldik, R.; Asono, T.; Le Noble, W. *J. Chem. Rev.* **1989**, *89*, 549. For the latest review see: Drljaca, A.; Hubbard, C. D.; Van Aldik, R.; Asono, T.; Basilevsk, M. V.; LeNoble, W. *J. Chem. Rev.* **1998**, *98*, 2167.

portion of the curve (above log(N/X) = 0, when $P_{i,rel} = 1$) can be treated as the salting-out zone. The lower zone encompasses the salting-in effects of the salts in this reaction. The term $(\partial(P_i/\partial(M_i))$ can indicate the salting-out and -in phenomena as shown in Figure 6. Since the log(N/X) and P_i are dependent on the concentrations of SSRM as shown by eqs 1 and 5, the relationship of log(N/X) with P_i is evident, which can also be established by manipulating eqs 1 and 5.

Another point to consider in this regard is the volume of activation of both the endo- and exo-stereoisomers. Since there are no side products of the reaction, it is safe to presume that log(N/X) is equivalent to $\log(k_N/k_X)$, where k denotes the rate constant. The ratios of activation volumes for the endo- and exo-stereoisomers, i.e., $\Delta(V_N^{\#})/\Delta(V_X^{\#})$, can be calculated from k_N/k_X and pressure terms with the procedure outlined elsewhere.[9] The calculated $\Delta(V_N^{\#})/\Delta(V_X^{\#})$ being 1.17 indicates that the transition state for the endo-form is more compact than that for the exo-form (note $\Delta(V_N^{\#}) < \Delta(V_X^{\#})$, where $\Delta(V_N^{\#})$ or $\Delta(V_X^{\#})$ is negative). This implies that if the internal pressure is increased by manipulating the salt concentrations, the endo-stereoisomer will be favored over the exo-isomer in view of the relationship between pressure and volume. It is the hydrophobic packing of the endo transition state that determines the rate enhancement. The reverse effect is seen when the salting-in agents are used as SSRM. A detailed discussion on this aspect is deferred till experimental data on a set of dienes and dienophiles under different reaction conditions become available.

Conclusions

In summary, we have presented a systematic study on the role of different ionic species on the endo- and exo-stereoisomers in aqueous Diels–Alder reactions (cyclopentadiene with methyl acrylate). Salts, for example, LiCl, NaCl, etc., increase the N/X ratios, while $LiClO_4$ and GnCl solutions decrease them. The (N/X) ratios are functions of the type of salt and its concentration. The variations in the N/X ratios have been discussed in terms of the salting-out and -in phenomena. Useful correlation between the N/X values and internal pressures of the salt solutions has been presented. Though a correlation between the N/X ratios and the surface tension of SSRM is possible, a more detailed study of the energetics involved in this reaction possibly occurring at the electrolyte–water interface is being conducted in this laboratory.

Experimental Section

Cyclopentadiene was freshly cracked from its dimer (Merck) just before its use. Methyl acrylate obtained from Merck was used after distillation. All the salt solutions (SSRM) were prepared in deionized water by dissolving high-purity A.R. grade salts.

In a typical run 0.6 mL (7.26×10^{-3} mol) of the freshly cracked cyclopentadiene was dissolved in 2 mL of SSRM. Then, 0.6 mL ($6.66\ 10^{-3}$ mol) of methyl acrylate was dissolved in 8 mL of SSRM. The solution containing cyclopentadiene was added to the solution with methyl acrylate. The reaction mixture was magnetically stirred at 30 °C for about 5 h.

The endo- and exo-stereoselectivities were determined using NMR as discussed in the literature.[27] Each reaction was carried out three times, and the N/X ratios were reproducible to within 5%.

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(27) Nakagawa, K.; Ishii, Y.; Ogawa, M. *Tetrahedron* **1976**, *32*, 1427.