Pergamon

Tetrahedron 58 (2002) 8759–8762

TETRAHEDRON

Salt effect on the *endo*/*exo* ratio of the reaction of cyclopentadiene with methyl methacrylate

Suvarna S. Deshpande,[a] Usha D. Phalgune[b] and Anil Kumar[a,*]

[a]*Physical Chemistry Division, National Chemical Laboratory, Pune 411 008, India*
[b]*OCS Division, National Chemical Laboratory, Pune 411 008, India*

Received 27 June 2002; revised 26 July 2002; accepted 22 August 2002

Abstract—The salt effect on the stereoselectivity of the reaction of cyclopentadiene with methyl methacrylate has been investigated. $CaCl_2$, Na_2SO_4, KCl and LiCl enhance the *endo*/*exo* ratios, while guanidinium chloride (GnCl) and $LiClO_4$ decrease them. The results are supported by independent calculations of salting-out and in coefficients. © 2002 Published by Elsevier Science Ltd.

1. Introduction

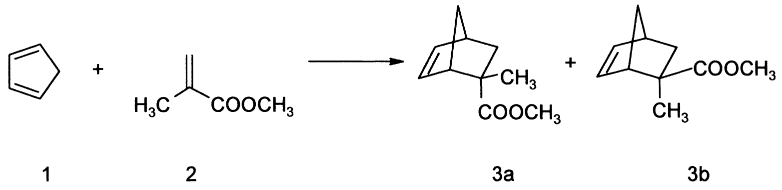
The rates and stereoselectivities of Diels–Alder reactions can be greatly varied in the presence of water, non-aqueous solvents and salt solutions. The use of solvent manipulation for enhancing the rates, stereoselectivities and *endo*/*exo* ratios was based upon the classic work from the laboratories of Breslow[1] and Grieco.[2] Whereas Breslow and co-workers demonstrated the spectacular effect of water and its salt solutions on Diels–Alder reactions,[1] the use of 5 M $LiClO_4$–diethylether, LPDE was established by Grieco and co-workers in accelerating sluggish Diels–Alder reactions and in obviating the high pressure conditions during the synthesis of cantharidin.[2] The developments in this area have been reviewed recently from this laboratory.[3]

As a part of the efforts being made in this laboratory it was shown that the *endo*/*exo* ratios for the reaction of cyclopentadiene with methyl acrylate increased in aqueous LiCl, NaCl, NaBr and $CaCl_2$, while $LiClO_4$ and guanidinium chloride (GnCl) lowered them.[4] As shown several years ago, the reaction of cyclopentadiene with methyl methacrylate (Scheme 1) in organic solvents yields more *exo* product.[5,6]

In the past, the research work from this laboratory has been focussed on delineating the origin of the forces responsible for rate variations in salt solutions.[3,7] The salt effect on the kinetics of the reaction of anthracene-9-carbinol with *N*-ethylmaleimide has recently been demonstrated in detail.[7b] The present paper deals with the study of *endo*/*exo* ratios for the reaction of cyclopentadiene with methyl methacrylate in different salt solutions. To the best knowledge of the authors, no reports exist in the literature describing the salt effect on this reaction. As more *exo* (less *endo*) product has been reported for this reaction in organic solvents, this investigation explores the possibility of altering the *endo*/*exo* ratio in salt solutions.

2. Results and discussion

Fig. 1 shows the $(endo/exo)_{rel}$ ratios obtained for the title reaction in LiCl, KCl, Na_2SO_4, $CaCl_2$, $LiClO_4$ and GnCl up to a concentration of 3 M. The $(endo/exo)_{rel}$ is defined as the *endo*/*exo* obtained in salt solution over that in water alone. As the reaction in water serves as a reference reaction, the reaction in this laboratory was carried out in each batch containing 18 mmol of cyclopentadiene and 15 mmol of



Scheme 1.

Keywords: salting-out; Diels–Alder reaction; salt solution.

* Corresponding author. Tel./fax: +91-20-5893044; e-mail: akumar@ems.ncl.res.in

PII: S0040-4020(02)01055-4

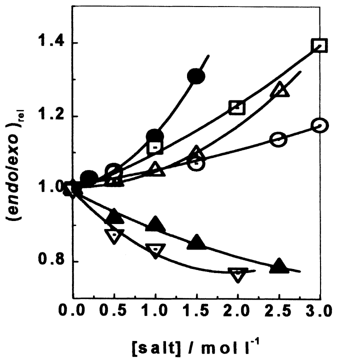


Figure 1. $(endo/exo)_{rel}$ as a function of salt concentration, [salt] for the reaction of cyclopentadiene with methyl methacrylate; (●) $CaCl_2$, (□) Na_2SO_4, (Δ) KCl, (○) LiCl, (▲) GnCl, (▽) $LiClO_4$.

methyl methacrylate in 10 ml of water for about 9 h to reach completion. The reaction in water was repeated four times with the average value of *endo*/*exo* being 0.40±0.02 (*endo*=29%, *exo*=71%) showing that water alone cannot reverse the *endo*/*exo* value of this reaction, in agreement with the earlier report.[6d]

From the above plot, it is clear that $CaCl_2$, Na_2SO_4, KCl and LiCl increase the $(endo/exo)_{rel}$ ratios, indicating that these salts enhance the amount of *endo* product. Of these salts, $CaCl_2$ is the most effective additive. This suggests that the *endo* product is preferred over *exo* in the presence of $CaCl_2$. On the other hand, both GnCl and $LiClO_4$ decrease the *endo*/*exo* ratios, thereby increasing the dominance of the *exo* product. From Fig. 1, it is clear that *endo* products in water can be greatly enhanced if the reaction is carried in $CaCl_2$, Na_2SO_4, KCl and LiCl. The *endo* product can be increased by 1.3 times in a 1.5 M $CaCl_2$ solution. The order in which the these salts increase the *endo*/*exo* values is: $CaCl_2 > Na_2SO_4 > KCl > LiCl$. Similarly, $LiClO_4$ is a more effective salt than GnCl in decreasing the *endo*/*exo* ratios for this reaction.

The increase and decrease of *endo*/*exo* values and rates of Diels–Alder reaction in salt solutions are attributed to the salting-out and in phenomena.[1,3,8] The salts that enhance rates also increase the hydrophobic effect operating in the solvent medium. Thus, $CaCl_2$, Na_2SO_4, KCl and LiCl are the salting-out agents and GnCl and $LiClO_4$ the salting-in ones. Accordingly, the salting-out agents lower the solubilities of diene and dienophile as compared to the solubilities in water. The reverse effect takes place in presence of salting-in agents. An effort was made to compute the solubility of methyl methacrylate in different salt solutions by using the method based on Universal Functional Group Contribution Model, UNIFAC as modified in this laboratory and tested for different cases.[4,9] Fig. 2 shows the relative solubility of methyl methacrylate, $(S/S^0)_{MMA}$ in different salt solutions. The quantity $(S/S^0)_{MMA}$ is defined as the solubility of methyl methacrylate in salt solution over that in water. The agreement between the computed[10a] and experimental solubilities[10b] confirms the validity of our computational methodology. As seen in Fig. 2, $CaCl_2$, Na_2SO_4, KCl and LiCl lower the solubility of methyl methacrylate as compared to in water and thus methyl methacrylate salts-outs. On the other hand, GnCl and $LiClO_4$ increase the solubility of methyl methacrylate through the salting-in effect.

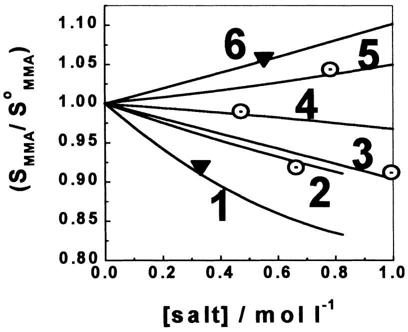


Figure 2. Relative solubilities of methyl methacrylate, (S_{MMA}/S^0_{MMA}) in (1) $CaCl_2$, (2) Na_2SO_4 (3) KCl (4) LiCl (5) GnCl (6) $LiClO_4$; lines are calculated, points experimental.

Table 1. Contributions of κ_a, κ_b and κ_c, and total salting coefficients, κ_S for the reaction of cyclopentadiene with methyl methacrylate in salt solutions

Salt	κ_a	κ_b	κ_c	κ_S
$CaCl_2$	0.568	−0.051	0.016	0.533
Na_2SO_4	0.461	−0.041	0.008	0.428
KCl	0.313	−0.029	0.004	0.288
LiCl	0.239	−0.017	0.003	0.225
GnCl	0.078	−0.373	−0.029	−0.324
$LiClO_4$	0.048	−0.483	−0.055	−0.490

In order to rationalize the salting effects in this reaction, the salting-out and in coefficients were computed using scaled particle theory[11a] because of its successful application to a variety of properties, including solubilities.[4,11b,c] The salting coefficients, κ_S obtained from the computational methodology advanced by Shoor and Gubbins,[12] and Pierotti[11d] are listed in Table 1. In essence, κ_S is a combination of three terms: κ_a accounting for cavity formation by the diene or dienophile, κ_b introducing the diene or dienophile in the cavity and κ_c giving the number density of solution species.

As seen from Table 1, positive κ_S (salting-out) values are observed for $CaCl_2$, Na_2SO_4, KCl and LiCl, while negative (salting-in) for GnCl and $LiClO_4$. The κ_S values follow the order, in which the salts affect the *endo*/*exo* values. For all the *endo*/*exo* ratio-enhancing salts, the κ_a values are high and positive suggesting that cavitation is not easier in the presence of these salts. Thus, the effect of these salts stems from the salting-out. The small magnitude of κ_b in these salts suggest that solvation of diene and dienophile is not possible. On the other hand, highly negative κ_b values in GnCl and $LiClO_4$ indicate strong solute–solvent interactions leading to the salting-in effect. The resultant κ_S is a product of competition between κ_a and κ_b. Scaled particle theory is noted to predict the correct sign and magnitude of κ_S in this reaction unlike the simplified Debye–McAulay theory.[13]

The cavity formation and solvation phenomena in relation to *endo*/*exo* ratios can also be independently supported by the Gibbs free energy computations.[14] The relative change in the Gibbs free energy on addition of a salt in a reaction

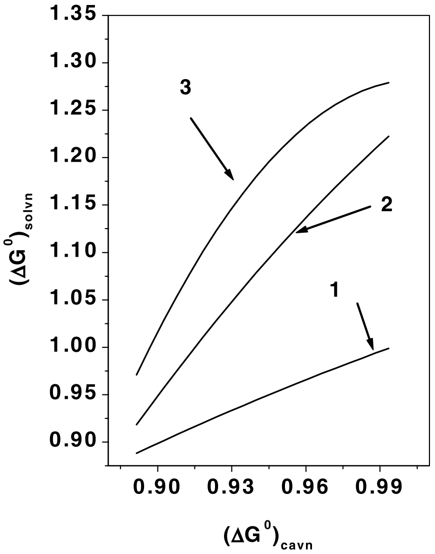


Figure 3. Plots of $\delta(\Delta G^0)_{\mathrm{solvn}}$ against $\delta(\Delta G^0)_{\mathrm{cavn}}$ for the reaction of cyclopentadiene with methyl methacrylate in $CaCl_2$, GnCl, $LiClO_4$, see Fig. 2 for symbols.

$\delta(\Delta G^0)_{\mathrm{soln}}$ can be given as that in Gibbs free energies of cavitation, $\delta(\Delta G^0)_{\mathrm{cavn}}$ and solvation, $\delta(\Delta G^0)_{\mathrm{solvn}}$ as:

$$\delta(\Delta G^0)_{\mathrm{soln}} = \delta(\Delta G^0)_{\mathrm{cavn}} + \delta(\Delta G^0)_{\mathrm{solvn}}$$

The computed $\delta(\Delta G^0)_{\mathrm{cavn}}$ and $\delta(\Delta G^0)_{\mathrm{solvn}}$ values from scaled particle theory[11,12] are plotted in Fig. 3. For GnCl and $LiClO_4$, the $\delta(\Delta G^0)_{\mathrm{solvn}}$ is larger than $\delta(\Delta G^0)_{\mathrm{cavn}}$ confirming that the salting-in effect by these salts originates from solvation effects. On the other hand, due to the electrostriction effect[14,15] in $CaCl_2$, Na_2SO_4, KCl and LiCl, less empty space is available for accommodating the diene and dienophile leading to salting-out. This is consistent with the trend of κ_a values shown in Table 1 for these salts.

The viscosity, conductance and hydration data from the literature show that $CaCl_2$, Na_2SO_4, KCl and LiCl are hydrophilic salts and GnCl and $LiClO_4$ hydrophobic ones, which alter the arrangement of water molecules due to the electric field created by cation or anion.[16,17] From the above study, it is clear that the hydrophilic salts enhance the *endo*/*exo* ratios, while the hydrophobic decrease them.

The role of activation volume, $\Delta V^{\#}$ in understanding the kinetics of Diels–Alder reactions carried out in solvents is well established.[18] Diels–Alder reactions are accompanied by negative $\Delta V^{\#}$ suggesting compact transition states. In the Diels–Alder reaction, where *endo* product is preferrable over *exo*, the $\Delta V^{\#}$ of the *endo* transition state is lower (more negative) than that of the *exo* (less negative). For the present reaction carried out in organic solvents, the ratio of activation volume of *endo* over that of *exo*, $\Delta V^{\#}_{endo}/\Delta V^{\#}_{exo}$ is less than unity (0.78) suggesting preference of the *exo* transition state over the *endo*.[19] The calculations of $\Delta V^{\#}$ from the method developed in this laboratory[7i,8a] offer a value of $\Delta V^{\#}_{endo}/\Delta V^{\#}_{exo}$ as 0.83, which indicates that $\Delta V^{\#}$ does not vary with the nature and type of salt solution.[20]

3. Experimental

Cyclopentadiene was freshly cracked from its dimer (Merck) just before its use. Methyl methacrylate obtained from Merck was used immediately after its distillation. High purity AR grade salts were used for preparing solutions in de-ionized water.

In a typical run, 1.5 ml (18 mmol) of freshly cracked cyclopentadiene was transferred into 5 ml of salt solution. Then, 1.5 ml (15 mmol) of methyl methacrylate was dissolved in 5 ml of the salt solution. The solution containing cyclopentadiene was added to the solution having methyl methacrylate. The reaction mixture was magnetically stirred at 30°C for about 9 h.

The *endo* and *exo*-products were determined using NMR as described in the literature.[21] Each reaction was carried out three times and the *endo*/*exo* ratios were reproducible to within 5%. GC and NMR were used to check the dimerization of cyclopentadiene, which was found to be negligible.

Acknowledgements

The authors thank Sanjay Pawar for his technical help during this work. The Department of Science and Technology, New Delhi is acknowledged for funding this research through a grant-in-aid (SP/S1/G19/99).

References

1. (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Breslow, R.; Maitra, U.; Rideout, D. C. *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.* **1995**, *117*, 6601. (e) Breslow, R.; Rizzo, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 4340. (f) Rizzo, C. J. *J. Org. Chem.* **1992**, *57*, 6382.
2. (a) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595. (b) See for a comprehensive review Grieco, P. A. *Aldrichim. Acta* **1991**, *24*, 59.
3. Kumar, A. *Chem. Rev.* **2001**, *101*, 1.
4. Pawar, S. S.; Phalgune, U.; Kumar, A. *J. Org. Chem.* **1999**, *64*, 7055.
5. Berson, J. A.; Hamlet, Z.; Muller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297.
6. (a) Inukai, T.; Kojima, T. *J. Org. Chem.* **1966**, *31*, 2032. (b) Seguchi, K.; Sera, A.; Maruyama, K. *Tetrahedron Lett.* **1973**, 1585. (c) Mellor, J. M.; Webb, C. F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 15. (d) Gonzalez, A.; Holt, S. L. *J. Org. Chem.* **1982**, *47*, 3186. (e) Houk, K. N. *Tetrahedron Lett.* **1970**, 2621. (f) Houk, K. N.; Luskus, L. J. *J. Am. Chem. Soc.* **1971**, *93*, 4606.
7. (a) Kumar, A.; Deshpande, S. S. *J. Phys. Org. Chem.* **2002**, *15*, 242. (b) Kumar, A.; Pawar, S. S. *Tetrahedron* **2002**, *58*, 1745. (c) Kumar, A.; Pawar, S. S. *J. Org. Chem.* **2001**, *66*, 7646. (d) Kumar, A.; Pawar, S. S. *Tetrahedron Lett.* **2001**, *42*, 8681. (e) Kumar, A.; Phalgune, U. D.; Pawar, S. S. *J. Phys. Org. Chem.* **2001**, *14*, 577. (f) Kumar, A.; Phalgune, U. D.; Pawar,

S. S. *J. Phys. Org. Chem.* **2000**, *13*, 555. (g) Kumar, A. *Pure Appl. Chem.* **1998**, *70*, 615. (h) Kumar, A. *J. Org. Chem.* **1994**, *59*, 230. (i) Kumar, A. *J. Org. Chem.* **1994**, *59*, 4612.

8. (a) Long, F. A.; McDevitt, F. W. *Chem. Rev.* **1952**, *51*, 119. (b) McDevitt, F. W.; Long, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 1773.
9. (a) Kumar, A. *Sep. Sci. Technol.* **1993**, *28*, 1799. In the present work the calculation procedure described in (b) Kikic, I.; Fermegha, M.; Rasmussen, P. *Chem. Engng Sci.* **1991**, *46*, 2775 was followed. In this procedure, a modified Debye–Huckel term accounting for ionic effects is added with UNIFAC terms dealing with organic components.
10. (a) Though UNIFAC theory can also be employed to compute solubilities of organic molecules in different solvents, it fails to differentiate between cavity formation and solvation terms. Use of scaled particle theory can allow the computation of the cavitation and solvation terms in salting-out and in processes. (b) The solubilities of methyl methacrylate in salt solutions were measured with a Varian Cary 50 U.V. spectrophotometer at 196 nm. The changes in the salt concentrations produced negligible changes in the absorptivity of methyl methacrylate. See: Closson, W. D.; Brady, S. F.; Orenski, P. J. *J. Org. Chem.* **1965**, *30*, 4026.
11. (a) Reiss, H.; Frisch, H. L.; Lebowitz, J. L. *J. Chem. Phys.* **1959**, *31*, 369. (b) Reiss, H. *J. Phys. Chem.* **1992**, *96*, 4736. (c) For application to organic molecules of different sizes see, Kumar, A. *J. Am. Chem. Soc.* **1993**, *115*, 9243. (d) Pierotti, R. A. *Chem. Rev.* **1976**, *76*, 717. and references cited therein.
12. Shoor, S. K.; Gubbins, K. E. *J. Phys. Chem.* **1969**, *73*, 498.
13. Debye, P.; Mc Aukay, J. *Phys. Z.* **1925**, *26*, 22.
14. The Gibbs free energy computations are approximate and are performed in order to establish the importance of cavitation and solvation. The $\delta(\Delta G^0)$ is a relative term rather than a difference property and defined as $\delta(\Delta G^0)_{\text{salt-water}}/\delta(\Delta G^0)_{\text{water}}$. Breslow[1c] used the term ‘relative’ in place of ‘difference’ defined by $\delta(\Delta G^0)_{\text{salt-water}}-\delta(\Delta G^0)_{\text{water}}$.
15. (a) Kumar, A. *Biochemistry* **1995**, *34*, 12921. (b) Kauzmann, W.; Bodanszky, A.; Resper, J. *J. Am. Chem. Soc.* **1962**, *84*, 1777. (c) Millero, F. J. *Chem. Rev.* **1971**, *71*, 147.
16. Marcus, Y. *Ion Solvation*. Wiley: New York, 1986.
17. (a) Kumar, A. *J. Phys. Chem. B* **2000**, *104*, 9505. (b) Kumar, A. *J. Phys. Chem. B* **2001**, *105*, 9828.
18. Drljaca, A.; Hubbard, C. D.; van Aldik, R.; Asono, T.; Basilevsk, M. V.; Le Noble, W. *J. Chem. Rev.* **1998**, *98*, 2167. and references cited therein.
19. Seguchi, K.; Sera, A.; Maruyama, K. *Tetrahedron Lett.* **1973**, 1585.
20. McCabe, J. R.; Eckert, C. A. *Acc. Chem. Res.* **1974**, *7*, 251.
21. Nakagawa, K.; Ishii, Y.; Ogawa, M. *Tetrahedron* **1976**, *32*, 1427.