potential well and dotted lines translation.[21]

A singular exception to this model for the transition state seems to be the report that $k_{H_2O}/k_{D_2O} = 3.1$ for the decomposition of 1-ethyl oxalacetate.[5] However, all attempts in our laboratory to reproduce this work have failed.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society (M.W.L. and R.M.P.), and the National Institutes of Health (V.P.V.) for support of this research.

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Received June 5, 1975

Lyophobic Binding of Substrates by Cyclodextrins in Nonaqueous Solvents

Sir:

Extensive studies of binding and catalysis by cyclodextrins and their derivatives have been described.[1] This work has always involved aqueous solutions[2] and "hydrophobic" binding[1,3] of nonpolar substrate groups into the relatively nonpolar cyclodextrin cavity. While an aqueous solution might seem the natural one for enzyme model systems, it is not necessarily ideal. Many rates, including catalytic rates, are smaller in water than in polar aprotic media.[4] The interior of a protein can be largely nonaqueous, and this fact is sometimes invoked[5] in explaining the high rates of enzymatic processes.

Table I. Dissociation Constants for β-Cyclodextrin–Substrate Complexes in Dimethyl Sulfoxide Solution (25.0°)[a]

Substrate	K_d (m*M*)
m-tert-Butylphenyl acetate	18
Ferrocene[b]	20
4-*tert*-Butylcyclohexanol	300
Fluorobenzene	350
Anisole	400
Toluene	450
Pyridine	600

[a] Determined by an Eadie plot of optical rotation data. [b] By varying the temperature, we have determined $\Delta H°$ to be +4.4 kcal/mol and $\Delta S°$ to be +7.1 gibbs/mol for dissociation.

It seemed likely to us that the cyclodextrins should also be able to bind suitable nonpolar substrates in a polar nonaqueous medium. The "lyophobic" force involved should be similar to that in aqueous solution—the energy of the system is lowered by increased solvent-solvent interaction when the solvent-substrate and solvent-cavity interfaces are diminished. We now wish to report that this is indeed the case. Furthermore, an improved rate of a cyclodextrin-substrate reaction has been observed in such media.

Our studies to date have involved principally β-cyclodextrin (cycloheptaamylose), with dimethyl sulfoxide as solvent. Binding constants were conveniently determined by plotting the change in optical rotation[6] of a 5 m*M* β-cyclodextrin solution as a function of added substrate concentration, and are good to 20%. In the case of ferrocene as substrate, the binding constant was confirmed by plotting the uv absorption change at 440 nm as a function of β-cyclodextrin concentration, as well as by a polarographic determination of unbound ferrocene. All three methods showed normal saturation binding behavior, and the linear Eadie plots[7] indicate formation of a one-to-one complex. The data are listed in Table I.

Ferrocene is also bound to β-cyclodextrin in dimethylformamide solution, with K_d of 15 m*M*. In H_2O, K_d for *m-tert*-butylphenyl acetate is[8] 0.1 m*M*, and that for anisole is[9] 5 m*M*. Although the binding of substrates by β-cyclodextrin in nonaqueous solvents is thus not as strong as in H_2O, it is still strong enough to permit complete binding by cyclodextrin of nonpolar species which can fit into the cavity.

Moreover, the binding is strong enough to permit intracomplex reactions. For a direct comparison with a case already well-studied[8] in H_2O, we have examined the reaction of β-cyclodextrin with *m-tert*-butylphenyl acetate. Two approaches have been used. In the first, sodium carbonate and sodium borate buffers (at 10 m*M*; a small decrease[10] in rates at 100 m*M* is observed) were used corresponding to an aqueous pH of 9.5. Pseudo-first-order rates of deacylation of the substrate (increase of absorption at 290 nm) were determined at 25.0° in the absence (k_{un}) and presence at kinetic saturation (k_{CD}) of β-cyclodextrin in H_2O, in DMSO, and in mixtures of the two. From the saturation kinetics observed with β-cyclodextrin, a one-to-one complex with substrate has K_d values of 0.1, 2.0, and 15 m*M* in H_2O, 50% (v/v) H_2O–DMSO, and 99% DMSO, respectively. In 99% DMSO K_d was determined to be 18 m*M* by the optical rotation method.

The value of k_{CD} describes a bell-shaped curve as a function of solvent composition (Figure 1). In H_2O k_{CD} is 0.008 sec^{-1}, in agreement with the literature,[8] but it has a value of 0.38 sec^{-1} in 60% DMSO. Thus in this latter medium an additional rate enhancement of almost 50-fold is realized for the cyclodextrin-promoted reaction. Part of this may be

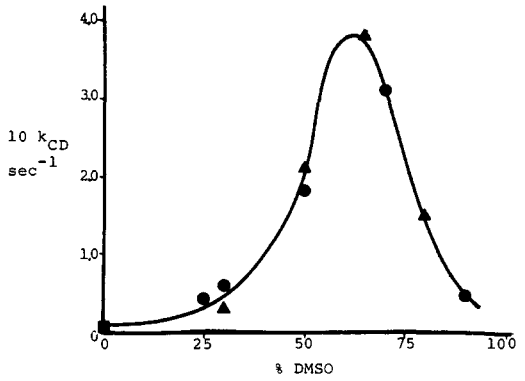

Figure 1. The rate constant at 25.0° for deacylation of *m-tert*-butylphenyl acetate at kinetic saturation with β-cyclodextrin as a function of the volume percent dimethyl sulfoxide in H_2O. Buffers were used, at 10 m*M*, which had an aqueous pH of 9.5: ●, Na_2CO_3-$NaHCO_3$ buffer; ▲, $Na_2B_2O_7$ buffer; ■, both buffers.

due to an altered pK_a of the buffer in this medium (k_{un} also changes, from 3×10^{-5} sec^{-1} in H_2O through 7.5×10^{-4} sec^{-1} in 60% DMSO to a maximum 1.3×10^{-3} sec^{-1} in 80% DMSO before decreasing at higher DMSO concentrations). Thus β-cyclodextrin in 60% DMSO accelerates substrate cleavage 13000-fold compared with the rate using a simple aqueous solution of the same buffer.

The second approach simplifies the system by eliminating buffers, and stoichiometrically generating the anion of β-cyclodextrin (pK_a = 11.8)[8] with NaOH. At kinetic saturation with β-cyclodextrin, the pseudo-first-order rate constant for substrate deacylation was proportional to the fraction of cyclodextrin ionized. Thus a rate constant k_{CD}' for reaction within the substrate-cyclodextrin monoanion complex could be determined. In H_2O k_{CD}' was 1.1 sec^{-1}, in 65% DMSO it rose to 5.0 sec^{-1}, while in 99% DMSO k_{CD}' was 2.3 sec^{-1}.

Obviously the solvent dependences of this particular reaction are complex, and other reactions will show different detailed behavior. However, significant rate increases in nonaqueous and mixed solvents can also be anticipated for many other cyclodextrin-promoted processes. Thus a new area of investigation is opened by our observation that cyclodextrin-substrate complexing can occur in nonaqueous polar solvents. It might also be noted that some other types of binding forces between molecules, such as hydrogen bonding or ion pairing, are likely to be disrupted by highly polar solvents. Thus cyclodextrins, which can utilize lyophobic binding of substrates, are particularly attractive for studies in such media.

Acknowledgment. This work was supported by the National Institutes of Health, including a Postdoctoral Fellowship to Brock Siegel.

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Received August 4, 1975

Metal-Assisted Terpenoid Synthesis. I. Regioselective Isoprene Insertion into an Allyl-Magnesium Bond and the Applications to Synthesis of Natural Terpenoids

Sir:

Olefin or diene insertion into Grignard reagents assisted by transition metal compounds has long been known.[1] Uncatalyzed reactions of allylic Grignard reagents with 1,3-butadiene and isoprene to yield cyclohexane derivatives have been reported.[2] To the best of our knowledge, however, regioselective insertion of isoprene has not yet been reported. We wish to report here highly regioselective isoprene insertion into an allyl-magnesium bond effected by a catalytic amount of Cp_2TiCl_2 (Cp = η^5-C_5H_5) or $TiCl_2(OEt)_2$ and the synthetic application for natural terpenoids.

Upon treating a THF solution of crotylmagnesium chloride (**1a**, 1 mol) with isoprene (1.5 mol) containing Cp_2TiCl_2 (0.01 mol) at 50-60° a 90% yield (based on the Grignard reagent) of 3,6-dimethyl-1,5-heptadiene (**4a**) was obtained after hydrolysis, no isomeric products being detected in the GLC (Apiezon 45 m, Golay column). Similarly prenylmagnesium chloride (**1b**) gave a nearly quantitative yield of 3,3,6-trimethyl-1,5-heptadiene (**4b**). The absence of coupling products is remarkable in view of the reported transition metal-catalyzed coupling reactions of Grignard reagents.[1,3]

When the reaction mixture, after the isoprene insertion into **1b** (step 1), was treated with carbon dioxide, the corresponding carboxylic acid (**5b**) was obtained in 80% yield. These results imply that a substituted allyl Grignard compound (**3a-c**)[4] is formed by regioselective isoprene inser-

Scheme I