Experimental Evidence to Support Viscosity Dependence of Rates of Diels−Alder Reactions in Solvent Media

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Abstract: This note is aimed at ascertaining whether rates of Diels−Alder reactions depend on the viscosity of solvent media in which the reactions are performed. On the basis of the data collected from the literature and in this laboratory, it is seen in general that the rates increase in the solvents with their viscosities ranging up to ~1.2 cP. In solvents possessing viscosities above 1.2 cP, a drop in the reaction rates is observed in all cases. The effect of temperature on the above phenomena is also examined.

In a recent paper, we addressed the issue of using 5 M $LiClO_4$-diethyl ether (LPDE) solution in achieving maximum rate enhancement of several Diels−Alder reactions.[1] We demonstrated for the first time a substantial fall in rates of these reactions when carried out in the LPDE solutions of concentrations above 5 M. Our results offered experimental evidence for using 5 M LPDE in the synthetic work for maximizing rates and yields of Diels−Alder reactions.[2] Originally, the rate enhancement of Diels−Alder reactions in 5 M LPDE was explained by Dailey and Forman in terms of the Lewis acid catalysis.[3] We attributed the subsequent rate drops in LPDE solutions of above 5 M to the decreased Lewis acid catalytic activity of Li^+ due to the increased formation of dietherate and monoetherate complexes.[4] As a result of the complexation, fewer effective "naked" Li^+ cations become available to act as a catalyst, thereby decreasing the rates to a substantial degree. Second, it was noted that the rate decrease above 5 M LPDE was also related to very high viscosity of LPDE solution. No dramatic increase in the solution viscosity of LPDE was seen up to a concentration of 5 M. However, the viscosity of nearly saturated LPDE ($\approx$6.06 M) increased by about 800%, as compared to that of pure DE.[5] Therefore, a highly viscous environment was considered to play an inhibitive role due to diffusional problems causing the reaction rates to fall.

The role of viscosity on the kinetics of Diels−Alder reactions was investigated by Firestone and Vitale and others.[6] These authors showed that the intramolecular Diels−Alder cyclization of *N*-propargyl-9-anthramide increases with viscosity of several glymes.[6] It is important to note that they carried out the reaction in tetraglyme, the viscosity of which is two times higher than that of glyme itself. These authors noted that the slope of relative rates versus relative viscosities for the above intramolecular Diels−Alder reaction was much greater than the one noted during the kinetic study of Claissen rearrangement in these solvents. Diels−Alder reactions share some common features with the Claissen rearrangement like low solvent dependence, unrelated to polarity. The dimerization of cyclopentadiene was also examined with respect to the viscosities of different solvents, and a linear increase in the dimerization rate was seen.[7,8] From these examples, it is clear that in the lower end of the viscosity scale, the increase in the rates is sharp with viscosity. The reaction rates level off at ~1.3 cP before dropping with increasing viscosity above ~1.3 cP. The 1,3 dipolar cycloaddition of diphenyldiazomethane with ethyl phenylpropiolate was found to be enhanced with the rise in viscosity of different solvents to about 1 cP. Above 1 cP, a decline in the reaction rates was observed.[7] According to these authors, since pressure increased viscosities, a part of the pressure-induced rate accelerations of these reactions was due to the enhanced viscosity.

The above examples demonstrate that rates of Diels−Alder reactions and viscosity are correlated with each other. However, very recently, questions have been raised whether viscosity contributes to the rate acceleration in Diels−Alder reactions.[9,10] Firestone and Swiss, on the other hand, have attempted to establish that the rates of dimerization of cyclopentadiene in several solvents are dependent on the viscosities of the solvents.[11] Though the dependence of rates of Diels−Alder reactions on the solvent viscosity has been supported and criticized,[9,10] we strongly feel that this issue, when supported by experimental data, should receive attention of organic chemists through a more appropriate vehicle of communication. In view of the current work from this laboratory in identifying the origin of forces responsible for rate enhancement of Diels−Alder reactions in different solvents and their salt solutions,[12] we set out to assess the

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TABLE 1. Diels-Alder Reactions Investigated in Connection with the Viscosities of Solvents

reactions	t (°C)	ref
(1) intramolecular Diels−Alder reaction of N-propargyl-9-anthramide	100	6
(2) dimerization of cyclopentadiene	25, 40	7, 8
(3) diphenyldiazomethane + ethyl phenyl propionate	30	7
(4) cyclopentadiene + methyl acrylate		
solvent (I)	3−170	13
solvent (II)	22	14
solvent (III)	25	16
solvent (IV)	30	15
(5) cyclopentadiene + methyl vinyl ketone	30	15
(6) cyclopentadiene + methyl methacrylate	3−139	13
(7) cyclopentadiene + methyl *trans*-crotonate	3−66	13
(8) cyclopentadiene + acrylonitrile	22	14
(9) cyclopentadiene + (−)-menthyl acrylate	30	17
(10) cyclopentadiene + methyl (E)-α-cyanocinnamate	25	18
(11) 2,3-dimethyl butadiene + 1,4-naphthoquinone	80	19
(12) N-(2′-4′-dichloro-6′-oxo-2′,4′-cyclohexadien-1-ylidine)-4-nitrobenzamide + 2,3-dimethyl butadiene or + ethyl vinyl ether	80	20
(13) 2,3-dimethyl butadiene + 5-substituted (hydroxy, methoxy, acetyl)-1,4-naphthoquinone	80	21

existing data as a step to resolve the issue of the role of viscosity on rates of Diels−Alder reactions. The main objective of this work, therefore, is to examine the rate−viscosity data to ascertain whether the viscosity of the solvent plays any effective role in governing the kinetics of Diels−Alder reactions. This issue, if resolved, will be helpful in improving the reaction conditions, including at high pressures, where viscosity of the solvent is likely to influence the reaction kinetics.

Before analyzing the published data, it should be mentioned here that we have chosen the viscosity of a solvent at the temperature at which the rates of a given reaction have been measured. Therefore, both the *y*- and *x*-axes belong to the same temperature. The experimental data examined in this study are summarized in Table 1.

We first examine the simple reaction of cyclopentadiene with methyl acrylate in different solvents.[13−16] The authors observed the *endo/exo* values to be dependent on the solvent polarity. The *endo/exo* values, when plotted against viscosity of solvents (Figure 1), show an increase up to ~1 cP before declining sharply. Interestingly, the *endo/exo* plot for this reaction carried out in the aqueous mixtures of many organic solvents also shows similar behavior. If the *endo/exo* data collected at high temperatures are plotted against the corresponding viscosities of solvents, the maximum in the *endo/exo* values shifts to ~0.8 cP.

We, however, observed a serious contrast to this observation. Nakagawa et al. measured *endo/exo* for this reaction and for the reaction of cyclopentadiene with acrylonitrile at 22 °C.[14] These data showed that *endo/*
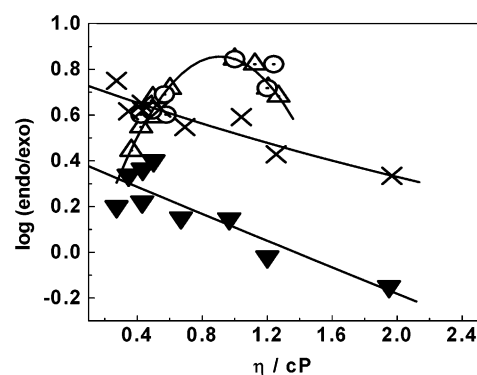
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FIGURE 1. Plots of log(*endo/exo*) for the reactions of (1) cyclopentadiene with methyl acrylate (△) at 30 °C, ref 13, (▼) at 22 °C, ref 14, and (○) at 30 °C, ref 15, and (2) cyclopentadiene with acrylonitrile at (×) 22 °C ref 14.
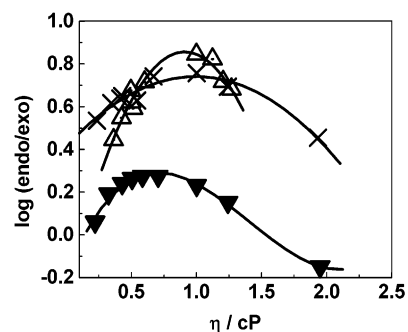

FIGURE 2. Log(*endo/exo*) − η plots from our experiments under identical conditions: cyclopentadiene + methyl acrylate reaction (△); (X) and cyclopentadiene + acrylonitrile (▼) reactions.

exo values for the reaction of cyclopentadiene with methyl acrylate decreased monotonically with an increase in viscosity.

Similarly, the reaction of cyclopentadiene with acrylonitrile showed a noticeable decrease in *endo/exo* values with respect to viscosities of the solvents at 22 °C.[14] In view of the puzzling situation created by the opposite trends, we decided to repeat the reactions of cyclopentadiene with methyl acrylate and with acrylonitrile under the reaction conditions specified by the original authors. These results are shown in Figure 2 in the form of log(*endo/exo*) plotted against the solvent viscosities. The earlier experiments on the reaction of cyclopentadiene with methyl acrylate by Berson et al.[13] at 30 °C were found to be reproducible within experimental accuracy. However, we observed a complete reversal of trend when we carried out the reaction under the conditions reported by Nagakawa et al. at 22 °C.[14] The log(*endo/exo*) values for the reaction of cyclopentadiene with methyl acrylate first increased up to ~1cP viscosity and then gradually declined up to the viscosity range of 1 to 2 cP. The log(*endo/exo*) − η plot for the reaction of cyclopentadiene with methyl acrylate from Berson et al.[13] is steeper than the one obtained from Nagakawa et al.[14] as shown in Figure 2.

Another noteworthy observation was with regard to the reaction of cyclopentadiene with acrylonitrile at 22 °C. We obtained a completely different curve for this reaction. Like other reactions as shown above, the log(*endo/exo*)
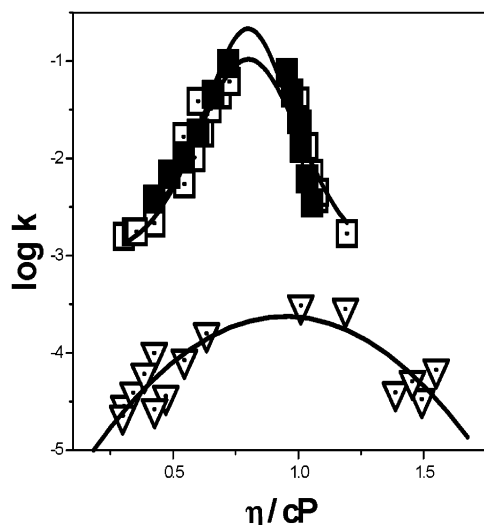
FIGURE 3. Plots of log k vs η for the reactions of cyclopentadiene with methyl acrylate ($\square$), with ($-$) menthyl acrylate ($\blacksquare$), and with methyl (E)-α-cyanocinnamate ($\triangledown$) in different solvents.
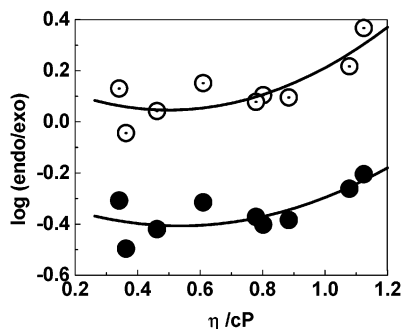

FIGURE 4. Plots of log($endo$/exo) $-$ η for the reaction of cyclopentadiene ($\bigcirc$) methyl $trans$-crotonate and with ($\bullet$) methyl methacrylate at 30 °C.[13]

values increased with η with the maximum being around $\eta \approx 0.5-0.6$ cP. Again a clear decrease in log($endo$/exo) values was witnessed from 1 to 2 cP.

The $endo$/exo values for reaction of cyclopentadiene with methyl vinyl ketone also showed first an increase with the viscosity up to 1 cP followed by a sharp decline between η values of 1 and 2 cP.

To get a clear picture, we plotted log k (k = rate constant) as a function of solvent viscosity (Figure 3) for the reactions of cyclopentadiene with methyl acrylate,[16] with ($-$)-menthyl acrylate[17] and with methyl (E)-α-cyanocinnamate.[18] The rates for the reaction of cyclopentadiene with methyl acrylate[16] in methanol, acetone, dioxane, and their aqueous mixtures, ethanol, formamide, etc., increased with viscosity up to ~0.75 cP before declining in the viscosity range of 0.75$-$1.25 cP. The reaction of cyclopentadiene with methyl (E)-α-cyanocinnamate has been reported in several aqueous mixtures of acetone and dioxane. If log k for this reaction is plotted against the viscosities of these aqueous mixtures (Figure 3), the rates

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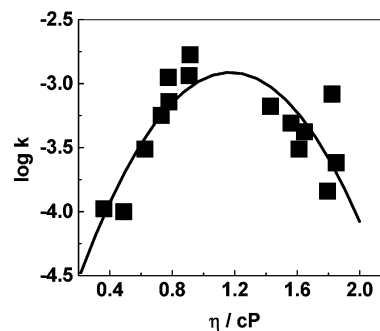

FIGURE 5. Plots of log k for the reactions of 2,3-dimethylbutadiene with 1,4-naphthoquinone, 80 °C.
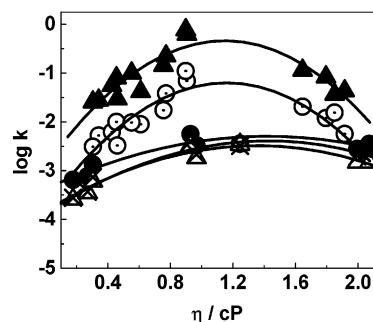

FIGURE 6. Dependence of log k on the solvent viscosity: 2,3-dimethyl butadiene + 5-hydroxy-1,4-naphthoquinone ($\bullet$), + 5-methoxy 1,4-naphthoquinone ($\triangle$), + 5-acetyl 1,4-naphthoquinone (X); N-(2'-4'-dichloro-6'-oxo-2'-4'-cyclohexadien-1- ylidine)-4-nitrobenzamide + ethyl vinyl ether ($\blacktriangle$), and + 2,3-dimethyl butadiene ($\bigcirc$).

increase up to ~0.75 cP and then show a fall in the viscosity range of 0.75$-$1.25 cP. The log k $-$ η plots for both these reactions are quite steep. However, the rates of the reaction of cyclopentadiene with ($-$)-menthyl acrylate in several solvents with the viscosity range from 0.25 to 1.5 cP show a slow increase before reaching nearly a maximum at ~1 cP. There is a regular drop in the rates in the viscosity range between 1 and 1.5 cP.

The reaction of cyclopentadiene with methyl methacrylate offers higher proportions of exo-products (anti-Alder rule) as compared to that with methyl acrylate (Alder rule), which yields higher proportions of $endo$-products.[13] Similarly, the reaction of cyclopentadiene with methyl $trans$-crotonate gives slightly higher proportions of $endo$-products in polar solvents and higher proportions of exo-products (borderline Alder rule) in nonpolar solvents.[13] The log($endo$/exo) $-$ η plots for these two reactions at 30 °C are shown in Figure 4, where we see a very small positive rise in the $endo$/exo ratio in the viscosity range of 0.37$-$1.1 cP. As the reactions were not carried out in the solvents having viscosity above 1.2 cP, it was not possible to see any decline in the rates. The log($endo$/exo) values for both these reactions shown in Figure 4 do not include the data in methanol due to the points falling beyond the trend shown herein. The log($endo$/exo) values for the reactions of cyclopentadiene with methyl methacrylate and methyl $trans$-crotonate are reported as $-$0.056 and 0.272, respectively.[13]

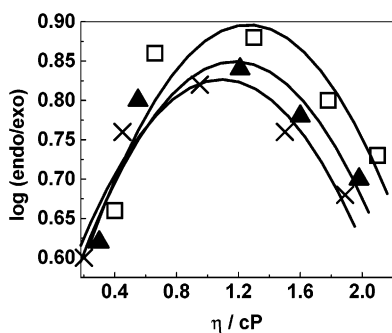We then examined the viscosity dependence of the rate constants for the reaction of 2,3-dimethyl butadiene with

FIGURE 7. Plots of log(*endo/exo*) against the solvent viscosity for the reaction of cyclopentadiene with methyl acrylate, 2 °C (■), 25 °C (▲), 33 °C (×).

1,4-naphthoquinone in different solvents at 80 °C.[19] These data shown in Figure 5 indicate that the rates show a steep increase in the solvents possessing viscosity in the range of 0.4−0.9 cP. A decrease in rates can be witnessed in the viscosity range of 1.4−2 cP.

Further, the rates of the reactions of *N*-(2′-4′-dichloro-6′-oxo-2′,4′-cyclohexadien-1-ylidine)-4-nitrobenzamide with 2,3-dimethylbutadiene or with ethyl vinyl ether[20] show prominent maxima at ∼1.2 cP before declining sharply in the viscosity range up to 2 cP (Figure 6). The log $k - \eta$ plots for the reactions of 2,3-dimethylbutadiene with 5-substituted (hydroxy, methoxy, acetyl)-1,4-naphthoquinone in a variety of solvents[21] are shown in Figure 6, where we note a modest increase in rates with the solvent viscosity reaching a maximum at ∼1.2 cP followed by a leveling of the curves and then a mild decrease in the rate of the reactions.

From the above, it is clear that both the *endo/exo* ratios and the rates of Diels−Alder reactions show dependence on viscosities of solvents. Another important observation is that although the viscosity increases by about 3 times, the rates can vary by as much as 100 times. This is contradictory to the general observation that for a diffusion-controlled bimolecular reaction, the ratio of rate change should be comparable with that of the viscosity. No explanation is available to describe this observation, which is entirely based on the examination of the experimental rate data (Figures 3 and 6), and no theoretical assumptions are involved in this observation. Though Berson et al.[13] have carried out temperature-dependent studies of the reactions of cyclopentadiene with different dienophiles at three or four temperatures, their data cannot be deemed the best data set in the present context, as temperatures selected for each solvent are not common. In view of this, we carried out the reaction of cyclopentadiene with methyl acrylate in five solvents (acetone, methanol, acetic acid, 2-methoxyethanol, and 1-propanol) of graded viscosities at three different temperatures, i.e., 2, 25, and 33 °C (Figure 7). It is interesting to note that log(*endo/exo*) increases sharply

in the η range of ∼0.3 to ∼1 cP before showing a sharp decline in these solvents with viscosities varying between ∼1.5 and ∼2 cP. The aim of conducting temperature-dependent studies was to examine whether changes in temperature in the reaction brought any changes in the plot shown in the foregoing studies. It is clear from the plot that as the temperature increases and the solvent viscosity decreases, a drop in the log(*endo/exo*) value is witnessed. With the rise in temperature, the solvent viscosity decreases (in this temperature range) and the maximum log(*endo/exo*) value shifts to the left: log(*endo/exo*) ≈ 0.9 at η = 1.3 cP at 2 °C; log(*endo/exo*) ≈ 0.83 at η = 1.2 cP at 25 °C; and log(*endo/exo*) ≈ 0.82 at η = 0.91 cP at 33 °C.

From the above examples, it is clear that rates of different Diels−Alder reactions vary with the solvent viscosities. Both the rate increase and decrease are seen in the viscosity range observed above. Though this observation is not yet understood on a molecular level, the contents described in this work clearly dispel the confusion over the relationship between rates of Diels−Alder reactions and solvent viscosities. The strength of the observations made in the above study lies in the fact that both the reaction rates or *endo/exo* ratios and the viscosities of solvents in which the reactions were carried out were measured at the same temperature, thereby eliminating any discrepancy in the correlation. In the above text, it has not been our main objective to put forward any theory in support of data but to demonstrate by plotting the rate−viscosity data in a consistent manner whether a correlation between rates of Diels−Alder reactions and the solvent viscosity exists at all. This work shows that there is such a correlation. The rate enhancement in the low viscosity range cannot be accounted for in terms of current kinetic theory, as the bond-forming reactions are independent of viscosity in this collision-controlled regime. Firestone and co-workers have interpreted this behavior in terms of the vibrational activation theory.[6,7,11] Accordingly, high vibrational and low translational energies (favored with increasing viscosity) promote the bond making. The translational mode of a molecule is retarded with increasing viscosity, resulting in a shifting of the translational to the vibrational mode. At very high viscosities, the situation pertains to encounter-controlled regime. In this regime, the relative freedom of movement of the reactants in the microenvironment of the encounter pair becomes limited. In such a highly viscous environment, reactants cannot see each other, and the reaction is consequently slowed.

Supporting Information Available: Names of solvents used for reactions mentioned in Table 1, experimental procedure and values of log(*endo/exo*) (plotted in Figure 7) for the reaction of cyclopentadiene with methyl acrylate carried out in different solvents at three temperatures. This material is available free of charge via the Internet at http://pubs.acs.org.

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