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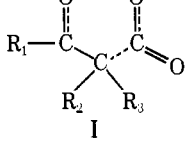
The Nature of the Transition State for the Decarboxylation of β-Keto Acids

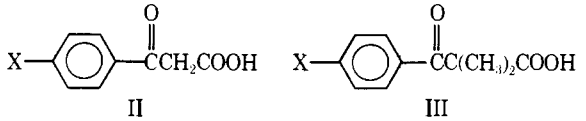
Sir:

Although it is generally accepted that the mechanism for the decarboxylation of β-keto acids involves unimolecular decomposition through a cyclic transition state (I), the timing of the hydrogen transfer relative to carbon–carbon bond cleavage is highly controversial.[1-6] Particularly perplexing



I

is the report[2] that hydrogen isotope effects vary from 0.8 to 2.8 (k_H/k_D) for the decomposition of ring substituted benzoylacetic acids in benzene, suggesting that hydrogen transfer is part of the reaction coordinate in some systems but not in others, or that the degree of hydrogen transfer varies markedly with substituent. In addition, substituent effects on the decarboxylation of a series of ring substituted benzoylacetic acids (II) in water ($\rho = 0.03$)[6] and in benzene (ρ



II III

a, X = H
b, X = NO_2
c, X = Cl
d, X = CH_3O

$= -1.0$)[2] have been interpreted[6] in terms of a transition state with significant charge separation in benzene and a nonpolar transition state in water. Although the observed substituent effects seemed to demand such an explanation, this unusual conclusion, coupled with the highly variable hydrogen isotope effects, prompted us to investigate these reactions further. We now wish to report that (1), contrary to a previous report,[2] enolization of benzoylacetic acid (IIa) in benzene is extensive and complicates the interpretation of the experimental results for decarboxylation of β-keto acids in nonpolar solvents and (2) hydrogen isotope effects for the decarboxylation of ring substituted α,α-dimethylbenzoylacetic acids (IIIa-d), which cannot enolize, are uniformly small (k_{H_2O}/k_{D_2O} = ca. 1.3) and vary only slightly with substituent (Table I).

Table I. Substituent Effects and Hydrogen Isotope Effects in the Decarboxylation of Substituted α,α-Dimethylbenzoylacetic Acids at 47.7°[a]

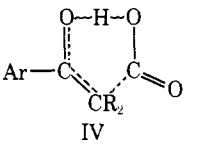
Substituent	10^4k_H (sec^{-1})[b]	10^4k_D (sec^{-1})[b]	k_H/k_D[b,c]
p-CH_3O	2.72 ± 0.07	2.47 ± 0.12	1.14 ± 0.02
H	5.09 ± 0.27	4.34 ± 0.34	1.20 ± 0.02
p-Cl	4.18 ± 0.26	3.47 ± 0.17	1.20 ± 0.02
p-NO_2	6.29 ± 0.41	4.40 ± 0.14	1.41 ± 0.04

[a] Rates were measured spectrophotometrically in 0.200 *N* HCl and 0.185 *N* DCl solutions. At these acid concentrations, the rates of decarboxylation are independent of acid concentration and represent decomposition of the un-ionized acid. The synthesis of these compounds has been described (M. W. Logue, *J. Org. Chem.*, 39, 3455 (1974). [b] Errors are standard deviations. [c] Isotope effects were determined by running H's and D's simultaneously in order to minimize systematic errors.

Ultraviolet spectra of benzoylacetic acid (IIa) in benzene (λ_{max} 289, ϵ 6600),[10] as well as cyclohexane (λ_{max} 287, ϵ 11300) suggest extensive enolization in these solvents,[7] whereas the uv spectrum of IIa in 0.2 *N* aqueous HCl (λ_{max} 249, ϵ 13400, and λ_{max} 285 (s), ϵ 2800) suggests little or no enolization. Further evidence for this interpretation is provided by the fact that the uv spectra of α,α-dimethylbenzoylacetic acid (IIIa) in water (λ_{max} 248, ϵ = 10700, and λ_{max} 280(s), ϵ 900), benzene (λ_{max} 282, ϵ 750),[10] and cyclohexane (λ_{max} 242, ϵ = 12500, and λ_{max} 280, ϵ 900) are virtually identical. In addition, IIa adds ca. 85% of the theoretical[11] amount of bromine practically instantaneously in benzene solution.

The existence of this complicating side reaction, earlier believed to be absent, means that the previously measured[2] substituent effects and isotope effects do not refer solely to the decarboxylation process. Consequently, conclusions regarding the nature of the transition state for decarboxylation in benzene are unreliable. Use of dimethylbenzoylacetic acids (III) as substrates would obviate this problem; however, dimerization of these acids in nonpolar solvents[15] presents an additional complication. Thus, in view of other available evidence (solvent effects[1] and substituent effects), we prefer a nonpolar transition state in all solvents.

The uniformly small isotope effects which we observed in the decarboxylation of α,α-dimethylbenzoylacetic acids in water suggest that the hydrogen is not undergoing translation in the reaction coordinate. These low isotope effects stand in marked contrast to the isotope effects of 2.4-4.8 (extrapolated to 50°) observed in the thermal decarboxylation of 2,2-dimethyl-3-phenylbut-3-enoic acids.[18] We interpret these low isotope effects in terms of the model proposed by Swain and Schowen in which proton transfer between electronegative elements accompanying heavy atom reorganization is not part of the reaction coordinate motion.[19,20] Application of this concept to the decarboxylation of β-keto acids predicts that the transition state should involve a proton in a stable potential well during cleavage of the carbon–carbon bond and, consequently, low isotope effects are expected. The transition state for decomposition of these acids would then look like IV with the wavy lines representing a



IV

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.

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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