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Hydrophobic Effects Are Dominant over Secondary Orbital Interactions for a Simple Diels–Alder Reaction in Salt Solutions

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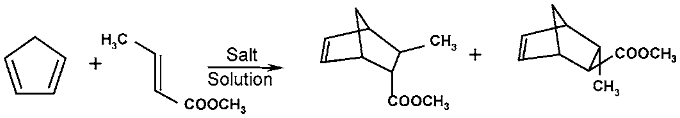
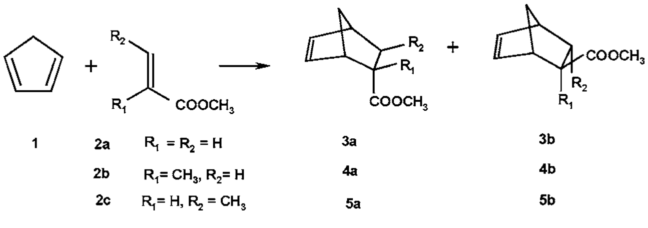
ABSTRACT



The stereoselectivity ratios for a Diels–Alder reaction between cyclopentadiene with methyl *trans*-crotonate carried out in salt solutions demonstrate the dominance of hydrophobic effects over secondary orbital interactions.

The pioneering contribution made by Rideout and Breslow[1] on the special role of water on Diels−Alder reactions has stimulated numerous investigations on promoting otherwise sluggish organic reactions and understanding the forces responsible for remarkable rate enhancement.[2] It was also demonstrated by Breslow and co-workers[3] that some salts promote Diels−Alder reactions, while others inhibit them. The salts that promote Diels−Alder reactions are prohydrophobic and those which inhibit these reactions are antihydrophobic in nature.[3g,h] The former class of salts enhances hydrophobic effects, while the latter decreases them. The possible origin of forces includes hydrophobic packing, solvent pressure, hydrogen bonding, hydrophobic hydration, and salting-out (S-O) and salting-in (S-I) effects, etc.[2a,4] As part of our studies to delineate and quantify the origin of these forces, we have investigated the reactions of cyclopentadiene **1** with methyl acrylate **2a** and with methyl methacrylate **2b** (Scheme 1) in aqueous salt solutions.[5,6]

Scheme 1. Reactions of Cyclopentadiene **1** with Methyl Acrylate **2a**, Methyl Methacrylate **2b**, and Methyl *trans*-Crotonate **2c**



Original contributions from Breslow and his group on the spectacular role of water and its salt solutions[1,3] and subsequent investigations from our group on the salt effect

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on the kinetics of Diels−Alder reactions have established that salts such as LiCl, NaCl, NaBr, KCl, $MgCl_2$, $CaCl_2$, and Na_2SO_4 enhance the rates and endo/exo ratios of Diels−Alder reactions in water, whereas guanidinium chloride (GnCl) and $LiClO_4$ lower them.[5−7] Accordingly, LiCl, NaCl, $CaCl_2$, $MgCl_2$, etc. are the S-O agents, while GnCl, $LiClO_4$, urea, etc. are the S-I agents. These effects are discussed in detail elsewhere.[2a,4] The salt effects on the reactions of **1** with **2a** and with **2b** follow the expected results within the framework of Breslow's work on the salting effect and its relation with kinetic data of Diels−Alder reactions.[2a,3] The salt effect on the endo/exo ratios for the reaction of **1** with **2b** was less pronounced than that of **1** with **2a**.

In this paper, we demonstrate a simple Diels−Alder reaction between **1** with methyl *trans*-crotonate **2c** (Scheme 1) for which the salt effects on the endo/exo ratios are opposite to what Diels−Alder reactions in general exhibit. It will be shown that "apparent contrasting" salt effects are actually normal effects with respect to the correct definitions of endo and exo stereoisomers.

In organic solvents, the reaction of **1** with **2a** is endo-selective, while that with **2b** is exo-selective. The reaction of **1** with **2c** in organic solvents gives the endo/exo ratio as nearly 1:1.[8,9] Some comments on the definitions of endo and exo stereoisomers are in order here. In the case of **2c**, the products are defined with respect to the stereochemistry of carboxylate as is the convention. Here, the conventional endo/exo refers to endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$. Thus, for this reaction, the endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratio is equivalent to exo$_{\text{mt}}$/ endo$_{\text{mt}}$. The subscripts carboxy and mt stand for carboxylate and methyl group, respectively. It should be noted here that for the reaction involving **2c**, endo and exo stereoisomers should be referred to with explicit use of carboxylate or methyl groups, as the case may be. A simple statement of endo and exo does not convey appropriate meanings of stereoisomers formed as a result of the reaction of **1** with **2c**.

The endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratios (the same ratio for exo$_{\text{mt}}$/ endo$_{\text{mt}}$ is implied) shown in Figure 1 were obtained for the reaction of **1** with **2c** carried out in aqueous solutions of LiCl, NaCl, KCl, $MgCl_2$, $CaCl_2$, GnCl, $LiClO_4$, and urea up to 5 M (except for KCl up to 4 M due to its restricted solubility in water). ^1H NMR and GC analyses were extensively used to determine the endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratios of the adduct.[10] The precision of the endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratios as determined from the average of triplicate reactions was observed as ±0.03. The maximum deviation at some salt concentration did not exceed ±0.05. An examination of Figure 1 shows that the salts such as LiCl, NaCl, KCl, $MgCl_2$, and $CaCl_2$ that are known to increase the endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratios of simple reactions of **1** with **2a** and with **2b** showed opposite effects on the reaction of **1** with **2c**.

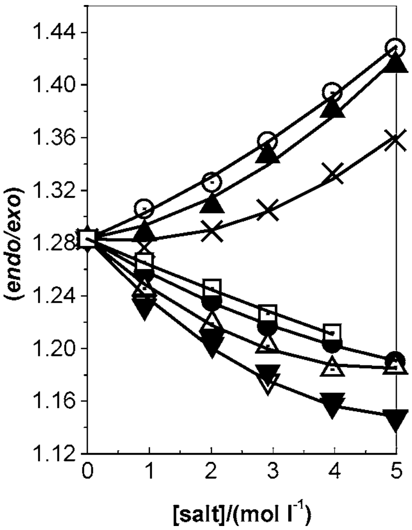

Figure 1. Plots of (endo/exo) vs salt concentration for the reaction of **1** with **2c** in KCl (□), LiCl (●), NaCl (△), $MgCl_2$ (▽), $CaCl_2$ (▼), urea (○), GnCl (▲), and $LiClO_4$ (×).

As can be seen in the plots shown in Figure 1, LiCl, NaCl, KCl, $MgCl_2$, and $CaCl_2$ decrease the endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratios from that in water (endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ =1.28) alone. This reaction in *n*-heptane, a nonpolar solvent, gave the endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratio as 0.97. This decrease is monotonic in nature but shows the signs of tapering off at higher salt concentration possibly due to the solubility of these salts in the solutions. The endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratios are consistently lower in these salts solutions when compared to that in water. $MgCl_2$ is the most effective salt in decreasing the endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratios of this reaction, while KCl is the least effective.

When the reactions were performed in urea, GnCl, and $LiClO_4$, higher endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratios of the products were obtained, as compared to that in water. As noted previously, these results are opposite to the trends obtained for the reactions of **1** with **2a** and **1** with **2b** or other Diels−Alder reactions in general. $LiClO_4$ showed the least effect on the increase of endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratios. This observation is again in contrast to the observations made in the cases of reactions of **1** with **2a** and with **2b**. GnCl, which was the least effective salt for the reactions of **1** with **2a** and **1** with **2b**, was noted to be the most effective of the three salts studied. Urea is the most effective agent for this reaction.

Intrigued by the above observations in water solutions, we decided to perform the reaction in other two self-associated solvents, namely ethylene glycol and formamide. The reaction in ethylene glycol gave an endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratio of 2.14, which was reduced to 1.18 in 5 M LiCl−ethylene glycol solution (see Table 1). A gradual reduction in the endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratios is seen from pure ethylene glycol to 1, 3, and 5 M LiCl solutions. On the other hand, this reaction gave higher endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratio in 5 M $LiClO_4$−ethylene glycol as compared to that in ethylene glycol. The endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratio of 2.09 obtained in pure formamide was lowered to 1.53 in 5 M LiCl solution of formamide. Further, when the reaction was carried out in 5

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Table 1. Endo$_{carboxy}$/Exo$_{carboxy}$ Ratios[a,b] for the Reaction of **1** with **2c** in Ethylene Glycol (EG), Formamide (FM), and Their Salt Solutions

solvent system	endo$_{carboxy}$/exo$_{carboxy}$	solvent system	endo$_{carboxy}$/exo$_{carboxy}$
EG	2.14	3 M $LiClO_4$−EG	2.57
1 M LiCl−EG	1.08	5 M $LiClO_4$−EG	2.83
3 M LiCl−EG	1.33	FM	2.09
5 M LiCl−EG	1.18	5 M LiCl−FM	1.53
1 M $LiClO_4$−EG	2.16	5 M $LiClO_4$−FM	2.75

[a] Also implies the same ratios for exo$_{mt}$/endo$_{mt}$. [b] An average of triplicate data with a standard deviation of 0.03.

M $LiClO_4$−formamide, the endo$_{carboxy}$/exo$_{carboxy}$ ratio increased to 2.75.

As for conformity, LiCl, NaCl, KCl, $MgCl_2$, and $CaCl_2$ should have increased the endo$_{carboxy}$/exo$_{carboxy}$ ratios of this reaction as they did for the reactions of **1** with **2a** and with **2b**. These results indicate that these salts show a different behavior and no longer act as the S-O agents for the reaction of **1** with **2c**. Similarly, $LiClO_4$, GnCl, and urea have increased the endo$_{carboxy}$/exo$_{carboxy}$ ratios and therefore no longer act as the S-I agents. This observation is noted in all three solvents.

The S-O and S-I phenomena are directly related to the solubility of reactants in a salt solution when compared to that in the pure solvent.[11,12] We attempted to confirm our observations on endo$_{carboxy}$/exo$_{carboxy}$ ratios by first measuring solubility of **2c** in water, aqueous LiCl, and $LiClO_4$ (Table 2). The solubility of **2c** in aqueous 5 M LiCl was substantially lower in aqueous 5 M LiCl than that in water alone, suggesting the role of LiCl as a S-O agent. On the other hand, the solubility of **2c** in aqueous 5 M $LiClO_4$ was higher than that in water, indicating $LiClO_4$ to be a S-I agent. The solubility of **2c** in 1 M LiCl−ethylene glycol is less than that noted in ethylene glycol alone, while **2c** is more soluble in 1 M $LiClO_4$−ethylene glycol than in ethylene glycol itself. The infinite miscibility of **2c** in formamide and its salt solutions did not allow us to measure its solubility in these media. The solubility data of **2c** in water and ethylene glycol media demonstrate that LiCl should have increased the endo$_{carboxy}$/exo$_{carboxy}$ ratio due to the S-O, while $LiClO_4$ decreased them owing to the S-I effects. But this is not the case for the reaction of **1** with **2c**. It is therefore clear that the reaction of **1** with **2c** cannot be interpreted in terms of salting phenomena.

Table 2. Solubility of **2c** in Different Solvent Systems

solvent system	solubility of **2c** (mM)	solvent system	solubility of **2c** (mM)
water	36.70	EG	18.21
aq 5 M LiCl	5.56	1 M LiCl−EG	11.70
aq 5 M $LiClO_4$	39.10	1 M $LiClO_4$−EG	19.31

These interesting salt effects can be explained within the framework of hydrophobic packing as proposed by Breslow in the past.[2a] Thus, accordingly, the lower endo$_{carboxy}$/exo$_{carboxy}$ values for this reaction in aqueous LiCl, NaCl, KCl, $MgCl_2$, and $CaCl_2$ as compared to in water shown above suggest that exo$_{mt}$ is less than endo$_{mt}$ in water. Since the methyl group is more hydrophobic than the carboxylate group, the hydrophobic packing of the methyl group in the transition state would lead to higher endo$_{mt}$, which corresponds to higher exo$_{carboxy}$. These prohydrophobic salts enhance the hydrophobic packing of diene and dienophile as compared to water alone. This is exactly what we have noted in this investigation of the reaction of **1** with **2c** in the above salt solutions. On the other hand, the antihydrophobic salts such as GnCl, $LiClO_4$, and urea decrease the hydrophobic packing resulting in lower endo$_{mt}$ corresponding to lower endo$_{carboxy}$. This suggests that hydrophobic effects dominate during the stabilization of the geometry of transition state rather than secondary orbital interactions[13] as advocated in the past. For the past three decades, secondary orbital interactions have been employed to explain the stereoselectivites of Diels−Alder reactions. However, the explanation of stereoselectivities of Diels−Alder reactions on this basis been questioned.[14] It is established from the theoretical calculations that the atoms presumed to be involved in secondary orbital interactions are situated relatively far (ca. 2.8 Å) in the corresponding transition-state structures. [14,15] This finding is against the existence of these interactions as the calculated geometries for transition-state structures of Diels−Alder reactions can lead to the estimation of the presence of other attractive effects.[16] Garcia et al. have deliberated on this issue to conclude that the hypothesis of secondary orbital interactions is not necessary to explain the stereoselectivity ratios.[14] Accordingly, a combination of solvent effects, steric interactions, hydrogen bonds, electrostatic interactions, etc. can be used in their place.

A similar change in the endo$_{carboxy}$ /exo$_{carboxy}$ selectivity has been observed for the reaction of **1** with **2b** (Scheme 1); however, this reaction is exo-selective in water and its salt solutions.[6] In the absence of methyl group substitution, as in the reaction of **1** with methyl acrylate **2a** (Scheme 1), hydrophobic interactions become less important and SOI

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directs the reaction to be endo$_{\text{carboxy}}$ selective leading to a higher endo$_{\text{carboxy}}$/exo$_{\text{carboxy}}$ ratio in water (Table 1).[5]

It is important to state here that we have carried out Diels–Alder reactions of **1** with other dienophiles, but such types of salt effects both in aqueous and nonaqueous salt solutions were not observed. In summary, it is possible to invoke the role of hydrophobic packing over that of secondary orbital interactions to explain the stereoselective ratio of a particular Diels–Alder reaction in aqueous salt solutions. The "apparent contrasting" salt effects could be interpreted in terms of hydrophobic effects.

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Supporting Information Available: Experimental details, stereochemical assignments, and ^{1}H NMR spectra of concerned compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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