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Technical Notes

An Experimental Study of the Solvent Effect on Rate and Selectivity in a Concentrated Diels−Alder Reaction

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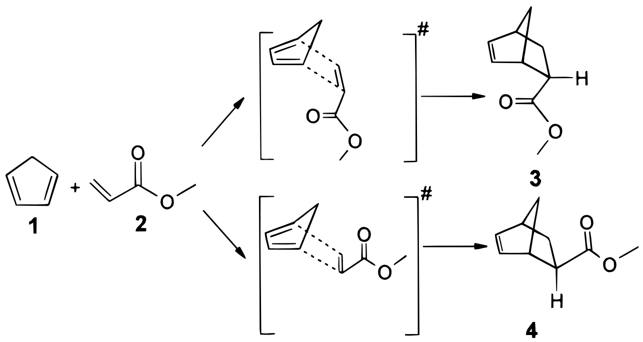
Abstract:

An experimental study of the effect of solvents on the rate and product selectivity of the solvated Diels−Alder reaction between cyclopentadiene and methyl acrylate is presented. The experiments were carried out in concentrated solution rather than the dilute solution used in previous studies by other workers. Gas chromatography and in situ Fourier transform infrared spectrophotometry were used to analyse the concentrated model reaction in the solvents, methanol and *n*-hexane. Reaction rates at 20 °C were 5 times faster, and the ratio of endo to exo adducts was initially 2.5 times greater in methanol. However, while the second-order rate constant remained approximately constant over the duration of the reaction, the selectivity for endo product in methanol dropped as the concentration of the products in solution increased. The origins of these effects are discussed in terms of solvent parameters, as are the implications for solvent selection.

Introduction

The properties of solvents and their impact on processes lie at the heart of process development of many industry sectors—particularly the fine chemical, pharmaceutical, and agrochemical industries. Solvents are commonly used as a reaction medium and to bring about a liquid-phase separation. Although their properties and usage are well-documented,[1,2] their effects on core engineering processes such as reactions and liquid−liquid separations are not well understood. As a result, general-purpose solvents are often used for these coupled processes. Unfortunately a poorly chosen reaction solvent may lead to reductions in yield and result in an increase in the environmental costs of downstream processes, such as recovery and disposal. Moreover, the common use of volatile organic compounds makes the decisions surrounding the choice of process solvents more relevant than previously believed.

Scheme 1



Concentrated solutions pose a particular problem for engineers and chemists. Kinetics are often easier to analyse in dilute solutions where the kinetic effects of solvents can be based on the properties of the solvent alone. However, most industrial reactions in the liquid phase are undertaken in solutions that are as concentrated as possible. Furthermore, mixtures of solvents are typical when multistage reactions are encountered. It is advantageous to process engineers and process chemists to investigate whether the kinetics in such solutions are significantly different from those in dilute solutions. Furthermore, a greater understanding of the solvent influence on concentrated reaction kinetics will enable better process solvents to be chosen. A model Diels−Alder reaction has been used to examine these issues in two solvents with different physical properties.

The Diels−Alder reaction between cyclopentadiene (**1**) and methyl acrylate (**2**) to produce an endo (**3**) and exo (**4**) product is a well-known reaction for illustrating solvent effects. The reaction has a straightforward single-step mechanism and second-order kinetics in both dilute and concentrated solutions. The reaction mechanism is illustrated in Scheme 1. The rate equation for this reaction is presented in eq 1.

$$\frac{\mathrm{d}[\text{cyclopentadiene}]}{\mathrm{d}t} = -(k_3 + k_4)[\text{cyclopentdiene}][\text{methyl acrylate}] \quad (1)$$

Here k_3 and k_4 are the elementary rate constants for the formation of compounds **3** and **4**, and $k_3 + k_4$ = the experimental second-order rate constant. By using this rate equation the selectivity has been defined as the ratio of the product concentrations and is shown in eq 2.

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$$k_3/k_4 = [\text{endo product}]/[\text{exo product}] \quad (2)$$

The effects of solvents on the selectivity and rate of the model reaction has been commonly explained by assuming a transition-state model. The mechanism is illustrated in Scheme 1, and the energy profiles are illustrated schematically in Figure 1. The selectivity changes can be related to the free energy difference between the solvated transition states, and the reaction rate changes can be related to the difference in the free energy of the solvated reagents and solvated transition states (minimum energy reaction path). For example, consider the dipole moments of the assumed transition states for compounds **3** and **4** (Scheme 2). As a result of the differences in orientation of the methyl acrylate molecule in the transition state (TS), **3-TS** has a larger dipole moment than **4-TS**. If the dipole moments are taken in isolation, this suggests that the selectivity will be greater in polar solvents where the TS leading to **3** will have a lower free energy. Similarly, the polarity of both TSs is greater than the polarity of the reagents. This implies an overall rate increase in polar solvents. These observations led Berson et al[3] to develop an empirical measure of solvent polarity that was based on the selectivity of this reaction.

Unfortunately, the dominant interactions leading to both rate and selectivity effects are more complicated than those represented by the differences in the TS dipole moments. Influences such as solvent polarity (π), the solvent-induced solvophobicity (*S*), dielectric properties (ϵ,μ) and the hydrogen-bonding characteristics of the solvent (α, acceptor; β, donor) have been shown[3-5] to be correlated with the overall rate of reaction and the selectivity.

Empirical links between the properties of solvents and the rate and product selectivity have been developed. Experimental studies of the dilute model reaction by Cativiela et al.[4-6] culminated in regression equations written in terms of these common solvent parameters. The regressions were developed using the Abboud−Abraham−Kamlett−Taft model[7] to alleviate problems arising from the parameters not being independent variables (such as *Et*(30) and π). Here the solvent influence on the overall rate of reaction was mostly attributed to differences in the solvent-induced solvophobicity. This is an effect that has been supported by studies in water-based solutions[8] where hydrophobic effects were the dominant influence. However, regressions for the selectivity were found to have a greater dependency on the effects of solvent polarity than on the solvent-induced solvophobicity. These contrasting influences illustrate the difficulty in making predictions of the effects of solvents on kinetics.

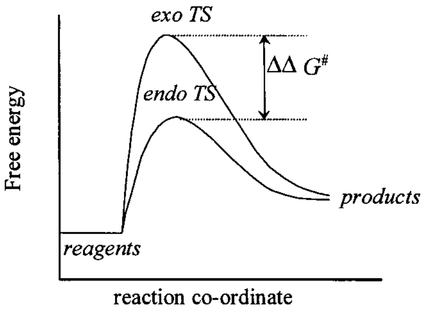
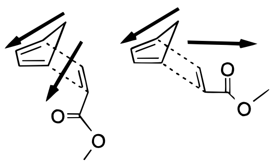


Figure 1. **Free-energy profile for the Diels−Alder reaction showing the free-energy difference ($\Delta\Delta G^{\ddagger}$) between the transition states for compounds 3 and 4. Here the free energy of 3 and 4 are shown for convenience and are not necessarily equal.**

Scheme 2



3 -TS **4 -TS**

Previous experimental studies of the Diels−Alder and other reactions have been undertaken in dilute conditions—clearly an unrealistic situation in chemical processing. As a consequence of running reactions in concentrated solutions, it becomes very difficult to make generalised assumptions for the parameter values to be used in these correlations. For example, the determination of the thermodynamics of mixtures requires some degree of experimental data. Alternatively, molecular simulation has been used to gain a better understanding of the local environment around the TSand has the potential to enable parameter estimation. Changes in the solution composition will occur over the course of the reaction (i.e., as the reagents are consumed and the products are created). As such, experiments conducted under concentrated conditions will be more representative of industrial conditions and allow a more relevant choice of solvent for better yields, selectivity, and ultimately recoverability.

Results and Discussion

Two independent experimental methodologies were developed to determine the kinetic properties of the Diels−Alder reaction system. Small laboratory-scale reactions in the solvents, hexane and methanol, were undertaken (see Experimental Section). GC was used as the predominant technique to measure the concentrations of the reaction solution components. The second method involved Fourier transform infrared spectroscopy (FTIR) to measure the overall reaction rates for comparison with those determined by the first method.

Different techniques are needed to analyse the raw data generated from each experimental method. Data analysis using FTIR was based on the determination of the concentration of compound **2**. This involved a multiparameter factor analysis to determine profiles for the absorbance changes of each of the species in solution. Simple extrapolation was then used to determine the concentration of **2**. Analysis by GC required a comprehensive procedure involving data reconciliation (outlined below). Unfortunately, the inability of the FTIR technique to distinguish between the endo and

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exo adduct, crucial for selectivity determination, required the use of GC techniques for that issue.

Data Reconciliation for GC. Experimental studies of this reaction have commonly used chromatography techniques to determine selectivity and reactions rates.[6,10] However, substantial errors (20−80%) have been encountered when determining the reaction rate in solution. Some of these problems are associated with the staggered sample collection, the drift and error in the detector performance, and the uncertainty in the response factors for compounds **3** and **4**. Data reconciliation techniques were developed to reduce these experimental errors.

The principal objective of the reconciliation technique is to interpret the component data by taking into account the mass balance equation for the model reaction. This is achieved by minimising the sum of the square error in the balanced equation shown in eqs 3 and 4 for an entire set of reaction data points (n).

$$\text{Error}^2 = \sum_{j=1}^{n}\left(\frac{\text{cyclopentadiene}_{\text{in}} - \text{cyclopentadiene}_{\text{out}}}{\text{cyclopentadiene}_{\text{in}}}\right)_j^2 + \left(\frac{\text{methyl acrylate}_{\text{in}} - \text{methyl acrylate}_{\text{out}}}{\text{methyl acrylate}_{\text{in}}}\right)_j^2 \quad (3)$$

Written in terms of the species concentration (o and i represent an initial and present condition respectively) this becomes

$$\text{Error}^2 = \sum_{j=1}^{n}\left(\frac{C_{1_o} - C_{1_i} - 2C_{5_i} - C_{3_i} - C_{4_i}}{C_{1_o}}\right)_j^2 + \left(\frac{C_{2_o} - C_{2_i} - C_{3_i} - C_{4_i}}{C_{2_o}}\right)_j^2 \quad (4)$$

Here the inclusion of compound **5** represents the parallel production of the dimer, dicyclopentadiene (**5**). With an excess of **2**, this term can be easily neglected. The GC response factors (R_i) for each component i, and the quantity of sample injected into the GC (I_j) were used as optimisation variables to minimise the error in the mass balance equation. Concentrations were calculated from the GC response and the response factors for each component (eq 5). Here the ratio of injection quantities accounts for differences in injection amounts between samples. I_j was taken as the value of the GC response for the solvent in each sample.

$$C_i = \frac{A_i}{R_i}\frac{I_j}{I_{j=1}} \quad (5)$$

In order to smooth the raw data reconciled from the response areas, an exponential curve was fitted by minimising the sum of square errors for the concentrations of **3** and **4** over the duration of the reaction. Exponential functions were based on best fit and bounded to impose the physical constraint of the completed reaction. The outcome was a set of concentration data that were as close as possible to the measured data but that satisfied the mass balance for the reaction. It is worth noting that no other species were detected, and thus the mass balance would be expected to be maintained.

***Table 1.* Average Second-order Rate Constants for the Diels−Alder Reaction in Methanol and *n*-Hexane at 20 °C and 1 Atmosphere**

reaction solvent	$(k_3 + k_4)$/ $\text{mol}^{-1}\,\text{h}^{-1}$	standard error (95%)/ $\text{mol}^{-1}\,\text{h}^{-1}$
methanol	0.130	3×10^{-3}
n-hexane	0.025	1×10^{-3}

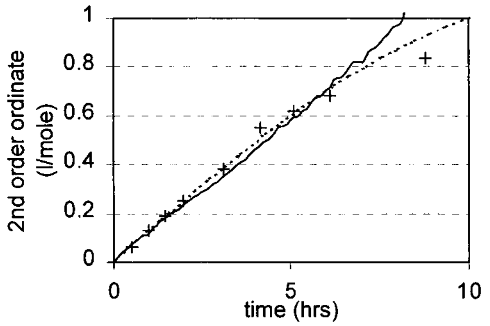

***Figure 2.* Integrated second-order reaction rate graph for reactions in methanol. FTIR data are shown as a solid line, fitted GC data are shown as a dashed line, and raw GC data are shown as crosses. The second-order ordinate is given by $1/[2]_o - [1]_o \ln([1]_o/[2]_o\,[2]_o - ([3]_i + [4]_i)/[1]_o - ([3]_i + [4]_i))$.**

Rates. The second-order rate constants (found by taking the average rate constant across all analyses) for the reactions in hexane and methanol are summarised in Table 1. As anticipated, the second-order rate constant ($k_3 + k_4$) in methanol solutions was approximately 5 times the magnitude of the second-order rate constant in hexane solutions. The preference for the reaction in methanol supported the assumption that the rate of the model reaction increases in more polar solvents. However, the magnitude of the difference between the second-order rate constants in methanol and in hexane is smaller than was anticipated from the use of solvent parameters and dilute regression equations. (k_{MeOH}: $k_{\text{n}-\text{C6}} = 12$ at 25 °C. Calculated with *Sp* and *Et* values from ref 6.) The reduced solvent influence in these solutions supports the hypothesis that changes in the characteristics of the solution (polarity and solvophobicity in this case) are incurred in concentrated solutions.

It is worthwhile noting the excellent match between the second-order rate constants calculated by in situ FTIR and GC approaches, and illustrated in Figure 2. The use of FTIR techniques for kinetic studies shows great promise both as a stand-alone technique and when used in conjunction with GC or HPLC to reduce the statistical errors of these approaches. Furthermore, FTIR techniques show the potential to measure changes in solution properties (such as the ability to form hydrogen bonds) by inferring these properties from frequency shifts. Unfortunately, the need to avoid overlapping group frequencies restricts both the reaction type and the solvent that can be observed.

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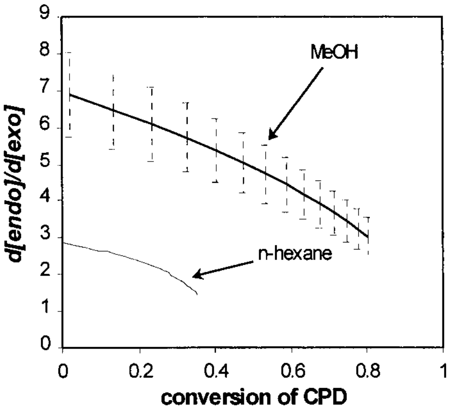

Figure 3. **Instantaneous selectivity along the reaction coordinate for reactions in MeOH and *n*-hexane. Error bars are shown for the reaction in methanol.**

Selectivity. Different measures of the selectivity of the model reaction in the solvents, methanol and hexane, were made. The “total selectivity” over the course of the reaction was determined from the concentration profiles of the products by simply taking the ratio of concentrations, [endo product]/[exo product]. The higher total selectivity in the more polar methanol solutions (initially 7 in MeOH and 3 in *n*-hexane) follows the anticipated behaviour for this reaction. However, this difference is not as marked as has been reported[11] for dilute solutions.

A more interesting measure of the selectivity of this reaction is the selectivity at any instant over the duration of the reaction. This “instantaneous selectivity” was determined from the ratio of the time rates of change in the fitted product concentrations (eq 6). These results are shown in Figure 3. Although there was uncertainty arising from the assumed response factors for **3** and **4**, this was not significant enough to account for the large changes in selectivity observed in methanol. Error bars are used to illustrate experimental and reconciliation errors.

$$d[3]/d[4] = d[3]/dt/d[4]/dt \qquad (6)$$

In contrast to popular belief,[12] the selectivity in the methanol and hexane reaction solutions was influenced by the changing reaction solution. The dependence of the endo selectivity on reaction was more marked in methanol, dropping from approximately 7 to 3 over the duration of the reaction, while the apparent rate constant remained unchanged. From an industrial standpoint, this behaviour could provide an opportunity to utilise the degree of reaction conversion to achieve a desired product selectivity (within limits).

The solvent influence on the model Diels−Alder reaction can be described in terms of well-known solvent parameters. Clearly the greater rate and selectivity in methanol is a function of the higher polarity and greater solvophobicity in methanol compared to hexane.

To examine more closely the origins of the changing selectivity it is assumed that the regression equations developed by Cativiela et al.[4,6] also hold for the concentrated solutions used in this study. The regressions suggest that the solvent-induced solvophobicity is a more important positive influence on the rate than the solvent polarity. Additionally, they found polarity to be the dominant solvent property influencing the product selectivity. It can be hypothesised for the reaction in methanol that changing the solution composition reduces the polarity of the reaction solution while retaining a strong solvophobic influence.

Conclusions

When compared to dilute solution kinetics, both the second-order reaction rate and the selectivity of the Deils−Alder reaction in concentrated solutions have been shown to be smaller. This places doubts over the predictive ability of empirical correlations that were developed from studies of dilute solution kinetics. However, dilute solution correlations provide insights into the mechanisms and the “solution” properties that are responsible for the kinetic differences.

From an engineer’s perspective, the ability to achieve a desired selectivity by altering the reaction conversion (within limits) could be used to help choose appropriate solvents for the Diels−Alder reaction in solution. For example, to achieve a high reaction rate it would be necessary to look for a solvent with a high solvophobic effect. A solvent with high polarity is also desirable to achieve high endo product selectivity. However, in concentrated solutions, the change in selectivity with conversion means the polarity of the solvent is less critical to achieving a desired selectivity.

Experimental Section

Raw Materials. Analytical grade (Methyl acrylate − 99%, CAS No. 96-33-3, Aldrich catalogue No. M2, 730-1. Dicyclopentadiene − 95% min, CAS No. 77-73-6, Aldrich catalogue No. 11, 279-8. Methanol − high purity analytical reagent. *n*-Hexane − 99.99%.) methyl acrylate, dicyclopentadiene, methanol, and *n*-hexane were used without further purification. The reagent cyclopentadiene was prepared by boiling the dimer (**5**) at approximately 160 °C using a 30 cm atmospheric Vigreux column. The pure distillate (**1**) (99% by GC) was collected at 40.5 °C to 41.5 °C and promptly used before polymerisation.

Reactions. Reactions between **1** and **2** in two different solvent media (*n*-hexane and methanol) were undertaken. Four sets of reactions in methanol and two sets of reactions in *n*-hexane were undertaken. The reaction concentrations (**1**:**2**:Solvent) where in the mole ratio 1:5:10 and were confined in a stirred 200 mL glass flask at 1 atm and 20 °C (constant temperature bath). The reaction solutions were vented to atmosphere using a microcondenser, and samples for GC were collected at half-hour intervals. Under these experimental conditions the overall reaction was found to be irreversible.

Gas Chromatography. Gas chromatography was undertaken on a FID Hewlett Packard 5890 II (HP-1). A polydimethylsiloxate column (25 m × 0.32 mm diameter) was used with N_2 as carrier gas. A flame ionization detector was used. Temperature programs were taken from the

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[12] Kim, S.; Johnson, K. P. *Chem. Eng. Comm.* **1988**, *63*, 49.

literature.[3] The column conditions were: column head pressure, 10 psi; split vent, 1.11 mL s^{-1}; purge vent, 3 mL min^{-1}. Residence times for methyl acrylate, cyclopentadiene, methanol, *n*-hexane, and dicyclopentadiene were determined from pure samples of these compounds. The product response times were inferred by reproducing the results of previous studies.[3] Calibrations (used for error analysis) were determined over the concentration range of interest for **2** and the ratio of **3** to **4**.

Infrared Spectrophotometry. IR spectra were collected online, over the wavelength range 1850−600 cm^{-1}. Background air and pure solvent spectra were collected prior to the reaction and automatically removed from the reaction spectra. Spectra of the reaction solutions were collected at regular intervals for a total of 800 points over 8 h. The time series of spectra were analysed using React-IR software (version 2.1).[13]

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(13) ReactIR version 2.1, ASI Applied systems, 1996.