Pergamon

Tetrahedron Letters 42 (2001) 8681–8683

TETRAHEDRON LETTERS

Abnormal effect of Gn_2SO_4 as compared to other guanidinium salts on rates and stereoselectivities of Diels–Alder reactions

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Received 10 August 2001; revised 17 September 2001; accepted 27 September 2001

Abstract—An abnormal effect in that guanidinium sulphate increases the rates and *endo* product formation of the reaction of cyclopentadiene with methyl acrylate is recorded for the first time in Diels–Alder chemistry. Other guanidinium salts like chloride, bromide, acetate and perchlorate inhibit the reaction rates and give rise to more *exo* products. This contrasting effect of Gn_2SO_4 on the kinetics of the Diels–Alder reaction can be attributed to the dominant role of SO_4^{2-} over the guanidinium cation.

Salt solutions have pronounced influences on rates and stereoselectivities of Diels–Alder reactions.[1] Special effects of water, aqueous LiCl, $LiClO_4$ and guanidinium chloride (GnCl) have been demonstrated by Breslow and co-workers.[2] The rate-enhancing effect in aqueous LiCl can be ascribed to salting-out phenomena, while the rate-inhibiting effects with $LiClO_4$ and GnCl to salting-in.[3,4] During our continued efforts to delineate the forces responsible for the salt effect on the kinetics of Diels–Alder reactions,[1] we encountered some interesting kinetic results for the reaction of cyclopentadiene with methyl acrylate in the presence of several guanidinium salts. In this work, we show, for the first time, that guanidinium sulphate, Gn_2SO_4 accelerates the reaction rate of the above reaction contrary to other guanidinium salts like GnBr, CH_3COOGn, $GnClO_4$, which reduce it. In general, it is assumed that the guanidinium salts inhibit the rates and endo products of Diels–Alder reactions.[1–4]

We measured[5] the reaction rates and stereoselectivities for the reaction of cyclopentadiene with methyl acrylate in aqueous GnCl, GnBr, CH_3COOGn, $GnClO_4$ and Gn_2SO_4. In Fig. 1(a), we plot the concentration depen-

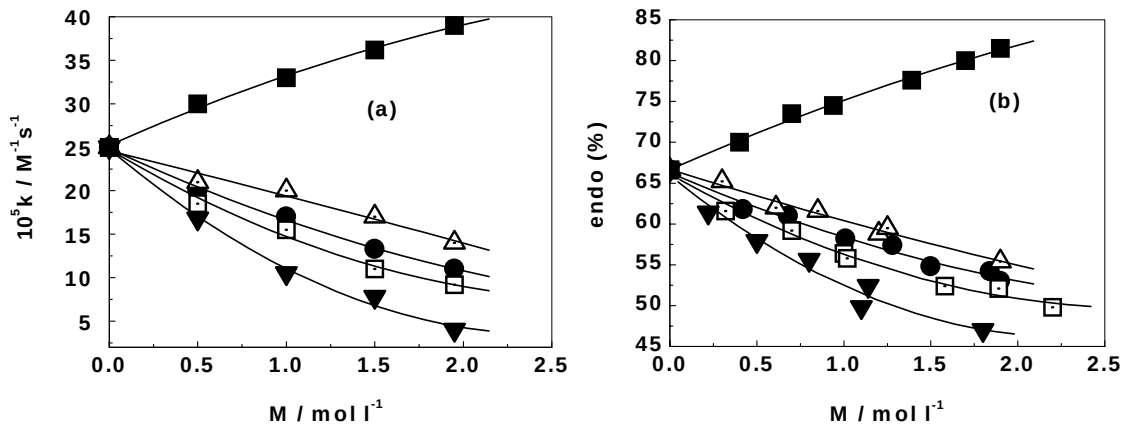

Figure 1. (a) Dependence of the rate constants, k_2 (M^{-1} s^{-1}) on the salt concentration for the reaction of cyclopentadiene with methyl acrylate in aqueous Gn_2SO_4 (■), CH_3COOGn (△), GnCl (●), GnBr (□) and $GnClO_4$ (▼); (b) *endo* (%) versus salt concentration for the reaction in the guanidinium salts, symbols are defined in Fig. 1(a).

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0040-4039/01/$ - see front matter
PII: S0040-4039(01)01819-6

dence of the rate constants, k_2 in the presence of different guanidinium salts. Similarly, the variation of *endo* products with the salt concentration is shown in Fig. 1(b). Data were also collected for Na_2SO_4 with a view to check the role of the SO_4^{2-} species. An examination of the rate constants, k_2 versus salt concentration [salt] plotted in Fig. 1(a) shows a decrease in the rate constants with respect to the salt concentration of GnCl, GnBr, CH_3COOGn and $GnClO_4$. For example, CH_3COOGn, GnCl, GnBr and $GnClO_4$ at 2 M salt concentration decrease the reaction rates by 44, 56, 63 and 84%, respectively. Thus, the order in which these guanidinium salts affect the progress of the reaction is $CH_3COOGn<GnCl<GnBr<GnClO_4$. This is also true for the presence of *endo* products obtained for this reaction. For example, at 1 M salt solution, the amount of *endo* product is decreased by 7, 13, 16 and 21% in aqueous CH_3COOGn, GnCl, GnBr and $GnClO_4$, respectively, as compared to that in water alone.

The most important point of this investigation is the effect of Gn_2SO_4, which enhances both the reaction rates and the amount of *endo* products. A 56% increase in the rate constant, k_2 at 2 M of Gn_2SO_4 is noted with respect to that in pure water. Similarly, the *endo* products are enhanced to 81.5% at 2 M of Gn_2SO_4, as compared to 66.6% obtained in pure water. The behavior of the guanidinium salts with different anions seems very interesting, particularly when Gn_2SO_4 displays opposite effects from those shown by GnCl, GnBr, CH_3COOGn and $GnClO_4$. The associated anions of the guanidinium cation i.e. Cl^-, Br^-, CH_3COO^- and ClO_4^- ions are seen to offer more *exo* product. However, Gn_2SO_4 reverses this trend by yielding more *endo* products. Since the guanidinium cation is a common cation in all the salts, this effect is expected to emerge due to anions. The variations in the reaction rates and *endo* products can be attributed to the salting-out (S-O) and salting-in (S-I) phenomena.[6] From this argument GnCl, GnBr, CH_3COOGn and $GnClO_4$ act as S-I agents, while Gn_2SO_4 acts as an S-O one. The guanidinium salts with SCN^-, Cl^- and CH_3COO^- ions are known to be potential destabilizers of tertiary structures of proteins. On the other hand, Gn_2SO_4 was noted to enhance the transition temperature of proteins, thus acting as a stabilizer unlike other guanidinium salts.[7] The SO_4^{2-} ion in aqueous solution is known to be an S-O species.[8] Thus, a strong salting-out anion, such as SO_4^{-2} will over compensate the S-I tendency of the guanidinium ion thereby leading to a positive effect on rates and *endo* products in Gn_2SO_4. The salting-coefficient computed from the scaled particle theory[4,9] for Gn_2SO_4 is 0.239 (S-O agent) as compared to −0.265, −0.321, −0.095 and −0.383 for GnCl, GnBr, CH_3COOGn and $GnClO_4$, respectively (all S-I agents). Solubility measurements of methyl acrylate, for example in aqueous guanidinium salts, support the above finding. In Fig. 2, we plot the relative solubilities of methyl acrylate $(S/S_o)_{MA}$, (S and S_o are the solubilities of methyl acrylate in the salt solution and water, respectively) in aqueous CH_3COOGn, GnCl, GnBr, $GnClO_4$ and Gn_2SO_4 solutions. It is noted from Fig. 2 that CH_3COOGn, GnCl, GnBr and $GnClO_4$ increase

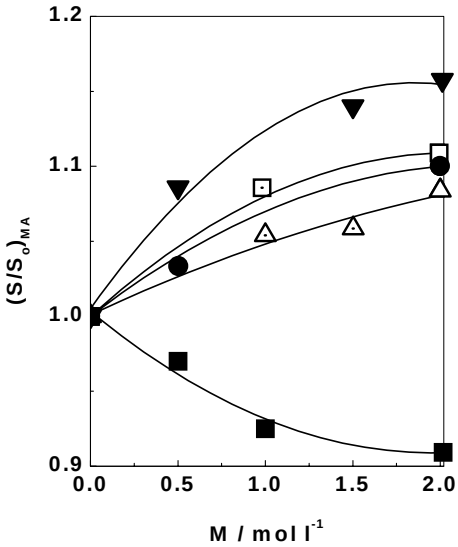

Figure 2. The relative solubilities of methyl acrylate, $(S/S_o)_{MA}$ in guanidinium salts; symbols are the same as in Fig. 1(a).

the solubility of methyl acrylate in up to 2 M salt solutions indicating the S-I behavior of these salts. The $(S/S_o)_{MA}$ values are weakly altered by CH_3COOGn. The decrease in the solubility of MA in Gn_2SO_4 clearly indicates the S-O phenomena governing the rate acceleration.

In addition, the partial volume and compressibility[10] of these salts also indicate that Gn_2SO_4 is a salting-out agent, while other guanidinium salts are salting-in ones.

In summary, it can be stated that Gn_2SO_4 enhances the rates and *endo* products formation, while other guanidinium salts inhibit the rates and offer more *exo* product for the reaction of cyclopentadiene with methyl acrylate. The anion with which the guanidinium cation forms a salt determines the course of the rates and stereoselectivities.

Acknowledgements

Our work is supported by a generous grant-in-aid (No. SP/S1/G-19/99) from the Department of Science and Technology, New Delhi.

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