

Converting the role of LiClO₄ from salting-in to salting-out in Diels–Alder reactions by solvent manipulation

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ABSTRACT: The low yield of *endo* products of a Diels–Alder reaction in aqueous LiClO₄ can be enhanced by using a simple solvent manipulation. This report on the use of salt solutions opens up the possibility of creating effective conditions for Diels–Alder reactions. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: Diels–Alder reaction; salting-out; salting-in; stereoselectivity; solubility

Diels–Alder reactions can be accelerated in the presence of water, aqueous salts (e.g. LiCl, NaCl, MgCl₂), organic solvents and their salt solutions (e.g. LiClO₄–diethyl ether). The work of the groups of Breslow¹ and Grieco² is noteworthy in this direction. These and several other such contributions have been recently reviewed from this laboratory.³ Following a suggestion from Breslow,⁴ it was possible to describe the rate enhancement and inhibition of Diels–Alder reactions in terms of salting-out and salting-in phenomena, respectively. Thus, aqueous salts such as LiCl, NaCl and MgCl₂ are salting-out agents, whereas LiClO₄ and guanidinium chloride are salting-in agents. About a 40% reduction in the rate and *endo/exo* ratios for the reaction of cyclopentadiene with methyl acrylate can be observed in 4 M LiClO₄ in water. As part of continuing efforts from this laboratory⁵ to gain insights into the causes of rate variations of these reactions and thereby creating better reaction conditions, it is shown for the first time how LiClO₄ can be made to convert its role in enhancing the *endo/exo* ratios by manipulating the solvents for a Diels–Alder reaction.

The reaction of cyclopentadiene (**1**) with methyl acrylate (**2**) (Scheme 1) was carried out in 1 M aqueous LiClO₄ resulting in 65% *endo* product **3a**, which was 7% lower than observed in water alone. The experimental procedure is discussed elsewhere.^{5d} Solutions of AR-grade LiClO₄ were prepared in de-ionized water and dried organic solvents. In a typical run, 0.6 ml (7.26 mmol) of freshly cracked cyclopentadiene from its dimer (Merck) was dissolved in 2 ml of the salt solution.

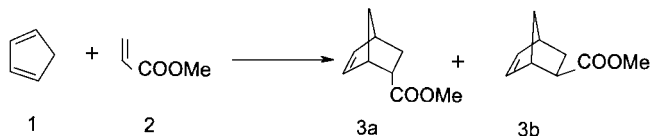
Then, 0.6 ml (6.66 mmol) of freshly distilled methyl acrylate (Merck) was dissolved in 10 ml of the salt solution. The solution containing cyclopentadiene was added to the solution with methyl acrylate. The reaction mixture was magnetically stirred for about 5 h. The *endo* and *exo* products were determined using NMR as discussed in the literature.⁶ Each reaction was carried out three times and the average was taken as the final reading.

Later, the reactions were carried out in aqueous mixtures of methanol with compositions ranging from 10 to 40% (v/v) methanol. Interesting results were noted when these reactions were carried out in these mixtures under similar conditions. First, 86% of *endo* product was observed in 10% methanol–water. The formation of the *endo* product was further accelerated in 20, 30 and 40% methanol–water, reaching 95% with a gain of 30% compared with that in 1 M LiClO₄ in water. These results are shown in Fig. 1. One can see a sharp rise in the *endo* products. This reaction resulted in 90 and 75% *endo* products in 60 and 80% methanol–water systems, respectively. There is a decline in the *endo* product in methanol-rich solvent. When this reaction was carried in 100% methanol (no salt), the *endo* product (53%, yield 48%) was observed to be lower than that obtained in water alone. The yield of 60% in water alone increased to 70, 76, 81 and 86% in 10, 20, 30 and 40% methanol–water solutions, respectively. Again, a substantial decrease in yield was noted in 60 and 80% methanol solutions. The reaction in 1 M LiClO₄–methanol, however, offered 58% *endo*, which was not remarkably higher than that obtained in methanol alone. The reactions were also carried in the aqueous mixtures of methanol without any LiClO₄ (controlled reaction), where *endo* products dropped by about 10% from 72% in pure water to 61% in 40% methanol–water. The behavior of LiClO₄ in some organic

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Scheme 1

solvents has recently been reported during investigation of its limitations in Diels-Alder chemistry⁷ (the acceleration of the reaction of cyclopentadiene with ethyl acrylate in LiClO_4 in diethyl ether is mild compared with that in other solvents). In this connection, it is important to differentiate the effect of LiClO_4 from that of LiCl (a salting-out agent in water) on the *endo* products. This reaction in LiCl -methanol-water did not offer any noticeable changes in the *endo* product. The *endo* product obtained in 1 M LiCl -100% water (78%) changed to 84% when the reaction was carried in 1 M LiCl in 40% methanol-water. This suggests that the effect of LiCl in water is not altered by the presence of methanol as observed in the case of LiClO_4 .

In order to test the role of aqueous mixtures on the stereoselectivities, this reaction was also carried in aqueous mixtures of ethanol, acetone and dioxane. A 40% ethanol-water mixture containing 1 M LiClO_4 showed about a 17% increase in the *endo* product compared with the reaction carried out in LiClO_4 -water solution (no ethanol). The increase in the *endo* product in 40% ethanol-water with salt is only 11% with respect to that in

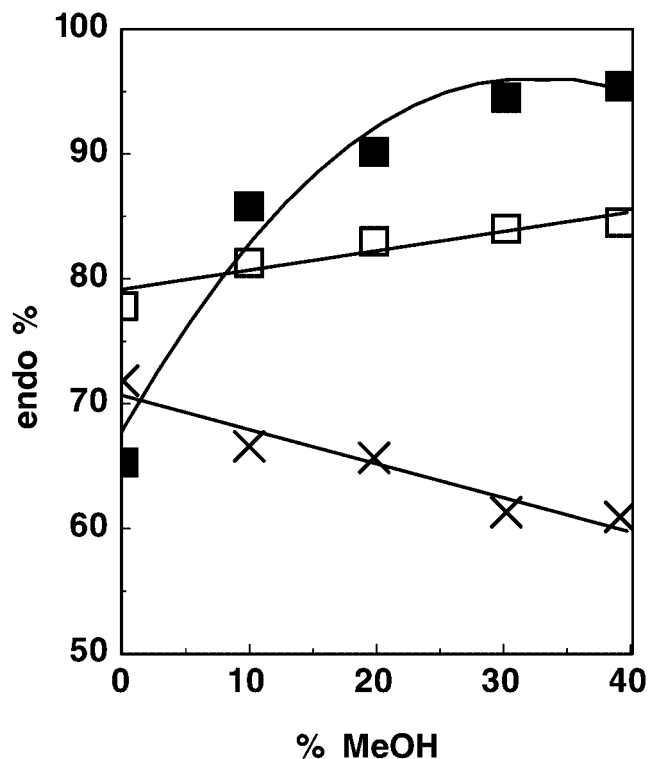


Figure 1. Effect of aqueous methanol on the formation of *endo* products in (■) LiClO_4 and (□) LiCl ; (×) no salt, control reaction

water alone. LiClO_4 in 100% ethanol gave 60% *endo* product. This reaction in 1 M LiClO_4 in 10% acetone-water gave only 70% *endo* product, which increased to 82% in 40% acetone-water. The results in LiClO_4 -dioxane-water were not encouraging. Four different compositions of dioxane-water containing 1 M LiClO_4 resulted in *endo* products ranging from 62 to 68%. When the reactions were carried in salt-free dioxane-water mixtures (10–40% dioxane), the *endo* products varied between 63 and 67%. LiClO_4 in dioxane did not have any effect on the *endo* product.

The reactions were further carried in solutions of LiCl prepared in aqueous ethanol, acetone and dioxane. Although the *endo* products increased in these solutions, the increase was very mild.

It is surprising that another potential salting-in agent, guanidinium chloride, when subjected to the above experiments in methanol-water mixtures did not produce noticeable change in the *endo* products. This resulted in us discontinuing further experiments in other solvents. It appears that the interaction of ClO_4^- with aqueous methanol plays a significant role in converting a salting-in to a salting-out agent. This was observed in our earlier studies, where we found that LiClO_4 could complex with some organic solvents in order to form clathrates. The presence of these clathrates can enhance the *endo* products.⁷ Water-rich methanol solutions do not favor clathrate formation, thereby decreasing *endo* product formation. Guanidinium chloride, on the other hand, does not form clathrates with pure methanol.

In support of the above work, salting coefficients⁸ were calculated for this reaction in LiClO_4 -methanol-water using the method outlined earlier.^{5d} The salting coefficient of LiClO_4 -water for this reaction was found to be -0.469 , which became $+0.125$ in 40% methanol-water. (A negative salting coefficient means salting-in and positive salting-out; a zero value of the salting coefficient denotes that salt has no effect on a reaction. The solubility measurements were not performed to seek further support of the statements made here, as excellent agreement of the salting coefficients had been reported from this laboratory between those obtained from experimental solubility data and theory.) These salting coefficients show that it is possible to convert a salting-in to a salting-out agent by appropriate mixing of solvents in water.

In conclusion, the results presented here demonstrate that it is possible to change the role of LiClO_4 , a salting-in agent in water, to a salting-out agent by changing the solvent composition. Methanol appeared to be the most effective solvent, aqueous mixtures of which can bring noticeable changes in the formation of *endo* products. It is hoped that these studies will allow synthetic organic chemists to apply more effective reaction conditions by simple solvent manipulation. Several permutations and combinations of solvents may be useful, and results on this aspect will be published in the near future, and the

molecular basis of this observation with detailed experimental data will also be communicated.

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