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Salt solutions in different solvents and their effect on the stereoselectivity of products of Diels–Alder reaction

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ABSTRACT: A salt solution prepared in one solvent promotes higher *endo* products of a Diels–Alder reaction, such as the cyclopentadiene–methyl acrylate reaction, but yields less *endo* products when prepared in another solvent. The reactions of cyclopentadiene with methyl acrylate were carried out in solutions of $LiClO_4$ and LiCl in several organic solvents and water. Aqueous $LiClO_4$, which lowers the amount of *endo* product of the above reaction, enhances it in solvents such as diethyl ether and ethyl acetate. Similarly, aqueous LiCl, which acts as a rate-promoting agent, reduces the amount of *endo* products in several organic solvents. The experimental solubility measurements support this change in the characteristics of a salt from salting-in to salting-out in different solvents and *vice versa*. The dual role of a salt in solvents is also supported by salting coefficients calculated based on theory. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: salt effect; Diels–Alder reaction; stereoselectivity; salting-out

INTRODUCTION

The pioneering work of Breslow and co-workers[1] demonstrated that LiCl enhances the reaction rates of Diels–Alder reactions in water, whereas $LiClO_4$ and guanidinium chloride (GnCl) retard them. Breslow and Guo[2] examined the effect of LiCl, $LiClO_4$, urea, tetrabutylammonium bromide (Bu_4NBr) and GnCl on the stereoselectivity ratios (*endo/exo*) and reaction rates of the reactions of cyclopentadiene with methyl vinyl ketone and of nitrosobenzene with 1,3-cyclohexadiene in water, formamide and ethylene glycol. They concluded that $LiClO_4$ and urea, which lowered the *endo/exo* ratios in water, failed to produce any noticeable change in 'water-like' solvents such as formamide and ethylene glycol. Further, Grieco *et al.*[3] showed that 5 M LPDE ($LiClO_4$–diethyl ether) could be a very powerful solvent medium in accelerating the reaction rates of several sluggish Diels–Alder reactions. The high-pressure synthesis of cantharidin was also shown to proceed at atmospheric pressure with ease when using 5 M LPDE. After the work of Breslow and co-workers[1] and Grieco *et al.*,[3] salt solutions have frequently been employed in Diels–Alder chemistry.[4]

As seen above, $LiClO_4$ in water acts as a rate-retarding agent,[1] but changes into a powerful rate-enhancing agent in diethyl ether[3] for Diels–Alder reactions. Solutions of $LiClO_4$ in dichloromethane and nitromethane have also been reported to be effective in some Diels–Alder reactions, benzoin condensation, etc.[4ab] As $LiClO_4$ is common in the above media, the contrasting effect of $LiClO_4$ in different media should depend on the solvent in which the salt solution is prepared. Thus, the salt–solvent interactions gain importance in relation to the kinetic behavior of Diels–Alder reactions. In view of the dual role of a given salt in two different solvents, we set out to investigate in detail the influence of a given salt in different solvents on the *endo/exo* ratio of Diels–Alder reactions. For this purpose, we carried out the reaction of cyclopentadiene (CP) with methyl acrylate (MA) in solutions of $LiClO_4$ and LiCl in water, formamide, ethylene glycol, dichloromethane, nitromethane, acetone, ethyl acetate, tetrahydrofuran and diethyl ether. $LiClO_4$ and LiCl were chosen for this study as their aqueous solutions influence Diels–Alder reactions in opposite directions.[1] The CP + MA reaction is a good model reaction to study solvent effects on reaction kinetics. The above nine solvents were selected on the basis of their relative permittivity, polarity and solvophobicity. This work is part of our continuing efforts to delineate the origins of the forces responsible for the dramatic rate variations of Diels–Alder reactions in different salt solutions.[4a,5]

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Table 1. *Endo* products (%) for the CP + MA reaction in solutions of $LiClO_4$ and LiCl in different solvents

	$LiClO_4$					LiCl			
Solvent	Pure solvent	0.1 M	0.2 M	0.4 M	0.6 M	0.1 M	0.2 M	0.4 M	0.6 M
Water	68	66	64	62	60	70	72	74	76
Formamide	63	62	61	63	62	63	62	62	63
Ethylene glycol	62	63	62	61	62	63	62	61	63
Nitromethane	57	59	60	62	63	56	54	52	50
Acetone	55	58	60	63	63	53	52	50	49
Dichloromethane	54	57	60	62	63	53	51	50	48
Tetrahydrofuran	54	57	58	63	65	51	50	48	46
Ethyl acetate	53	57	59	62	65	52	50	49	47
Diethyl ether	53	56	58	64	66	51	50	48	46

EXPERIMENTAL

AR-grade $LiClO_4$ and LiCl purchased from Aldrich Chemical were recrystallized from water and dried under vacuum. For preparing aqueous solutions, deionized water was used. All the organic solvents procured from Aldrich Chemical, were used after purifying and drying according to standard procedures.

Cyclopentadiene was freshly cracked from its dimer (Merck) just before use. Methyl acrylate obtained from Merck was used after distillation.

In a typical run, 0.6 ml (7.26 mmol) of the freshly cracked cyclopentadiene was dissolved in 2 ml of the salt solution, then 0.6 ml (6.66 mmol) of methyl acrylate was dissolved in 8 ml of the salt solution. The solution containing cyclopentadiene was added to the solution of methyl acrylate. The reaction mixture was magnetically stirred at 298 K for about 5 h.

The *endo* and *exo* stereoselectivities were determined using NMR as discussed in the literature[6] as investigated in our earlier work.[5b] Each reaction was carried out three times and the *endo*/*exo* ratios were reproducible to within 5%.

Solubilities were obtained by the method described earlier.[5b] The solubilities of MA were determined by measuring the optical densities of solutions saturated with MA in both pure water and salt solutions with a Lambda 15 UV spectrophotometer (Perkin-Elmer) at 196 nm.[7] The changes in the ionic concentrations produced negligible changes in the absorptivity of MA.

Table 2. Average yields of cyclo-adduct in salt solutions prepared in different solvents for the CP + MA reaction

	Yield (%)	
Solvent	$LiClO_4$	LiCl
Water	72	83
Formamide	68	63
Ethylene glycol	66	64
Nitromethane	84	73
Acetone	81	70
Dichloromethane	74	69
Ethyl acetate	91	68
Tetrahydrofuran	78	70
Diethyl ether	89	67

RESULTS AND DISCUSSION

Several reactions were conducted in the solutions of $LiClO_4$ and LiCl in the above-mentioned nine solvents at 0.1, 0.2, 0.4 and 0.6 M concentrations together with control experiments. The *endo* products obtained in pure solvents and their salt solutions in $LiClO_4$ and LiCl are presented in Table 1. The average yields of the reactions as calculated from the values obtained at different salt concentrations for each medium are given in Table 2. The CP + MA reaction has been thoroughly investigated in pure solvents. Cativiela *et al.*[8] have reviewed the application of several methods for the analysis of reaction rate and stereoselectivity data. The log(*endo*/*exo*) values obtained in pure solvents can be successfully correlated with a combination of a normalized solvent polarity, E^{N}_{T}, and solvophobicity, *Sp*, parameters of the solvents. E^{N}_{T} is a normalized E^{30}_{T} parameter, which indicates the electron acceptance polarity index, and *Sp* is the solvophobicity power of a solvent. It is therefore possible to describe the log(*endo*/*exo*) values for the CP + MA reaction in pure solvents as

$$\begin{aligned}\log(endo/exo) = {} & 0.013\ (\pm 0.003) \\ & +0.178\ (\pm 0.017)E^{N}_{T} \\ & +0.156\ (\pm 0.018)Sp \end{aligned} \qquad (1)$$

with $\sigma = 0.07$ and correlation coefficient $r = 0.982$.

First let us discuss the effect of solutions of $LiClO_4$ in different solvents. The *endo* products obtained in different solutions are plotted as a function of $LiClO_4$ concentration in Fig. 1(a) and (b) [Figure 1 is divided into (a) and (b) for the sake of clarity]. Figure 1(a) contains the plots for $LiClO_4$–water (LPWA), –formamide (LPFO), –ethylene glycol (LPEG),–nitromethane (LPNM) and–diethyl ether (LPDE). It can be seen that LPWA solution decreases the amount of *endo* products of

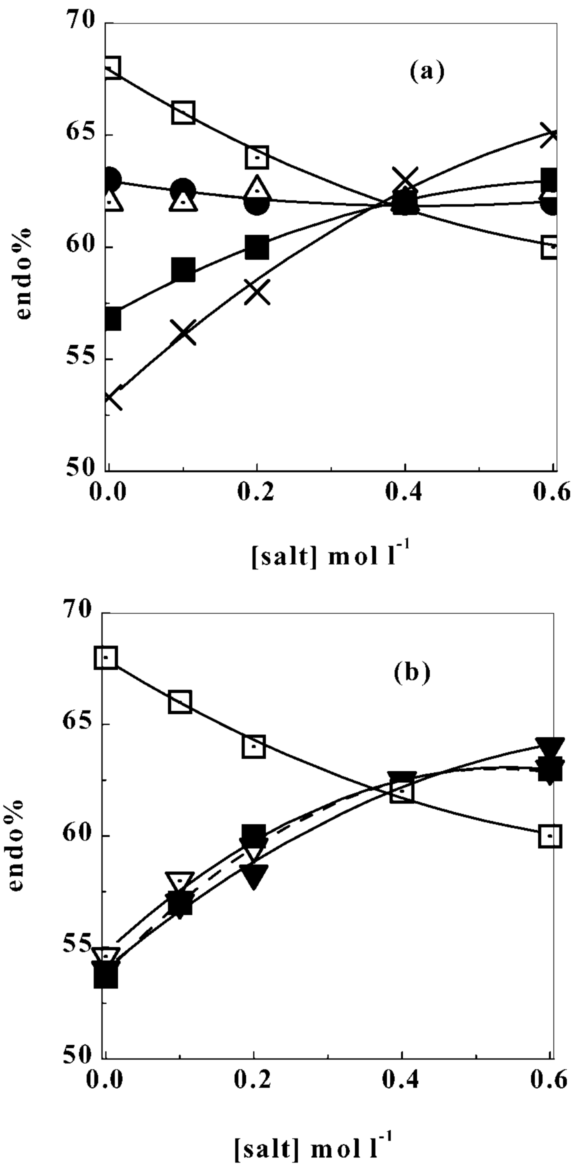

Figure 1. *Endo* products versus $LiClO_4$ concentration in different solvents for the CP + MA reaction: (a) (□) LPWA, (●) LPFO, (△) LPEG, (■) LPNM, (×) LPDE; (b) (▽) LPAC, (■) LPDM, (▼) LPEA. Data for LPTF are not shown to avoid clustering. The curve for LPWA is repeated for the purpose of comparison

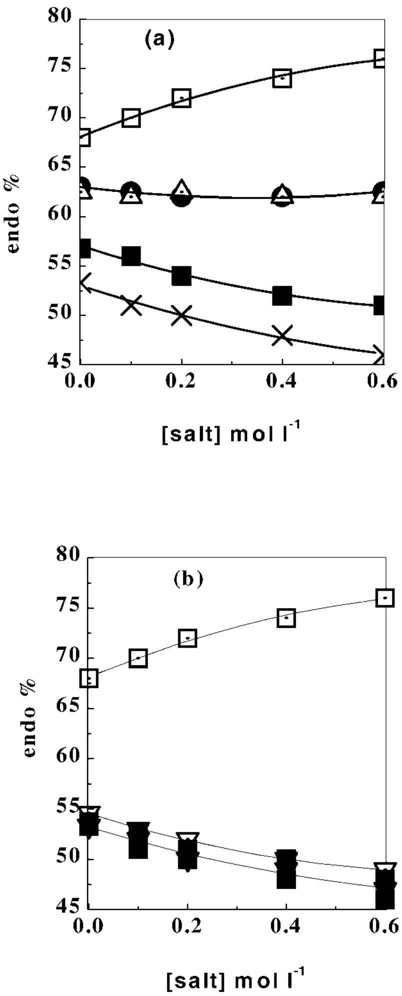

Figure 2. *Endo* products versus LiCl concentration in different solvents for the CP + MA reaction: (a) (□) LCWA, (●) LCFO, (△) LCEG, (■) LCNM, (×) LCDE; (b) (▽) LCAC, (■) LCDM, (▼) LCEA. Data for LPTF are not shown to avoid clustering. The curve for LCWA is repeated for the purpose of comparison. Lines for all the solutions are not plotted for clarity

the CP + MA reaction. This decrease is directly proportional to the concentration of $LiClO_4$ in the range covered above. The amount *endo* product in pure water, 68%, decreases to 60% at 0.6 M LPWA. In both LPFO and LPEG solutions, no change in *endo* products is noted up to 0.6 M solutions. Breslow and Guo^2 noted that second-order rate constants for the reactions of cyclopentadiene with methyl vinyl ketone and of nitrosobenzene with 1,3-cyclohexadiene increased in formamide and ethylene glycol as compared with those in methanol. No special effects were seen, however, concerning the stereoselectivity data for these reactions in LPFO and LPEG. Our current studies on the stereoselective products of the CP + MA reaction in these salt solutions agree well with the observations made by Breslow and Guo.^{2} However, interesting results are obtained in LPNM solutions. A clear enhancement of the *endo* products can be noted in LPNM solutions compared with nitromethane alone. A 63% yield if *endo* product is obtained at 0.6 M LPNM solution compared with 57% in pure nitromethane only. The concentration dependence of *endo* products is stronger in LPDE than in LPNM. One can easily note the contrasting behavior of $LiClO_4$ in water and diethyl ether. An increase in the amount of *endo* product is observed in $LiClO_4$ solutions in acetone (LPAC), dichloromethane (LPDM), ethyl acetate (LPEA), tetrahydrofuran (LPTF) and diethyl ether (LPDE) compared with the pure solvents under identical reaction conditions. In Fig. 1(b) are shown the concentration dependences of *endo* products in $LiClO_4$–acetone (LPAC),

–dichloromethane (LPDM),–tetrahydrofuran (LPTF) and –ethyl acetate (LPEA). An increase in the amount of *endo* products in these solutions is evident over the corresponding solvents in which these solutions are prepared.

In Fig. 2(a) are shown the *endo* products obtained in LiCl solutions in water (LCWA), formamide (LCFO), ethylene glycol (LCEG), nitromethane (LCNM) and diethyl ether (LCDE), and Fig. 2(b) shows those obtained in acetone (LCAC), dichloromethane (LCDM), tetrahydrofuran (LCTF) and ethyl acetate (LCEA). The results plotted in Fig. 2 show that there is an increase in the amount of *endo* products at different concentrations of LiCl in water. This observation is in agreement with earlier reports on the reaction of cyclopentadiene with methyl vinyl ketone[1] and methyl acrylate.[5b] An increase of 8% in the amount of *endo* product is seen in 0.6 M LCWA compared with pure water alone. LiCl, like $LiClO_4$, fails to show any effect on the *endo* products in formamide and ethylene glycol. In nitromethane, LCNM decreases the amount of *endo* product up to 0.6 M. Similarly, LCAC, LCDM, LCEA, LCTF and LPDE solutions decrease the amount of *endo* products. In fact, one can see that the amounts of *exo* products become slightly higher in 0.6 M solutions of LCAC, LCDM, LCEA, LCTF and LCDE solutions.

As the solution of $LiClO_4$ in water is a rate-reducing salt in water and a rate-promoting salt in diethyl ether, it appears that the solvents with high relative permittivity (e.g. water) cause a rate acceleration compared with those with low relative permittivity (e.g. diethyl ether). The opposite is true in the case of LiCl solutions.

According to Breslow,[9] the rate variations of Diels–Alder reactions in water and its salt solutions can be attributed to the changes in hydrophobic effects. Thus, LCWA, which also increases the amount of *endo* products, enhances the hydrophobic effect resulting in higher reaction rates over water. The hydrophobic effect is decreased in aqueous $LiClO_4$, which leads to a decrease in the reaction rates. In the terminology of Breslow and Connors,[10] aqueous LiCl and $LiClO_4$ can be termed prohydrophobic and antihydrophobic agents.

It is possible to analyze the *endo/exo* ratios in terms of the salting-in and -out effects.[5b,9,11] In general, the decrease in the reaction rates and *endo/exo* ratios has been attributed to a salting-in effect and the increase to a salting-out effect. In order to determine these effects in Diels–Alder reactions, we measured the solubilities of methyl acrylate in different salt solutions. In Fig. 3 are plotted the relative *endo* values, $endo^R$ (*endo* product in salt solution/*endo* product in pure solvent) as a function of relative solubility of methyl acrylate, $S^R{}_{MA}$ (solubility of methyl acrylate in salt solution/solubility of methyl acrylate in solvent) for 0.6 M $LiClO_4$ and LiCl solutions. An examination of Fig. 3 shows that the solubilities of methyl acrylate in both formamide and ethylene glycol solutions of LiCl and $LiClO_4$ do not vary compared with those noted in pure solvents. In the case of LPWA, the solubility of MA causes a salting-in effect. However, the reduced solubilities of methyl acrylate in LPNM, LPAC, LPDM, LPTF, LPEA and LPDE confirm the salting-out effect, which can be related to the increase in the amount of *endo* products. On the other hand, LCWA yields a higher $endo^R$, suggesting a decrease in solubility of methyl acrylate in aqueous LiCl solution. This is a clearly a salting-out effect. The solubility of methyl acrylate in LCNM, LCAC, LCDM, LCTF, LCEA and LCDE is higher than that in the corresponding solvents in which the solutions of LiCl are prepared. The decreased values of $endo^R$ are therefore, the result of a salting-in process.

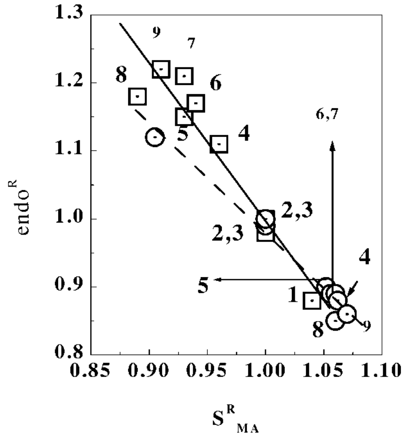

Figure 3. Correlation of $endo^R$ with $S^R{}_{MA}$ in $LiClO_4$ (□) and LiCl (○) solutions in solvents for the CP + MA reaction: 1, water; 2, formamide; 3, ethylene glycol; 4, nitromethane; 5, acetone; 6, dichloromethane; 7, ethyl acetate; 8, tetrahydrofuran; 9, diethyl ether

The above correlation of *endo* products with solubilities argues strongly in favor of the changing behavior of a salt in different solvents, verifying that a given salt, which acts as a salting-in agent in one solvent, can change its characteristics in another solvent. Breslow and Guo[2] explained their results on the use of LiCl, GnCl and urea in water, ethylene glycol and formamide in terms of the chaotropic and antichaotropic nature of salts. Our results also show that $LiClO_4$, which is chaotropic in aqueous medium, changes into antichaotropic in solvents such as diethyl ether, ethyl acetate and dichloromethane. The antichaotropic nature of LiCl in water changes to chaotropic when used in diethyl ether, ethyl acetate, etc.

We also calculated the salting-in and -out coefficients for the CP + MA reaction carried out in different solutions according to the procedure[12] used by us in this context.[5b] Accordingly, the salting coefficient, κ_S is composed of three terms, κ_a, κ_b and κ_c. κ_a and κ_b describe the contributions due to cavitation and introduction of non-electrolyte into the cavity, respectively. In general, κ_S is the outcome of the competition between κ_a and κ_b. κ_c denotes the number density of solution species. The values of κ_a, κ_b, κ_c and κ_S as calculated using the input parameters[5b,13,14] are given in Table 3. In the case of $LiClO_4$ a negative κ_S value is obtained in water,

Table 3. The salting coefficient, κ_S, and its components in salt solutions of $LiClO_4$ and LiCl in different solvents

Solvent	$LiClO_4$				LiCl			
	κ_a	κ_b	κ_c	κ_S	κ_a	κ_b	κ_c	κ_S
Water	0.06	−0.462	−0.067	−0.469	0.546	−0.062	0.010	0.494
Formamide	0.418	−0.371	−0.059	−0.012	0.242	−0.245	0.008	0.005
Ethylene glycol	0.413	−0.344	−0.062	0.007	0.220	−0.227	−0.005	−0.012
Nitromethane	0.463	−0.130	−0.050	0.283	0.229	−0.317	−0.009	−0.097
Acetone	0.458	−0.109	−0.028	0.321	0.217	−0.327	−0.012	−0.094
Dichloromethane	0.454	−0.118	−0.019	0.317	0.251	−0.353	−0.019	−0.122
Tetrahydrofuran	0.401	−0.091	−0.012	0.298	0.200	−0.330	−0.025	−0.155
Ethyl acetate	0.470	−0.080	0.009	0.399	0.225	−0.382	−0.038	−0.195
Diethyl ether	0.452	−0.077	0.002	0.377	0.260	−0.378	−0.042	−0.160

suggesting the salting-in effect. The higher negative value of κ_b in LPWA suggests that strong solute–solvent interactions play a dominant role in reducing the amount of *endo* products in this solution. No change in the amount of *endo* products in formamide and ethylene glycol solutions of $LiClO_4$ over the pure solvents is confirmed by the nearly zero value of κ_S. The theoretical calculations of κ_S are also supported by our experimental solubility data for MA in these salt solutions. The rate-enhancing ability of $LiClO_4$ in LPNM, LPAC, LPDM, LPTF, LPEA and LPDE can be understood by the positive κ_S (~ 0.3–0.4) values. The cavitation phenomenon is difficult in $LiClO_4$ solutions except in water as shown by the high positive κ_a values, indicating a positive change in the Gibbs free energy of cavitation. The cavitation, solute–solvent interactions and the Gibbs free energy associated with them were discussed in detail by Breslow and Guo.[15]

A high positive value of κ_S is observed in the case of an aqueous solution of LiCl. The κ_b values are dominant over κ_a for those solutions of LiCl, which reduce the amount of *endo* products. Small values of κ_S for solutions of LiCl in formamide and ethylene glycol confirm that stereoselective products are unaffected in these solutions compared with the pure solvents. Breslow and Guo[2] suggested that the absence of such an effect in these solutions possibly reflected a weaker water-like structure.

Another point of relevance is the effect of counter-ions in water. The ion–solvent interaction coefficient, *B*, derived from the dilute viscosity data for Li^+, Cl^- and ClO_4^- at 298 K are 0.146, −0.007 and −0.082, respectively.[13a] The *B* values suggest that Li^+ is a strong structure maker in aqueous solution, whereas Cl^- and ClO_4^- are structure breakers, with ClO_4^- being stronger than Cl^-. The structure-making tendency of Li^+ is neutralized in the presence of the strong structure breaker ClO_4^-, thus completely eliminating the salting-out effect of Li^+ in water. On the other hand, the effect of Cl^- on the structure-making tendency of Li^+ is negligibly small. The *B* coefficients calculated from viscosity data (A. Kumar, unpublished results) for dilute solutions of $LiClO_4$ are 0.064, 0.015, 0.025, 0.121, 0.166, 0.196, 0.190, 0.172 and 0.219 in water, formamide, ethylene glycol, nitromethane, acetone, dichloromethane, tetrahydrofuran, ethyl acetate and diethyl ether, respectively. The increasing order of the *B* coefficients agrees well with the effect of these solvents when used in preparing solutions of $LiClO_4$ in realizing the above Diels–Alder reaction.

The above studies also explain why solutions of $LiClO_4$ in nitromethane and dichloromethane are effective in realizing several reactions with ease, as they promote the reaction compared with that in water. In summary, we have demonstrated that a salt which produces a rate-reducing effect on the stereoselectivities of Diels–Alder reactions in one solvent can accelerate the reaction in another solvent.

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