Acceleration of Bimolecular Reactions by Solvent Viscosity[1]

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We report the first example of acceleration of a bimolecular reaction by increased solvent viscosity. In a series of hydrocarbon solvents of graded viscosity, the rates of two cycloadditions, the Diels−Alder dimerization of cyclopentadiene and the 1,3-dipolar cycloaddition of diphenyldiazomethane with ethyl phenylpropiolate, rise with increasing viscosity to about 1 cP and then fall thereafter. We interpret this rise as viscosity-induced acceleration up to ∼1 cP, which cannot be accounted for by current kinetic theory. Several examples from the literature are reinterpreted in these terms, providing further support for our concept.

Introduction

Viscosity is a measure of the force required to shear through a given fluid. Remarkably, the effect of solvent viscosity on reaction rates is a question that chemists seldom consider. Current kinetic theory[2,3] holds that the rates of bond-making reactions that have significant activation barriers are independent of viscosity at low viscosities, i.e., those of common mobile solvents, or gases at pressures well above the falloff region. This is defined as the collision-controlled regime, where encounters between the reactants are plentiful, and the rate is dependent on collision-dependent energy transfer.

However, consideration of the nature of enzymic catalysis[4] led us to predict different behavior, i.e., a positive effect of viscosity in the collision-controlled regime. In addition to the usual catalytic means such as proximity effects and push−pull, there are two features peculiar to enzymes, the catalytic cleft and the "ball of wax",[5] i.e., a preponderance of chemically unreactive amino acids, whose function was explained as creating a zone of high viscosity in which reactions are accelerated. The acceleration comes about because, according to the new theory, bond-making reactions having significant activation barriers are particularly sensitive to vibrational energy. Bond formation, it was proposed, takes longer than a single vibration, and therefore occurs more efficiently between mutually slow-moving reactants, one of which is vibrationally excited, than between vibrationally cold reactants with high line-of-centers translational energy.[6] Of course, at high viscosity encounter control still reigns, so that were the viscosity high throughout the entire solvent the reaction would still be very slow. The beauty of enzymes is that they offer a cleft of high viscosity to promote bond formation and yet avoid encounter control because the solvent is a mobile one.[1]

Clearly, the vibrational-activation theory clashes head-on with conventional theory, at least in the collision-controlled regime. The first experimental test was published in 1981 and verified the theory's prediction of a positive effect of viscosity on the rate.[7] Two unimolecular bond-making reactions, an intramolecular Diels−Alder and a Claisen rearrangement, were run in a solvent series of similar nature but gradually increasing viscosity and were indeed found to accelerate with rising viscosity. Since that time, several papers have appeared describing phenomena that could be interpreted as supporting our thesis.[8]

There were a few shortcomings in the early study.[7] The viscometry was somewhat inaccurate and was conducted on pure solvents rather than the reaction mixtures themselves, owing to solubility problems. The Diels−Alder reaction had been done in a series of glymes rather than the preferred hydrocarbon solvents, and the reactions chosen, while bond-making in nature, were both unimolecular, which precluded any investigation of the changeover from collision to encounter control.

We now report two new studies that surmount all the above shortcomings and provide more powerful data supporting the prediction of positive rate−viscosity correlation for bimolecular reactions under collision control. As the viscosity is progressively raised, the rates first rise and then fall.

To obviate the possibility that alterations in viscosity are accompanied by alterations in other solvent properties—most likely polarity-related—that might affect the rate, reactions were chosen that exhibit essentially no effect of polarity on the rate, namely Diels−Alder[9] and 1,3-dipolar cycloadditions.[10] Examples were chosen that proceed at moderate temperatures in the least interactive possible solvents, and concentrations were kept low to minimize microscopic inhomogeneities arising from aggregation or thermal effects.

Cyclopentadiene is soluble in nonpolar media, and its dimerization is particularly well-studied. There are already hints in the literature of a positive effect of viscosity on the rate.[11]

In a kinetic study in 1939, the data showed that in mobile solvents the rate varied little and was a simple function of neither polarity nor viscosity, but in paraffin oil the rate was twice that in CCl_4, and in neat cyclopentadiene it increased rapidly 3.3× toward the end, i.e., as the medium changed into the more viscous dicyclopentadiene.[12] Proceeding from *any* solvent into the gas phase involves a significant and discontinuous drop in viscosity,[7] and the rate fell to 0.22× that in paraffin oil.[12] The gas−liquid rate effect is a common one[7] and is suggested to be responsible for the correlation of Diels−Alder rate with solvent porosity.[13]

Another aspect of the gas−liquid rate effect is the observation that DA rates in CO_2 show enormous sharp increases as the pressure is raised from the sub- into the supercritical region. During this transit, but not below or above it, the apparent $\Delta V^{\ddagger}$ jumps to huge negative values,[14] −750 mL/mol.[15] This cannot be a true volume effect, and we attribute it to a discontinuity in

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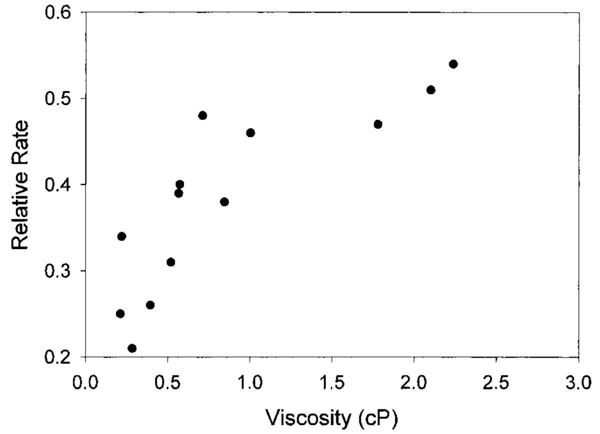


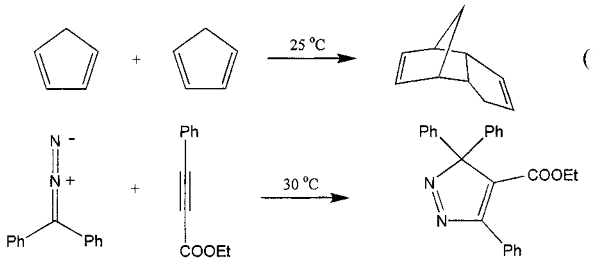
Figure 1. Relative rate constant vs viscosity for cyclopentadiene dimerization in various common solvents at 40 °C.[17]

viscosity arising from sudden change in phase. A rise in polarity cannot account for the phenomenon since it would affect the rate *negatively*.[16]

Another paper reported cyclopentadiene dimerization rates in a large group of solvents.[17] When their rate constants are plotted against solvent viscosity, there is scatter at low viscosities but a clear correlation emerges overall (Figure 1).[11]

Results and Discussion

We have measured the effect of viscosity on the rates of two bond-making bimolecular reactions, the dimerization of cyclopentadiene (reaction 1) and the 1,3-dipolar cycloaddition of



(1)

(2)

diphenyldiazomethane with ethyl phenylpropiolate[18] (reaction 2). Both reactions are known to be largely insensitive to solvent polarity, and to further ensure that the rate effects stemmed primarily from variations in viscosity, all solvents were pure linear saturated hydrocarbons. Only the chain length was varied, not the temperature or pressure.

The viscosity experienced by the reactant molecules (microviscosity) is not the same as that measured by the viscometer (macroviscosity). One would expect that micro- and macroviscosity would be alike when the solute and solvent molecules are the same size, but not when there is a great disparity in size.[19] As the hydrocarbon chains grow longer and longer, the relatively small cyclopentadiene molecules contact a smaller and smaller fraction of the entire solvent chains. Thus microviscosity, an increasingly local phenomenon, should rise more slowly than macroviscosity, whose measurement always involves the entire length of the hydrocarbon chains. This expectation is borne out by measurements of microviscosity reported for toluene molecules in linear saturated hydrocarbons, the very ones we are using. Microviscosity indeed rises more slowly than macroviscosity as the chain length grows.[20]

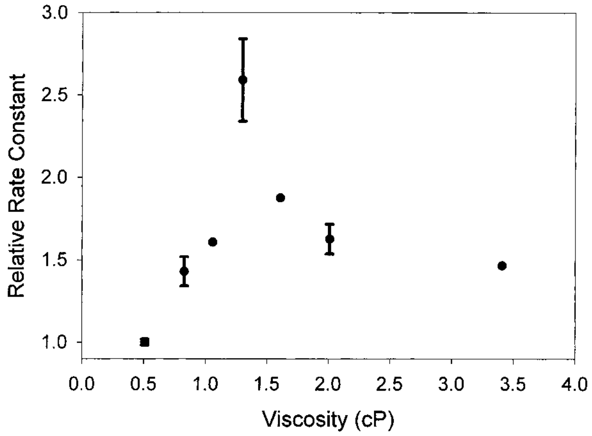


Figure 2. Relative rate constant vs viscosity of cyclopentadiene dimerization, 25 °C. Solvents used: (1) *n*-octane; (2) *n*-decane; (3) *n*-undecane; (4) *n*-dodecane; (5) *n*-tridecane; (6) *n*-tetradecane; (7) *n*-heptadecane.

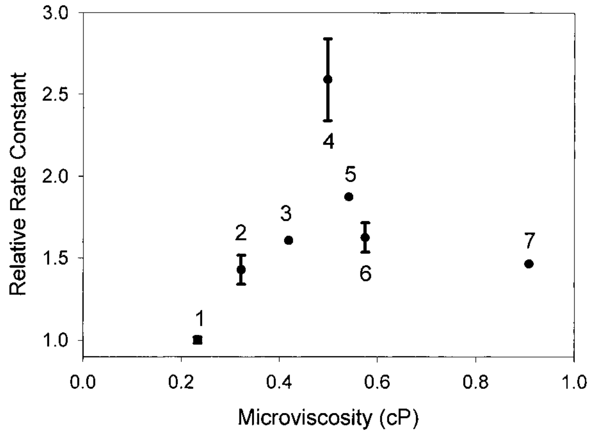


Figure 3. Relative rate constant vs microviscosity of cyclopentadiene dimerization, 25 °C. Solvents used: (1) *n*-octane; (2) *n*-decane; (3) *n*-undecane; (4) *n*-dodecane; (5) *n*-tridecane; (6) *n*-tetradecane; (7) *n*-heptadecane.

The results for cyclopentadiene are depicted in Figures 2 and 3. Viscosities were measured on the reaction mixtures themselves, not the pure solvents, and points 1, 2, 4, and 6 are duplicates. To minimize local heat effects with this exothermic reaction, reactions were stirred, and concentrations were the lowest that produced good data. The overall picture is the same whether scaled to macro- or microviscosity.

At the low end of the viscosity scale, rates rise sharply as viscosity rises. This observation *cannot* be accounted for by current kinetic theory[2,3] (vide supra). At ca. 1.3 cP (corresponding to ca. 0.5 cP microviscosity) the rate levels off and falls thereafter as viscosity continues to rise.

Reaction 2 produced a similar picture, shown in Figure 4. Once again the rate rises and then falls as viscosity is progressively increased. The crossover point is at about 2.1 cP (i.e., 0.75 cP microviscosity), close to that of reaction 1. The maximum positive slopes of reduced rate constant (k/k_0) vs viscosity for reactions 1 and 2 are 1.87/cP (for data points 1−4) and 0.17/cP (for data points 2−5), respectively. The maximum positive slopes for reduced rate constant versus microviscosity (η_μ) are 5.47/cP and 1.17/cP. We attribute the smaller slope for reaction 2 to preassociation of the more polar reactants, which reduces their relative translation prior to entering the TS. For the cyclopentadiene reaction in various solvents of differing macroviscosity shown in Figure 1,[17] we calculate a slope of 0.60/cP for all data, and 1.28/cP using data only from 0.21 to 1.0 cP inclusive.

Cycloaddition rates vs solvent of the same dipolarophile with *C*-methyl-*N*-phenyl sydnone at 140 °C [21] show the same vis-

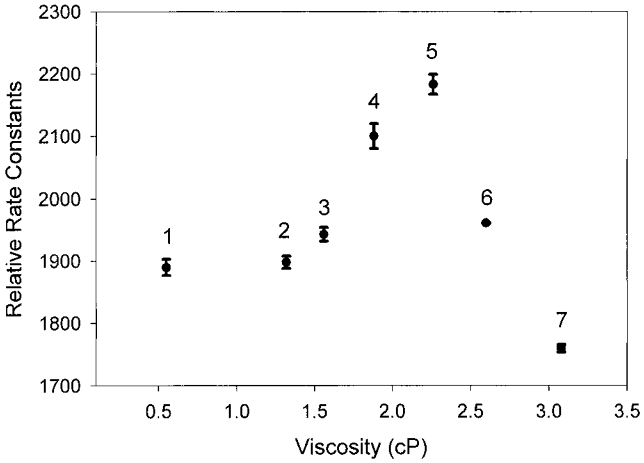
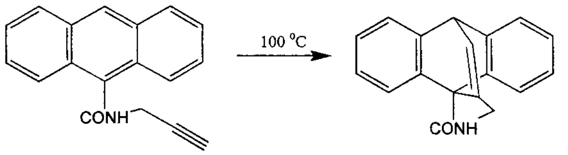


Figure 4. Viscosity vs relative rate constant of DPDM-EPP reaction, 30 °C. Solvents used: (1) *n*-octane; (2) *n*-dodecane; (3) *n*-tridecane; (4) *n*-tetradecane; (5) *n*-pentadecane; (6) *n*-hexadecane; (7) *n*-heptadecane.

cosity dependence.[11] Relative rates and viscosities (η, cP) at 140 °C in the hydrocarbon solvents, where dielectric constants are almost identical: mesitylene 92 (0.23), *p*-cymene 99 (0.32), Decalin 220 (0.42−0.58), paraffin oil 237 (2−3).[21] Other examples of viscosity-induced bimolecular acceleration: addition of methyl methacrylate to the growing polymer chain is faster in PhCN ((0.98) than in toluene (0.55);[22] reaction of excited 9-cyanoanthracene with 1,3-cyclohexadiene decelerates with rising viscosity (encounter control), but *intracage* reaction *accelerates*.[23]

We have accurately redone the viscometry for the intramolecular Diels−Alder reaction of ref 8 using the actual reaction mixtures (in this case glymes) and find that the corrected slope of reduced rate constant k/k_o vs macroviscosity η is 0.34/cP (Figure 5), less that that of reaction 1. This is expected because the relative translation of the two reactive moieties in the intramolecular Diels−Alder reaction is more restricted than that of two independent cyclopentadiene molecules and therefore has less to lose at elevated viscosity.



(3)

We report k vs η directly, for parsimony's sake. However, when this plot is made for numerous Diels−Alder cases where the pressure rather than the solvent is varied (using η calculated from data in the literature[24]), linear relationships are seen on log−log but not simple plots.[25] These plots have significance because an appreciable portion of the pressure-induced acceleration stems from pressure-induced viscosity increases. It is noteworthy that these log−log plots exhibit a downward departure from linearity as viscosities rise above ca. 1−2 cP,[26,27] just as they do with reactions 1 and 2.

The fact that elevated pressure affects reaction rates to a significant degree through viscosity as well as volume effects requires a revision of the pressure variant of the Arrhenius eq 4,[25] since an appreciable portion of the apparent $\Delta V^{\ddagger}$ arises from

$$[d(\ln k)/dp] = -\Delta V^{\ddagger}/RT \qquad (4)$$

viscosity and not volume effects.[27]

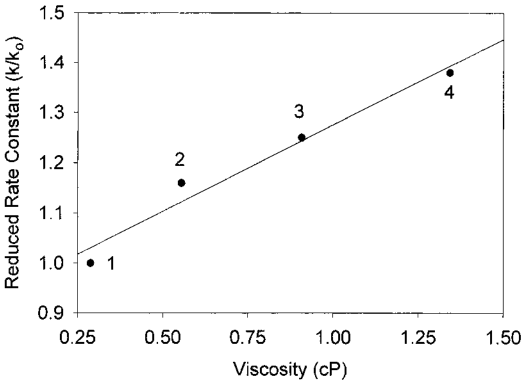


Figure 5. Viscosity vs reduced rate constant of intramolecular Diels−Alder reaction, reaction 3, 100 °C. Solvents used: (1) glyme; (2) diglyme; (3) triglyme; (4) tetraglyme.

This program arose from the hypothesis that enzymes accelerate reactions in part because their active sites are always zones of high viscosity.[4,7] However, active sites also have other attributes, most notably their capability, presumably honed through eons of evolution, of snugly fitting around their transition states (TS's) in a lock-and-key manner.[28] There is a difference between the two concepts, for a key experiences containment but not viscosity, but distinguishing between them seems difficult. However, we have found a way to do this by using tiny shapeless bits of viscous polyethylene widely dispersed in an excess of mobile solvent, which catalyze a Claisen rearrangement >12.8-fold.[1] This case cannot be accounted for by the lock-and-key model (which of course remains valid in other circumstances) and supports the premise of the present paper.

There is scant precedent known to us where elevated viscosity has been recognized as an accelerating factor in a *bond-forming* reaction at *ordinary* viscosities.[29] The rate of conformational rearrangement of cyclohexane increases with pressure at moderately low pressures, attributed by the authors to the pressure-induced viscosity increase.[30] This is of course a rotation and not a bond-forming reaction. Furthermore, it is possible that pressure and not viscosity is the agent here, since the first motion in a chair-to-chair rearrangement involves movement of a set of axial protons away from each other. This opens up space between them which solvent molecules may now enter, increasing the packing fraction and making the TS effectively smaller than the reactants.

At ultralow pressure (and viscosity) there is the so-called falloff region where inter alia bond-forming reactions slow, owing to the paucity of third-body collisions capable of cooling off the energized products. Even small pressure increases restore normal reaction rates.[31] This is a situation where bond-making rates indeed rise with increased viscosity, but one far removed from the realm of everyday chemistry where our attention is centered.

Conclusions

For two bimolecular bond-forming reactions, as the viscosity is progressively increased, the rates first rise and then fall. Other solvent properties such as polarity cannot account for the results. The rising portion, predicted by the vibrational-activation theory, is without precedent in preexisting theory or experiment. Whether it is a universal phenomenon or restricted to only some reactions can only be determined by investigating a greater variety of reactions.

Experimental Section

All reagents and solvents with the following exceptions were purchased from Aldrich Chemical Co. and used as is. Cyclopentadiene (distilled fresh each time and stored at −78 °C) was cracked from dicyclopentadiene (Lancaster Synthesis Ltd.). Diphenyldiazomethane was prepared by the method of Smith and Howard.[32] Cannon-Ubbelohde semi-micro viscometers were purchased from Cannon Instrument Co. A precision kinematic viscosity bath was used and temperatures were calibrated between this and the reactions using a digital thermometer. UV−vis spectrophotometry was run on a Perkin-Elmer Lambda 3.

Example of a Cyclopentadiene Kinetic Run. Into a weighed 25-mL volumetric flask was added approximately 20 mL of hydrocarbon solvent; then cold cyclopentadiene (ca. 0.200 g) and hydrocarbon solvent were added to the line (to make a ∼0.1 M solution). The solution was weighed (for density) and then thoroughly mixed. A small magnetic flea was added and the flask was placed in a constant-temperature bath at 25 °C and magnetically stirred. Aliquots (ca. 1 g) were removed every 24−48 h and diluted to 250 mL total volume in HPLC-grade hexane. The concentration of cyclopentadiene of the diluted aliquots was determined by UV spectrophotometry ($\epsilon = 3390$, $\lambda_{\max} = 241$ nm). After the last data point, the viscosity of the actual reaction mixture was determined at 25 °C. Viscosity in cP was determined by the following equation: η (cP) = density × time × (viscometer constant). Data points 1, 2, 4, and 6 (shown with error bars) are duplicates.

Example of a DPDM-EPP Kinetic Run. Into a weighed 25-mL volumetric flask was added diphenyldiazomethane (ca. 230.1 mg) and approximately 20 mL of hydrocarbon solvent. Ethyl phenylpropiolate (ca. 1.7 g, 7−10-fold excess) was added, and hydrocarbon solvent was filled to the mark, all at 30 °C. The solution was weighed (for density) and then thoroughly mixed. A 0.1-mm cuvette was filled and placed in a thermostated cell holder in the spectrophotometer. Absorbance over time was measured and plotted (in our hands, DPDM gave $\epsilon = 100$, $\lambda_{\max} = 525$ nm). The viscosity was measured at the same temperature using an appropriate-sized viscometer and constant-temperature bath. Viscosity in cP was determined by the following equation: η (cP) = density × time × (viscometer constant). All data points are duplicated.

Supporting Information Available: Tabular listing and plots of all solvent rates. This material is available free of charge via the Internet at http://pubs.acs.org.

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