Catalysis of Claisen Rearrangement by Low Molecular Weight Polyethylene[1]

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A recent report by Rebek et al. of 5.5-fold catalysis of a Diels−Alder reaction by a self-assembled molecular cavity[2] prompts us to report our own recent findings in a related area. Our conclusions, while not contradictory in any way to theirs, point nevertheless to yet another mode of catalysis available to enzymes.

Pericyclic reactions such as the Diels−Alder and Claisen rearrangements are not subject to catalysis by functional groups normally present in enzymes and catalytic antibodies. That is why abzymes catalyzing Claisen[3] and Diels−Alder reactions[4] have aroused continued interest.

It is generally held that transition-state binding, i.e., simple *containment* of the transition state, is responsible for these cases.[5,6] The nature of the catalysis is somewhat mysterious, however, since despite the term "binding" there are no actual chemical bonds formed, even transiently, between enzyme or abzyme and substrate.

We have proposed that what enzymes do (*inter alia*) is provide in the active site a zone of high *viscosity* which speeds the reaction and have shown that increased viscosity does indeed accelerate a Claisen rearrangement and an intramolecular Diels−Alder reaction.[7,8] However, it seems very difficult to distinguish between *containment* and *viscosity* as the method of operation of enzymes' active sites since both properties appear to inevitably go together. In this paper, we disclose experimental results of catalysis of a Claisen rearrangement that unequivocally point to viscosity rather than containment, at least for our case.

Earlier we had reported that the Claisen rearrangement of allyl phenyl ether to 2-allylphenol, contrary to currently accepted kinetic theory, goes faster as the solvent viscosity increases. All solvents and additives were 100% saturated hydrocarbon in nature, precluding any polar or electronic effects on the rate. An ancillary observation was that addition of a very small undetermined amount of low molecular weight polyethylene extracted from Parafilm "M" into mineral oil increased the rate significantly, although less than predicted by the rate vs viscosity relationship in homogeneous solvents. In this mixed solvent, reaction occurred in two zones: the mineral oil zone for the most part, and in the polyethylene zone to a small extent but at a greatly accelerated rate. Thus the polyethylene was acting as a catalyst. However, there was no way to isolate the rate in the polyethylene zone because its concentration could not be determined.

We have now found a way to evaluate, within limits, the polyethylene concentration and set a minimum figure for its catalytic power. In addition, we have repeated all the experiments using more accurate viscometry than before. This allows precise determination of the viscosity-induced acceleration in homogeneous hydrocarbon solvents, which is presented in Figure 1. The data points are ours combined with the earlier ones[7] with corrected viscometry. Equation 1 describes the effect of viscosity (η) on the relative rate constant of rearrangement.

$$k/k_0 = 0.108\eta + 0.956 \qquad (1)$$

Of greatest interest is the final kinetic point, obtained in Squibb brand heavy mineral oil−polyethylene, a macroscopically homogeneous but *microscopically inhomogeneous* medium. The rate is higher than in pure mineral oil but lower than the rate projected from eq 1. Clearly the elevation above the pure mineral oil rate results from a much greater acceleration for the small portion of reactions occurring in the polyethylene zone.

The polyethylene concentration could not be determined precisely but a *maximum* figure was obtained in this way: a Parafilm "M" piece was immersed in mineral oil for 6 h at 100 °C and then hot filtered though a very coarse frit. Clearly some of it had leached out into solution, for the viscosity of the mineral oil had greatly increased. Only saturated C−H could be seen in the NMR, neat. The residual piece of Parafilm "M" was washed repeatedly with dichloromethane to remove adherent mineral oil and then dried to constant weight. The loss in weight was a *maximum* figure for dissolved polyethylene since some was undoubtedly also lost during washing. The maximum wt/wt concentration of polyethylene in the mineral oil was 1.34%. GC analysis of extracted volatile paraffin compounds[9] (n-C_xH_{2x+2}, $x = 22-33$, which we have previously shown[7] not to increase the reaction rate compared to pure mineral oil) showed 1.05 mg/g Parafilm "M". Thus the corrected polyethylene content of the mineral oil is $\leq$1.27%.

The rate of the mineral oil−polyethylene reaction in this sample was found to be 15.0% higher than in pure mineral oil measured by GC analysis. We determined the rate in polyethylene by using the following equation: $k_{\text{mineral oil}}\chi_{\text{mineral oil}} + k_{\text{pe}}\chi_{\text{pe}} = k$. *Thus the rate in the polyethylene zone is 12.8 times faster than in the mineral oil zone.*[10]

Of paramount importance is the fact that the polyethylene catalytic moiety is viscous but *shapeless*.[6,11] Thus

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[4] Hilvert, D.; Hill, K. W.; Nared, K. D.; Auditor, M. T. *J. Am. Chem. Soc.* **1989**, *111*, 9261. Braisted, A. C.; Schultz, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 7340.

[5] Pauling, L. *Nature* **1948**, *161*, 707. Wolfenden, R. *Acc. Chem. Res.* **1972**, *5*, 10.

[6] However a famous example of enzyme-like catalysis that cannot invoke containment, but could be interpreted as a viscosity effect is: Kiefer, H. C.; Congdon, W. I.; Scarpa, I. S.; Klotz, I. M. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *69*, 2155.

[7] Firestone, R. A.; Vitale, M. A. *J. Org. Chem.* **1981**, *46*, 2160.

[8] Recent experiments to be published elsewhere show viscosity-induced acceleration of *inter*molecular cycloadditions as well.

[9] Gaskin, P.; MacMillan, J.; Firn, R. D.; Pryce, R. *J. Phytochem.* **1971**, *10*, 1155.

[10] For this calculation we used only our own data, since the earlier sample of mineral oil−polyethylene was no longer available.

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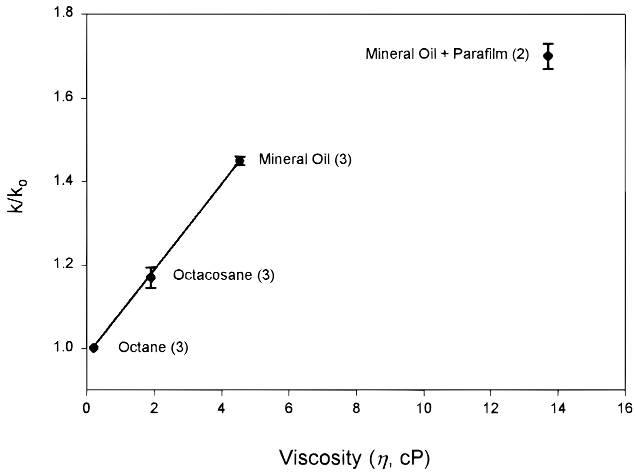

Figure 1. Reduced rate constant vs viscosity of Claisen rearrangement. Claisen rearrangement of allyl phenyl ether at 138 °C in the solvents shown. Number of separate data runs shown in parentheses.

there can be no question of transition-state binding by a shaped cavity as with enzymes, abzymes, or Rebek's case. This shows that, independently of the role played by transition-state binding, the enhanced viscosity of the active site in and of itself contributes significantly to enzymic catalysis.

From the enzymes' point of view, what is the advantage of having tiny pockets of high viscosity embedded in a low-viscosity medium, over simply having a high-viscosity world? The answer is that nothing would happen in a high-viscosity world, even one whose viscosity was as low as that of the Parafilm "M" extract, because bimolecular reactions would proceed slower, not faster, owing to the inability of the reaction partners to approach one another. We have observed[8] that for a typical bimolecular reaction, cyclopentadiene dimerization, in homogeneous unmixed *n*-hydrocarbon solvents the rate increases with size up to about *n*-dodecane and diminishes with further chain lengthening because the reaction leaves the collision-controlled regime and enters the encounter-controlled one. *n*-Dodecane is much less viscous than the Parafilm "M" extract. Thus the only way to utilize acceleration by high viscosity is with a microscopically inhomogeneous medium such as enzyme molecules in water.

Experimental Section

n-Octane, *n*-octadecane, and allyl phenyl ether were purchased from Aldrich Chemical Co. Squibb mineral oil was purchased at a local drugstore. Parafilm "M" (American Can Company) was purchased from VWR Scientific. Solution viscosities were measured at 118 °C using Cannon-Ubbelohde semimicro viscometers from Cannon Instrument Co.

Mineral Oil Parafilm "M" Analysis. A Parafilm "M" piece of 1.6716 g was immersed in 16.4951 g of mineral oil for 6 h at 100 °C and then hot filtered though a very coarse frit. The residual piece of Parafilm "M" was washed repeatedly with dichloromethane to remove adherent mineral oil and then dried to constant weight (1.6492 g). The maximum wt/wt concentration of polyethylene in the mineral oil was 1.34%. A suspension of Parafilm "M" (5.194 g) was stirred overnight in chloroform (40 mL). An aliquot (0.347 g, 0.52 mL) was removed and diluted by hexane (10 mL). This was analyzed by GC, and then *n*-eicosane was doped to quantify the peak heights. From this, amounts of *n*-C_xH_{2x+2} ($x = 22-33$) were determined, and the maximum wt/wt concentration of polyethylene was adjusted by 1.05 mg *n*-alkanes/g Parafilm "M". Thus the corrected polyethylene content of the mineral oil is ≤1.27%.

Kinetic Data Analysis. The kinetic runs were accomplished using solutions (50 μL/0.5 mL solvent) sealed in evacuated NMR tubes. The tubes were bundled together using copper wire and placed in a constant-temperature bath heated to 138 °C for 576 h. The tubes were cooled and opened, hexane (1 mL) was added, and relative amounts of allyl phenyl ether and 2-allylphenol were determined by GC to give product kinetic ratios in Figure 1.

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(11) A "nonspecific medium effect" which could be viscosity is proposed by: Hollfelder, F.; Kirby, A. J.; Tawfik, D. S. *Nature* **1996**, *383*, 60.