Salt effects on the Baylis–Hillman reaction

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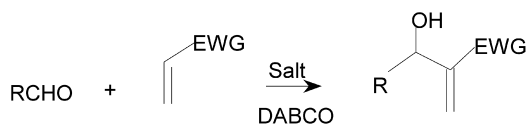Received 18 February 2003; revised 11 April 2003; accepted 8 May 2003

Abstract—The Baylis–Hillman reaction is shown to accelerate in salt solutions of water and the 'water-like' structured solvents, like formamide and N-methylformamide in the presence of DABCO. Ethylene glycol, another structured solvent and its salt solutions fail to make any impact on the reaction rates. The salts that are conventionally defined as salting-out or -in do not behave in a similar fashion, when employed in the Baylis–Hillman reactions. The results are supported by solubility measurements. It seems that the cation, anion, nature of solvent and of reactants together ascertain whether a salt will enhance or retard the Baylis–Hillman reaction. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

The Baylis–Hillman reaction (Scheme 1), one of the most important carbon–carbon bond-forming processes, is known to be very sluggish.[1–5] Several reports are available in the literature describing various attempts made to accelerate this reaction.[6–11] The studies have shown that water and other additives accelerate the reaction. In a very recent study, Aggarwal and co-workers demonstrated that the salt effects on the kinetics of these reactions could not be explained in terms of hydrophobic phenomena using salting-out and -in processes.[12] They further concluded that the hydrogen bonding in the 'water-like' solvents like formamide and N-methylformamide (NMF) played a dominant role over the hydrophobic effect. In order to reach this conclusion, they carried out the reaction of cyclohexenone with benzaldehyde (in amine catalyst) in the presence of guanidinium chloride (GnCl) and LiCl and noted that both GnCl and LiCl increased the reaction rates as compared to those in 1,4-diazabicyclo[2.2.2]octane (abbreviated as DABCO) and 3-hydroxyquinuclidine (abbreviated as 3-HDQ). GnCl is known to reduce the reaction rates owing to its salting-in tendency. On the other hand, LiCl enhances the rates as a result of salting-out

R = Ph / o-C$_6$H$_4$OMe / p-C$_6$H$_4$OMe

Scheme 1. Baylis–Hillman reaction.

phenomena. In fact, GnCl proved to be a more effective rate-enhancing agent than LiCl for the reaction of cyclohexenone with benzaldehyde. This effect in the Baylis–Hillman reactions is in contrast with what is observed in and benzoin condensation[13,14] and Diels–Alder reactions.[15] Recently, we have described the salting aspect in Diels–Alder reactions. In general, it is believed that the salts that enhance the hydrophobic effect are the salting-out agents. The hydrophobic effect is reduced in the presence of the salting-in agents. In the case of Diels–Alder reactions, rate enhancement and decrease in salt solutions can be correlated with salting-out and -in phenomena.[13,15]

As a part of our research program on delineating the origin of forces responsible for rate enhancement of organic reactions, we attempt to seek answers to the following questions with regard to the Baylis–Hillman reactions: (1) What is the effect of the salt solutions in water and other structured solvents on the Baylis–Hillman reactions? (2) How do the salts alter the rates of the Baylis–Hillman reaction? (3) If the salting effect plays governing role in controlling the Baylis–Hillman reactions, does the definition of salting effect remain uniform throughout as defined conventionally? or more specifically, does the solvent medium in conjunction with the nature of reactants decide whether a salt will enhance or inhibit the rates of the Baylis–Hillman reactions?, and (4) If the salting effect is significant in the Baylis–Hillman reactions, is it supported by solubility measurements?

2. Results and discussion

We first tried the reaction of benzaldehyde with methyl acrylate in the presence of DABCO. The results are shown in Table 1. The reaction took 19 h to complete with 65%

Table 1. The Baylis–Hillman reaction of benzaldehyde with methyl acrylate in different salt solutions

Entry	Solvent media[a]	Time[b] (h)	Yield[c] (%)	Entry	Solvent media	Time[b] (h)	Yield[c] (%)
1	DABCO	19	65	10	LiCl–NMF (1 M)	8	77
2	Water	12	68	11	LiCl–NMF (4 M)	6	75
3	Forma.[d]	11	70	12	LiCl–EG (1 M)	13	57
4	NMF	12	70	13	LiCl–EG (4 M)	9	59
5	EG[e] LiCl–water	15	55		LiClO$_4$–water	22	61
6	LiCl–water (1 M)	10	66	14	LiClO$_4$–water (1 M)	9	74
7	(4 M)	8	67	15	LiClO$_4$–forma. (1 M)*	10	72
8	LiCl–Forma. (1 M)	7	75	16	LiClO$_4$ –NMF (1 M)	10	72
9	LiCl–Forma. (4 M)	5	74	17	LiClO$_4$ –EG (1 M)	12	73

[a] Contains DABCO.
[b] No further increase in yield after the reported time.
[c] Isolated yields.
[d] Formamide.
[e] Ethylene glycol.

isolated yield. The same reaction in water offered a yield of 68% in 12 h. However, when the reaction was carried out in formamide, a yield of 70% was obtained in 11 h. Similarly, 70% yield in 12 h was obtained in NMF. On the other hand, this reaction when carried out in ethylene glycol (EG) offered 55% yield in 15 h. EG promoted the reaction as compared to pure DABCO, but the yield in EG was lower than in DABCO alone (Table 1, entries 1 and 5). The reaction of benzaldehyde with acrylonitrile was reported to be faster (7–8 h, 90% yield) in water, formamide and EG as compared to in other solvents like methanol (34 h), N-methylacetamide (48 h), DMSO, DMF, neat (3–5 days), THF and toluene (1 week).[6] However, such a rate acceleration is not observed for the reaction of benzaldehyde with methyl acrylate in EG (Table 1, entry 5), though EG like water and formamide falls in the category of the 'structured solvents'. In fact, this reaction is slower in EG with 20% less yield than achieved in water. The slowing down of the reaction of benzaldehyde with methyl acrylate as compared to that with acrylonitrile in EG suggests that the effect of a solvent on reaction rates will depend not only on the nature of solute and solvent, but also on the reactants. Aggarwal and co-workers pointed out that the hydrophobic effects and solvent polarity in such solvents might not be the sole reason to account for the rate enhancement noted in the Baylis–Hillman reaction and the hydrogen bonding in the structured solvents played important role in accelerating these reactions.[12] The favorable conditions for the Baylis–Hillman reactions in formamide were attributed to the hydrogen bonding. We then examined the effect of salt solutions prepared in the above mentioned solvents on this reaction. This was guided by the observation that salts could alter the hydrophobic effect in Diels–Alder reactions.[13] The reaction of benzaldehyde with methyl acrylate in 1 M aqueous LiCl gave 66% yield in 10 h. The reaction time of 10 h was reduced to 8 h with 67% yield in a 4 M aqueous LiCl, thereby accelerating the reaction. The use of 1 and 4 M LiCl solutions in formamide yielded 75 and 74% yields in 7 and 5 h, respectively. It is clear that LiCl solution in formamide is a powerful additive for achieving the rate acceleration because of high isolated yields obtained in relatively short time.

The reaction reached completion in 8 h (77% yield) and 6 h (75% yield) in 1 and 4 M solutions of LiCl in NMF, respectively. It is interesting to note that a 4 M solution of

LiCl in NMF can accelerate the reaction by a factor of 2 as compared to in NMF alone. However, we did not observe any noticeable changes in the yields (variation by 2–4% only) when the reactions were carried in the EG solutions of LiCl. Though the reactions became faster (from 15 h in EG to 9 h in 4 M LiCl solution of EG) it did not give any change in the yields.

Later, we investigated the influence of LiClO$_4$ (a salting-in agent in water) on the above reaction. We obtained 61% product in much higher time of 22 h in 1 M aqueous LiClO$_4$. This proves that aqueous LiClO$_4$ acts as a salting-in agent for this reaction by slowing it down as compared to in water (68%, 12 h), as it does in many other Diels–Alder reactions, like those of cyclopentadiene with methyl vinyl ketone[16] and with methyl acrylate[17] in aqueous environment. We noted a 74% yield in 9 h in 1 M solution of LiClO$_4$ in formamide. The yields do not vary (72%) in the LiClO$_4$ solutions of NMF and of EG. The reaction in the solution of LiClO$_4$ in NMF was, however, faster than that of LiClO$_4$ in EG (Table 1, entries 16 and 17).

Let us now comment on the effect of solvents and their salt solutions on Diels–Alder reactions with an objective to examine the similarities between the Baylis–Hillman reactions and Diels–Alder reactions. The rate enhancement of Diels–Alder reactions in formamide is possibly due to solvophobic interactions, as formamide is a structured solvent with higher dielectric constant (111) as compared to that of water (78.4).[16] The cycloaddition of 1,3-cyclohexadiene with nitrosobenzene was faster in formamide and EG than in other organic solvents.[16] Water, of course is proven to be the most effective rate-promoting solvents. The reaction of cyclopentadiene with methyl vinyl ketone was accelerated in solvents in the order of water>ethylene glycol>formamide>methanol>isooctane.[16] The rates of this reaction decreased with the addition of LiCl in formamide, while aqueous LiCl enhanced the reaction rate. On the other hand, the formamide solutions of LiClO$_4$ promoted the reaction. Similar effects could be seen if the reaction was carried in the solutions of these salts in EG. We wish to mention here that the reaction of cyclopentadiene with methyl vinyl ketone was faster in the EG solutions of LiCl, LiClO$_4$ and GnCl, though GnCl was less effective salt than LiClO$_4$. It should be emphasized here that again a salt plays a dual role of either salting-out or -in depending upon

the solvents. Similar results were observed in these salt solutions prepared in formamide. The commonly observed salting-in agents (LiClO$_4$ and GnCl) that inhibit the rates of Diels–Alder reactions in water promote the reaction when carried in their solutions prepared in EG and formamide by smaller magnitude than water. In terms of salting phenomena, it seems that the solubilities of diene and dienophile remain unaltered both in these solvents and their salt solutions. The relevant theory of salting phenomena is described elsewhere.[18–20]

The salting phenomena in reactions are directly related to the solubility of reactants in salt solutions. The salts that increase the reaction rates also promote the hydrophobic effect. Breslow and Connors called these salts as pro-hydrophobic and those, which inhibit the rates as anti-hydrophobic ones.[21] Thus, the salting phenomena, solubility of reactants and hydrophobic effect, are interrelated. At molecular level, ion-solvent interactions in conjunction with the nature of reactant molecule determine whether a salt will enhance or lower the reactant solubility. If a salt is dissolved in water, there is a volume contraction called electro-striction, as water collapses around the ions to solvate them.[17] This results in less empty space for a reactant. The energy cost to create space for a reactant is greater. We can imagine this as an energy cost of cavitation producing a hole of the reactant size in water. As the energy cost of cavitation increases due to electrostriction, the reactant precipitates out due to its lower solubility in the salt solution as compared to in water resulting into the rate enhancement. The salting-in effect is opposite in its physical process. In this case, the reactant becomes more soluble in the presence of a salt. These salts break the structural arrangement of water molecules making cavitation easier. This improves the solvation of the reactant in salt solutions. The reactant therefore, is not available for the reaction and hence the rate is lowered in the presence of such salts. The role of a salt in aqueous environment can also be extended to non-aqueous solvents in a similar fashion. The free energy of solution can be computed from solubility of solute in a solvent. The solubility of solute changes on addition of salt and thereby the Gibbs free energy of solution. The solubility of a reactant in the presence of salt over that in the absence is directly proportional to the change in Gibbs free energy in this process.[22]

The recent results on the reaction of cyclohexenone with benzaldehyde with GnCl and LiCl show that both these salts act as rate-enhancing agents, though in principle, the former is expected to inhibit the reaction rates and latter enhance them.[12] Both these salts therefore, act as the salting-out

agents for this reaction. To support these findings, we decided to examine the solubility of benzaldehyde in the salt solutions without and with DABCO (Table 2). The solubility of benzaldehyde (in the absence of DABCO) is 120, 63, 135 and 84 mM in formamide, water, NMF and EG, respectively. In aqueous LiCl containing DABCO, the solubility of benzaldehyde reduces to 35 mM resulting in the salting out of benzaldehyde. There is a marginal increase in the solubility of benzaldehyde in aqueous LiClO$_4$ (60 mM) as compared to that in water (54 mM) all in the presence of DABCO. Benzaldehyde is precipitated out in the presence of formamide solution of LiCl, as the solubility of benzaldehyde is lowered from 101 to 85 mM. The lowering of solubility of benzaldehyde in formamide solution of LiClO$_4$ from 101 to 60 mM is another example of the salting-out effect by LiClO$_4$. The solubility of benzaldehyde also reduces in the solutions of LiCl in NMF. However, we did not notice any change in the solubility of benzaldehyde in the LiCl–EG solutions, as it was in the range of 81–85 mM. Neither LiCl nor LiClO$_4$ in spite of strong solvating power of Li$^+$ or large sized ClO$_4^-$ fail to alter the solubility of benzaldehyde in EG thus indicating insensitivity of EG towards LiCl and LiClO$_4$. This suggests that the solubility can be a vital probe in determining whether the rate variation in the Baylis–Hillman reaction is an outcome of the salting-out or -in process, as the rate appears is inversely proportional to the reactant solubility.

We earlier noted that this reaction in EG remained sluggish and offered comparatively poor yield of about 55%. This yield did not improve in both LiCl and LiClO$_4$. These experiments in EG show that the salt solutions in EG cannot improve the reaction conditions.

It is interesting to note that the solubility of benzaldehyde is lower in LiCl with DABCO than without DABCO suggesting that LiCl with DABCO is a salting-out agent and hence the reaction rate increases in LiCl. It is surprising to observe that GnCl, which is a salting-in agent in water for several Diels–Alder reactions,[13,15,17] behaves in an entirely opposite manner in this case. GnCl in conjunction with DABCO suppresses the solubility of benzaldehyde, when compared without DABCO. Thus, GnCl for this reaction acts as a salting-out agent rather than salting-in one. We have recently shown in connection with Diels–Alder reaction that a given salt changes its salting-in property to the salting-out or vice versa in conjunction with the solvent in which its solution is made.[23] We confirmed the dual role of a given salt in two different solvents possessing very large difference in their dielectric constants by carrying out solubility measurements and calculations of salting coeffi-

Table 2. Solubility of benzaldehyde in different media; concentration of salt in each solution=1 M; DABCO=1 mmol

Entry	Medium[a]	Solubility (mM)	Entry	Medium[a]	Solubility (mM)
1	Water	54 (1)[b]	7	NMF	110 (1.2)
2	LiCl–water	35 (0.4)	8	LiCl–NMF	97 (1)
3	LiClO$_4$–water	60 (1)	9	LiClO$_4$–NMF	91 (0.8)
4	Formamide	101 (1)	10	Ethylene glycol	85 (0.4)
5	LiCl–formamide	85 (0.5)	11	LiCl–ethylene glycol	83 (0.4)
6	LiClO$_4$–formamide	60 (1)	12	LiClO$_4$–ethylene glycol	81 (0.5)

[a] Contains DABCO.

[b] Value in parenthesis is the average deviation in solubility calculated from triplicate measurements.
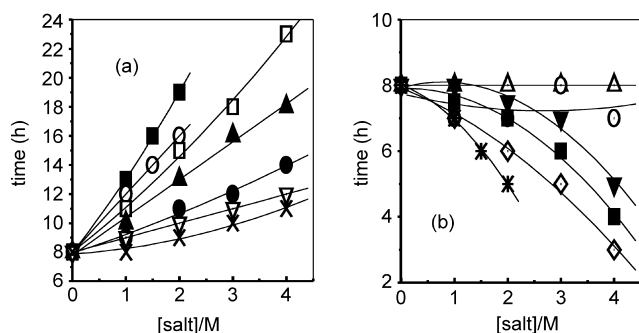
Figure 1. Time (h) as a function of the salt concentration, [salt] in water for the reaction of benzaldehyde and acrylonitrile, (a) (■) MgCl$_2$, (○) CaCl$_2$, (□) LiCl, (▲) NaCl, (●) LiBr, (▽) NaBr, (✗) CsI; (b) (△) KI, (○) KCl, (▼) NaI, (■) LiClO$_4$, (◇) LiI, (∗) Na$_2$SO$_4$.

cients. For example, LiClO$_4$ in water is a salting-in agent, but becomes a salting-out when dissolved in diethyl ether. This shows the significance of the solvent (water or diethyl ether) in which LiClO$_4$ was dissolved to make its solution. An example of the salting-in effect (rate-inhibiting) by LiClO$_4$–water was shown by Breslow and co-workers[13] in the case of Diels–Alder reactions. On the other hand, Grieco and his group have established the rate enhancement of several sluggish Diels–Alder reactions in LiClO$_4$– diethyl ether.[24] This can be attributed to the salting-out effect. Other effects, like viscosity, clatherates and Lewis acid catalysis are also possible.[25]

Encouraged by the above mentioned salt effects on the rates of the Baylis–Hillman reaction between benzaldehyde and methyl acrylate, we then examined the reaction of benzaldehyde with acrylonitrile in the presence of salts. Auge and co-workers showed that this reaction was faster in LiI and NaI as compared to in water and other organic solvents.[6] LiCl and CsI slowed the reaction, while the reaction remained unaffected by KI. The behavior of these salts on the reaction is not uniform considering the nature of ions. We therefore, decided to examine this effect in detail. We performed this reaction in several concentrations of aqueous LiCl, LiBr, LiI, LiClO$_4$, NaCl, NaBr, NaI, KCl, KI, CsI, MgCl$_2$, CaCl$_2$ and Na$_2$SO$_4$. DABCO was used in each reaction. The results are shown in Figure 1(a) and (b), where time is plotted as a function of the salt concentration. This reaction in water gave 90% yield in 8 h. The reaction in MgCl$_2$ and CaCl$_2$ was very slow with low yields. In a 2 M solution each of MgCl$_2$ and CaCl$_2$, for example, it took 19 and 16 h, respectively with ∼70% product. We were surprised to see that the reaction became slow with the increase in the salt concentration showing negative

influence of MgCl$_2$ and CaCl$_2$ on the reaction rates. The same reaction took 11 (in 1 M) to 23 h (in 4 M) of LiCl with 80% yield in good agreement with the literature values.[6] The rate-retarding effects were noticed in NaCl, LiBr and NaBr. CsI was a poor rate-inhibiting salt (from 1 to 4 M), where the reaction gave 88% yield in 8–11 h. Both KCl and KI did not exhibit any effect on the reaction; the reaction went in about 8 h with 90% product comparable to in water alone.

On the other hand, we obtained 93% yield in 4 M salts of LiI, LiClO$_4$ and NaI with rate almost doubled (reaction time 3–5 h) in 4 M salts. The reaction in a 2 M Na$_2$SO$_4$ solution gave 94% yield in about 5 h. The rate-enhancing capability of these salts varies in the following order: Na$_2$SO$_4$> LiI>LiClO$_4$>NaI>KCl≈KI>CsI>NaBr>LiBr>NaCl> LiCl>CaCl$_2$>MgCl$_2$.

The reaction goes faster in the salts having a common cation, but with increasing size of their anions. For example, the rate varies as: LiCl<LiBr<LiI; NaCl<NaBr<NaI.

In this connection, the work of Rizzo on the Diels–Alder reaction of anthracene-9-carbinol with N-ethylmaleimide in 2 M solutions of sodium and guanidinium salts with different anions is of relevance.[26] The reaction rates, which decreased with the increasing anionic radii, followed Hofmeister series.[27,28] The rates of the Baylis–Hillman reaction between benzaldehyde and acrylonitrile, however increases with the increase in anionic radii as seen above. This is an important point of the current investigation. It is therefore, clear that a classification of salts into salting-out and -in additives cannot be made on universal basis. For this reaction, MgCl$_2$, CaCl$_2$, LiCl, NaCl, LiBr, NaBr and CsI are the salting-in agents, while NaI, LiClO$_4$, LiI and Na$_2$SO$_4$ the salting-out ones. Otherwise, MgCl$_2$, CaCl$_2$, LiCl, LiI, NaCl, NaBr, NaI and Na$_2$SO$_4$ are the conventional salting-out agents in water. LiBr, CsI and LiClO$_4$ are known to be the salting-in agents in water.

We thought it appropriate to investigate the effect of salts on the Baylis–Hillman reaction between cyclohexenone and a deactivated and hindered aldehyde. o-Anisaldehyde is one of such aldehydes. The reaction of o-anisaldehyde with cyclohexenone in the presence of DABCO gave 68% yield in 27 h as compared to in 3-HDQ (74%, 24 h).[12] Table 3 summarizes these results.

This reaction in water gave 68% product in 27 h (Table 3, entry 1). However, a 68% product was obtained in 21 h in

Table 3. The reaction of cyclohexenone with o-anisaldehyde in 1 M salts in different solvents

Entry	Solvent media[a]	Time[b] (h)	Yield[c] (%)	Entry	Solvent media	Time[b] (h)	Yield[c] (%)
1	Water	27	68	7	KCl–forma	26	68
2	NaI–water	21	68	8	CaCl$_2$–forma.[d]	22	69
3	KCl–water	27	67	9	EG	28	60
4	CaCl$_2$–water[d]	32	65	10	NaI–EG	29	62
5	Forma.	20	69	11	KCl–EG	28	60
6	NaI–forma.	18	71	12	CaCl$_2$–EG	30	59

[a] Contains DABCO.
[b] No further increase in yield after the reported time.
[c] Isolated yields.
[d] 0.34 M salt.

NaI–water accelerating the reaction. Aqueous KCl did not exhibit any effect on the course of the reaction (Table 3, entry 3), as both the yield and time remained unaltered with respect to those noted in water alone. This reaction was further slowed down in aq. $CaCl_2$ and gave 65% yield in 32 h. Thus, NaI acted like the salting-out agent, while $CaCl_2$ as the salting-in. Formamide, another structured solvent like water accelerated the reaction giving 69% yield in 20 h. The formamide solution of NaI was also effective in speeding the reaction with 71% product in 18 h. The performance of the $CaCl_2$–formamide solution was better (22 h, 69%) (Table 3, entry 8) as compared to that in aqueous $CaCl_2$. Again the reaction rates did not improve in the solution of KCl in formamide (Table 3, entry 7). NaI is an effective salting-out agent both in water and formamide. However, aqueous $CaCl_2$ which is a salting-in agent, changed into a salting-out in the formamide solution. This reaction was quite slow in EG with 60% yield in 28 h. It is important to note that there were no apparent changes in reaction times and yields in the solutions of NaI, KCl and $CaCl_2$ in EG (Table 3, entries 10–12).

It is of interest to check how the salts can influence a Baylis–Hillman reaction containing a more reactive aldehyde than *o*-anisaldehyde. We therefore tested the salt effects for the reaction between *p*-anisaldehyde with ethyl acrylate, as *p*-anisaldehyde is more reactive than *o*-anisaldehyde. The results are summarized in Table 4. This reaction gave 38% product in 80 h in water alone. When this reaction was carried in aqueous $LiClO_4$ and LiCl, the reaction further slowed down with lower yields to be 19 and 15%, respectively in about 100 h as compared to in water alone. NaI showed very interesting effect by accelerating the reaction to give 50% product in 48 h (Table 4, entry 4), when compared to those in LiCl and $LiClO_4$ salts. Like LiCl and $LiClO_4$, NaCl did not improve the kinetics of this reaction (Table 4, entry 5). As compared to in formamide, its solutions with $LiClO_4$ and LiCl improved the reaction conditions by reducing the times to complete the reactions. This reaction did not go well in diethyl ether giving 2% product in 96 h. However, a 5 M $LiClO_4$–diethyl ether (LPDE) was noted to make a difference by yielding 50% product in 48 h (Table 4, entry 10). Use of LPDE in accelerating the Baylis–Hillman reaction of benzaldehyde with methyl acrylate has recently been demonstrated in which 70 mol% of $LiClO_4$ was used with 15 mol% of DABCO for the molar ratio of benzaldehyde/methyl acrylate as 0.83.[9] This reaction condition offered 81% yield. Once again, we noted that the reaction was not affected by EG or by the solutions of LiCl, $LiClO_4$ and NaI prepared in EG (Table 4, entries 11–14).

As pointed earlier, the salting-out and -in phenomena are related to ion-solvent interactions suggesting that the magnitude of ion-solvent interactions can help in rationalizing the rate variations in reactions. The ions and their salts can be classified as the structure-makers or the structure-breakers. One of the most important criteria to estimate these interactions is the analysis of viscosity data, which can be employed to extract the ion-solvent interaction parameter popularly called as the 'B-coefficients'. The B-coefficient of a salt can be divided into corresponding ionic B values. If a B value for a species (ion or its salt) is positive, the salt is termed as structure-maker. The structure-making and -breaking terms are meant to describe the changes in arrangement of water molecules around an ion and it depends upon the ionic radius, ionic charge and dielectric constant of water or in more general sense of a solvent. The B-coefficient of salt is an additive property and is the sum of the ionic B values. This term does not imply a making or breaking of a chemical species by chemical method. The structure-making and -breaking phenomena are purely physical in nature. The solubility changes in salt solutions can also rationalized in terms of the B-coefficients of salts. The B-coefficients of these salts in water as taken from the literature[29] are: Na_2SO_4 (−0.034), LiI (+0.067), $LiClO_4$ (+0.087), NaI (+0.006), KCl (−0.002), KI (−0.089), CsI (−0.127), NaBr (+0.054), LiBr (+0.115), NaCl (+0.079), LiCl (+0.140), $CaCl_2$ (+0.284) and $MgCl_2$ (+0.371). Though we have demonstrated use of this coefficient in correlating the kinetic data of Diels–Alder reactions, we are unable to trace such a correlation in the case of the Baylis–Hillman reaction. In the present study, it seems that the salts with very high B-coefficients (for example, $MgCl_2$ and $CaCl_2$) slow down the reaction, though with exception of NaCl, LiCl and LiBr. The salts with negative B values in general, promote the reaction. KCl is the only salt studied in this work which has its B value as −0.002 suggesting KCl cannot disturb the arrangement of solvent molecules with its cationic charge. Conventionally, KCl with a small negative B value is considered as a poor structure breaker. From the experimental results obtained on the above reactions, it is clear that irrespective of nature of reactants and solvents, KCl fails to influence the kinetics of the Baylis–Hillman reactions. In non-aqueous solvents like formamide, which accelerates the Baylis–Hillman reaction (Table 1, entry 3), the B-coefficient of LiCl from the literature viscosity data is −0.043. A change in the B-coefficient of LiCl from water

Table 4. The reaction of *p*-anisaldehyde with ethyl acrylate in 1 M salts in different solvents

Entry	Solvent media[a]	Time[b] (h)	Yield[c] (%)	Entry	Solvent media	Time[b] (h)	Yield[c] (%)
1	Water	80	38	8	LiCl–forma	58	48
2	$LiClO_4$–water	110	19	9	Diethyl ether	96	2
3	LiCl–water	96	15	10	LPDE[d]	48	50
4	NaI–water	48	50	11	EG	101	22
5	NaCl–water	85	30	12	LiCl–EG	98	23
6	Forma.	72	35	13	$LiClO_4$–EG	105	24
7	$LiClO_4$–forma	62	45	14	NaI–EG	95	22

[a] Contains DABCO.
[b] No further increase in yield after the reported time.
[c] Isolated yields.
[d] $LiClO_4$–diethyl ether, 5 M.

(+0.140) to that in formamide (−0.043) indicates that LiCl which was a structure-maker changed to structure-breaker when solvent was changed from water to formamide. LiCl in NMF has a value of *B*-coefficient as −0.029 showing again a strong change in the structure-altering ability of LiCl in water to NMF.[30] Analysis of viscosity data of LiCl in EG does not represent a noticeable change in its *B* value (+0.045). This suggests that LiCl act as a structure-maker in EG as it does in water, but its tendency to alter the solvent structure reduces by about 3 times. The above observations indicate that the structure-maker salts inhibit the reaction rates of the Baylis–Hillman reactions, the strong structure breakers enhance them. The salts that have poor or very weak influence on the arrangement of the solvent molecules seem to exhibit negligible effect on the progress of these reactions. We wish to state here such a classification of salts is still vague when seen in the perspective of the Baylis–Hillman reactions and calls for more physical-organic investigation.

We have recently shown that Na$^+$, a hydrophilic cation neutralizes the effect produced by guanidinium (Gn$^+$) cation in aqueous environment.[31] We studied this aspect to probe the origin of forces responsible for the rate enhancement and inhibition of Diels–Alder reaction in NaCl and GnCl by appropriate manipulation of ionic concentrations of Na$^+$ and Gn$^+$ for producing a water-like reaction medium.[32] For example, the rate of reaction of cyclopentadiene with methyl acrylate is reduced in the presence of 1 M GnCl relative to that in water. The rate inhibiting effect of GnCl can be neutralized by NaCl as shown in the case of Diels–Alder reactions and further supported by the solution data. If we want to neutralize the rate-inhibiting effect of GnCl, how much NaCl will be required so that the rate does not reduce and becomes equal to that noted in water alone? We discussed these results in terms of salting and structure altering properties of these salts. In Diels–Alder reactions, these effects can be easily ascribed to ion–water interactions among other factors. In nutshell, the hydrophilic tendency of Na$^+$ is neutralized by the hydrophobic nature of Gn$^+$ species. We examined this issue for the reaction of benzaldehyde with acrylonitrile in the mixtures of salts that gave opposite effects. As seen above, this reaction goes faster in NaI (4 h) and LiClO$_4$ (3 h) and becomes slow in NaCl (19 h) and LiCl (23 h). We performed this reaction in several compositions of the NaCl–NaI and LiCl–LiClO$_4$ mixtures. The results are shown in Figure 2.

This reaction becomes faster in the NaCl–NaI mixtures rich in NaI. There is an acceleration of the reaction with increase in NaI in NaCl. Similarly, a monotonous rate enhancement is witnessed in the LiCl–LiClO$_4$ mixtures. Again the reaction is faster in the LiClO$_4$-rich mixtures. As noted above, this reaction is carried in water in 8 h. From Figure 2, it is clear that a time of 8 h required to complete this reaction can be obtained by the mixtures of 70% (v/v) NaI–30% (v/v) NaCl. Similarly, a mixture of 55% (v/v) LiCl–45% (v/v) LiClO$_4$ offers a time of 8 h. In order to check this, we carried out this reaction in two different mixtures: (1) 70% NaI and (2) 55% LiClO$_4$ mixtures with the specified compositions. It was interesting to find that the reactions completed in 8 h with 89% product in both the mixed salts, which agrees well with the reaction carried in water alone
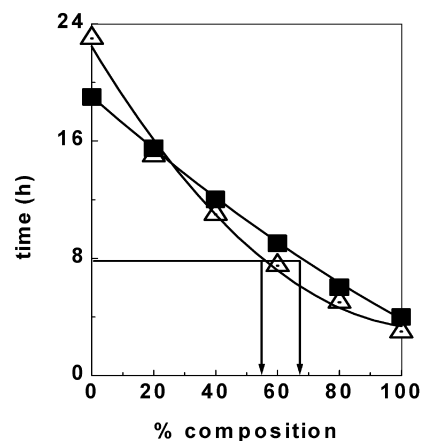

Figure 2. Time versus the mixture composition (% v/v) of mixed salts. (■) NaCl–NaI, (△) LiCl–LiClO$_4$.

(8 h, 90% yield). This finding confirms that the changes in the ion–water interactions due to NaCl were neutralized by those due to NaI, when mixed in appropriate combination. This is also true in the case of LiCl–LiClO$_4$ system. These experiments suggest that it is possible to mimic the water-like solvent conditions even in aqueous mixed salt solutions as a result of neutralization of the ion–water interactions of the opposite nature.

3. Conclusion

The findings of the above investigation based on the chosen reactions are summarized below:

1. The salt solutions have pronounced effect on the rates of the Baylis–Hillman reactions in the presence of DABCO. Water, formamide and NMF and their salt solutions promote the Baylis–Hillman reactions.
2. EG and its salt solutions fail to influence the Baylis–Hillman reactions.
3. The rate enhancement and inhibition in the presence of salts can be ascribed to the salting-out and -in phenomena.
4. The salting effect in the Baylis–Hillman reactions does not conform to conventional definitions of the salting-out and -in phenomena as noted in the case of Diels–Alder reactions. The cause of dual role of the salts on rates of the Baylis–Hillman reactions is yet to be ascertained.
5. The salting effect has been supported by the experimental solubility data.

As a matter of fact, the Baylis–Hillman reactions are accompanied by negative activation volumes.[6] This suggests that the rate variation in these reactions should be related to the hydrophobic or solvophobic effect. However, the results from the present studies do not conform to this view in full agreement of the literature.[12] How to quantify rates of the Baylis–Hillman reactions in terms of these ion-interactions arising from different types of ions is being currently investigated in our laboratory and will be communicated in the near future. We believe that the above study will be helpful in the synthetic aspects of

Baylis–Hillman reactions by manipulating solvent conditions.

4. Experimental

4.1. General remarks

All the aldehydes and cyclohexenone were distilled before use, while methyl acrylate, ethyl acrylate and acrylonitrile were used as such. DABCO obtained commercially was purified prior to use. Analytical reagents grade salts were used in preparing their solutions. (*Caution*: LiClO$_4$ is potentially explosive and must be handled with care.)[33] All other solvents were of high purity and used as purchased. Deionized water was used throughout the work.

The reaction procedures for carrying out these reactions were followed as described in the literature. Table 5 gives the reaction conditions used in this work.

Table 5. General conditions for the Baylis–Hillman reactions

Reaction	Reactant	Reactant
1	Benzaldehyde (1 mmol)	Methyl acrylate (1.2 mmol)
2	Benzaldehyde (1 mmol)	Acrylonitrile (1.2 mmol)
3	*o*-Anisaldehyde (1 mmol)	Cyclohexenone (2 mmol)
4	*p*-Anisaldehyde (1 mmol)	Ethyl acrylate (1.2 mmol)

DABCO 1 mmol; solvent or salt solution 1 mL.

As a general procedure, DABCO was added to the stirred mixture of reactants (Table 5) dissolved in a solvent. Diethyl ether was used to stop the reaction. The mixture was washed with 2 M HCl and then by water. The mixture was then dried and handled in a usual way. The product was purified by silica gel column chromatography and characterized by ^{1}H NMR.[6,9,12] All the products reported here have been successfully characterized in the literature and hence details are not given here. The reaction mixture was heterogeneous in water and its salt solutions. The reaction mixtures were therefore stirred vigorously. In the case of LiClO$_4$–diethyl ether, 1N HCl was added to quench the reaction. Dichloromethane was used to extract the aqueous layer. The reported yields throughout the work are the isolated yields.

The solubilities were determined by equilibrating benzaldehyde in a solvent or its salt solutions for 3 h in a Julabo-made constant temperature bath set at $25\pm0.1^\circ$C with vigorous agitation during the first 3 min. The lower phase was diluted 20 times with solvent (50 μL to 1 mL of solvent). The concentration of benzaldehyde was determined using a Varian UV–Visible spectrophotometer at 248 nm (in water), 255 nm (in formamide), 252 nm (in NMF) and 242 nm (in EG). The concentration of benzaldehyde was measured relative to a prepared standard in the same solvent. For example, the standard solution in the case of water–salt–benzaldehyde system was water–benzaldehyde with identical definitions for other systems. When the solubility of benzaldehyde was measured in the presence of DABCO, the standard solution also contained DABCO. The salt was noted to have negligible effect on the absorbance of benzaldehyde in solvents. The solubility

reported in this work is an average of three measurements with deviations not exceeding 1.7% from mean solubility value (see Table 2).

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