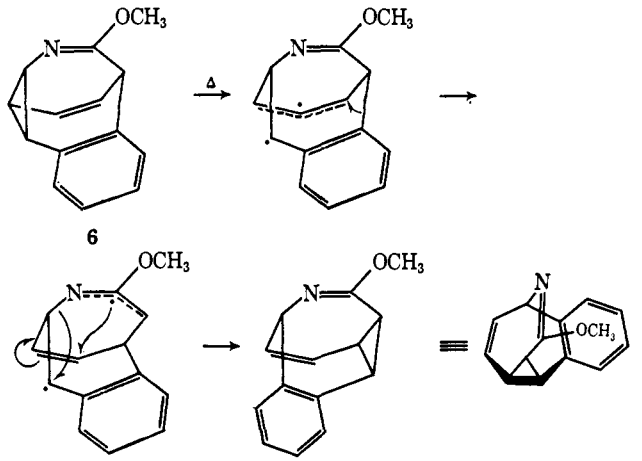
vinyl bonding observed.[12] The causative factors behind the contrasting photochemical behavior of **4** and **5** appear to be subtle and are presently the subject of further study.

Because of the benzo fusion in **6**, this molecule is not expected to exhibit a propensity for Cope rearrangement,[13] and such is the case. However, when a solution of **6** in tetrachloroethylene was heated to 125–150°, an *irreversible* reaction occurred in high yield. The rate of rearrangement could be conveniently followed by nmr; the following first-order rate constants and thermodynamic parameters were determined: $k_{125} = 1.68 \times 10^{-4}$ sec^{-1}; $k_{133} = 3.08 \times 10^{-4}$ sec^{-1}; $k_{143} = 7.52 \times 10^{-4}$ sec^{-1}; $\Delta H^{\pm} = 26.6$ kcal/mol; $\Delta S^{\pm} = -9.6$ eu. The nmr spectrum (Figure 1) of the thermal product is uniquely adaptable to benzazabullvalene formula **10**; mp 127–128.5°;[5] λ_{max}^{hexane} 265 (ϵ 350) and 276 mμ (ϵ 280), together with end absorption. Mechanistic passage to **10** requires a double migration; a possible reaction pathway is outlined.



10

The above-described thermal results would pass undetected in the case of benzobullvalene because of the obvious degeneracy of the rearrangement in this instance. At question, therefore, is whether there may be available to bullvalene and its congeners additional degenerate pathways which could compete with the Cope rearrangement at moderate to elevated temperatures.

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2268 (1962); (f) D. H. R. Barton, J. McGhie, and M. Rosenberger, *J. Chem. Soc.*, 1215 (1961), and earlier papers.

(12) After the completion of our study, H. E. Zimmerman, R. S. Givens, and R. M. Pagni [*J. Am. Chem. Soc.*, 90, 4191 (1968)] reported that benzo–vinyl bonding was also not the mechanism followed in the sensitized irradiation of benzobarrelene.

(13) The preclusion of degenerate Cope rearrangements upon introduction of a fused benzene ring in bullvalene [G. Schröder and J. F. M. Oth, *Angew. Chem. Intern. Ed. Engl.*, 6, 414 (1967)] and semibullvalene derivatives [J. A. Elix, M. V. Sargent, and F. Sondheimer, *J. Am. Chem. Soc.*, 89, 5081 (1967)] has already been noted.

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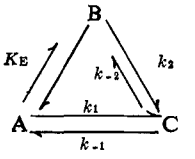
A Criterion for Catalytically Active Intermediates

Sir:

Chemically or physically generated reactive intermediates have played a major role in speculations concerning mechanisms of enzyme action.[1] This communication outlines a general condition which an unstable intermediate must meet to lie on the principal path of a chemical reaction. Although a simple corollary of the principle of detailed balance, this condition's relevance to models for enzyme mechanisms has been overlooked, and its generality, as well as its pertinence to the work outlined in the accompanying communication,[1c] prompts its discussion here.

In its simplest form the problem can be formulated as shown below. A conversion of A to C can occur directly, by a path described by forward and reverse rate constants k_1 and k_{-1}, or indirectly, *via* B, an unstable, reactive isomer of A. One can envisage a catalytic device which attempts to exploit the heightened



$$K_1 = \frac{k_1}{k_{-1}}$$

$$K_2 = \frac{k_2}{k_{-2}}$$

$$K_E < 1$$

$$\gamma \equiv \frac{\log (k_1/k_2)}{\log (K_1/K_2)} = \frac{\log (k_1/k_2)}{\log K_E} \quad (1)$$

$$\frac{\text{reaction A} \rightarrow \text{B} \rightarrow \text{C}}{\text{reaction A} \rightarrow \text{C}} = \frac{k_2[\text{B}]}{k_1[\text{A}]} = K_E^{-\gamma} K_E = K_E^{1-\gamma} \quad (2)$$

reactivity of B by facilitating the interconversion of A and B. One can then ask: under what further conditions will B lie on the major path linking A and C?

With the uncatalyzed conversion A → C as a standard, eq 2 may be derived which indicates that B can be a catalytically effective intermediate only if the parameter, γ, defined analogously to a Brønsted coefficient, can be made to exceed unity. The possible situations are illustrated in Figure 1 by reaction coordinate–energy diagrams. For $\gamma < 1$, both forward and reverse rate constants for the B–C interconversion show the expected effect of the instability of B: B is converted more rapidly than A to C, and C, more rapidly to A than B. This behavior must characterize all B species whose conversions to C bear a direct mechanistic correspondence to the conversion of A to C, quantitative differences between the two processes being assignable to rationalizable factors such as basicity. In this sense, noncatalytic high-energy intermediates are *normal* intermediates, for which heightened reactivity fails to compensate inferior concentration.[2]

(1) W. P. Jencks, *Ann. Rev. Biochem.*, 32, 639 (1963); M. Eigen and G. Hammes, *Advan. Enzymol.*, 25, 1 (1963); D. Koshland, *ibid.*, 22, 45 (1960); (c) D. S. Kemp and T. D. Thibault, *J. Amer. Chem. Soc.*, 90, 7154 (1968).

(2) Breslow[3] has applied this principle in a less formal way to elimination reactions.

(3) R. Breslow, *Tetrahedron Lett.*, 8, 399 (1964).

Intermediates for which $\gamma > 1$ are *hyperreactive* in that C must be converted more rapidly to B than to its stable isomer A, and such conversions must differ in kind in order that judgments based on correspondences cannot apply. Hyperreactive intermediates appear in neighboring amide displacements which occur with net inversion[4] and in assisted hydrolyses of *o*-formylbenzoate derivatives.[5] These examples strikingly combine high rate accelerations with mechanisms no step of which corresponds to the uncatalyzed reaction sequence.[6]

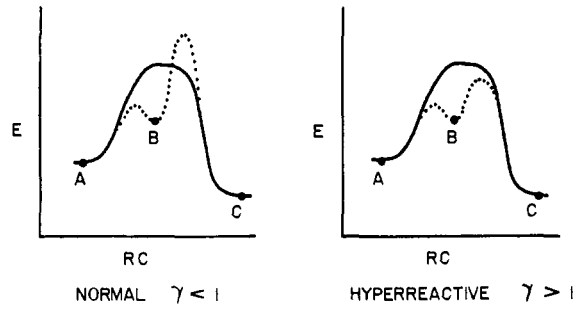


Figure 1.

The simple model just described can be generalized, and extensions apply particularly to a class of enzyme mechanisms which invoke the enzyme solely to generate a highly reactive intermediate. Such "midwife" mechanisms can be chemical in nature, facilitating generation of new, chemically activated species, or physical, inducing strain in substrate as with the simplest form of the "rack" proposal.[8] For these mechanisms, intermediates must be highly hyperreactive, and in the absence of models which exhibit the requisite reactivity such mechanisms must be regarded with circumspection.

It seems likely that an enzyme must be more intimately involved with the several stages of the process which it catalyzes, and that unstable, reactive species can be productive intermediates only to the extent that transition states connecting them with products are unusually susceptible to stabilization by the polyfunctional character of the enzyme.

(4) S. Winstein and R. Boschan, *J. Amer. Chem. Soc.*, 72, 4669 (1950); H. L. Wehrmeister, *J. Org. Chem.*, 28, 2589 (1963).

(5) M. L. Bender, J. A. Reinstein, M. S. Silver, and R. Mikulak, *J. Amer. Chem. Soc.*, 87, 4545 (1967).

(6) Acylimidazoles are well-known hyperreactive intermediates for the hydrolysis of phenolic esters. From the rate and equilibrium data of Jencks,[7] at equal phenol and imidazole concentrations, *p*-nitrophenyl acetate, comparable in stability to acetylimidazole, could be as much as 140 times less reactive toward water by a direct path than by a path involving acetylimidazole. At least in principle, for ethyl acetate the catalyzed path can nearly equal the efficiency of the uncatalyzed. On the other hand, reactions with hydroxide require a more direct correspondence between transition states for decomposition of acetylimidazole and ester; accordingly, the ratio of catalyzed to uncatalyzed paths can only be 30 for *p*-nitrophenyl acetate, 2 for *p*-methoxyphenyl acetate, and much less than 1 for ethyl acetate.

(7) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, 234, 1272, 1280 (1959); J. F. Kirsh and W. P. Jencks, *J. Amer. Chem. Soc.*, 86, 837 (1964); J. Gerstein and W. P. Jencks, *ibid.*, 86, 4655 (1964).

(8) For general statements of the "rack" mechanism see: R. Lumry in "The Enzymes," Vol. 1, P. D. Boyer, H. Lardy, and K. Myrbäck, Ed., 2nd ed, Academic Press, Inc., New York, N. Y., 1959, pp 222–224; H. Eyring, R. Lumry, and J. D. Spikes in "The Mechanism of Enzyme Action," W. D. McElroy and B. Glass, Ed., Johns Hopkins Press, Baltimore, Md., 1954, p 123.

(9) Fellow of the Alfred P. Sloan Foundation, 1968–1970. Financial support from the National Institutes of Health (GM 13453) and the National Science Foundation (GP-8329) is gratefully acknowledged.

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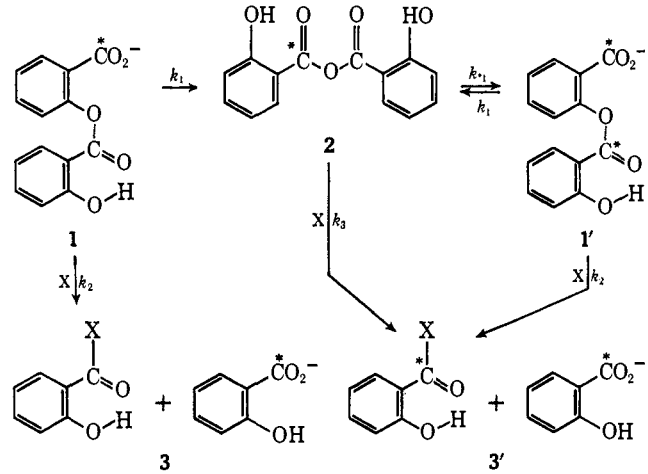
The Hydrazinolysis of Salicyloylsalicylic Acid. The Irrelevance of an Anhydride Intermediate

Sir:

Fersht and Kirby,[1] and more recently St. Pierre and Jencks,[2] have argued that reactions of acylsalicylic acids with nucleophiles, previously proposed to occur through intermediary anhydrides,[3] in fact occur by direct attack at the phenolic ester function, assisted by the neighboring carboxylate in the cases of water and certain other weak nucleophiles. We wish to report results of a study which provides substantive corroboration of these conclusions as well as detailed insight into the behavior of a particular acylsalicylic acid.

Necessarily the ease of interconversion of most acylsalicylic acids with their isomeric anhydrides has remained conjectural; however, the symmetry of salicyloylsalicylic acid (**1**) offers a chance of measuring not only the rate of equilibration of **1** with **2** but also the reaction path of **1** with an appropriate nucleophile. As anticipated, the hydrolysis of **1** exhibits the pH–rate profile of an aspirin derivative,[4] showing a constant



half-life in water, 30°, pH 5–9, of 4×10^3 min. More interestingly, when salicyloylsalicylic-carboxy-^{14}C acid[5] is recovered after 10 min in water, 25°, pH 8, the isotope is found to be distributed equally between the carbonyl

(1) A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, 89, 4853, 4857 (1967).

(2) T. St. Pierre and W. P. Jencks, *ibid.*, 90, 3817 (1968).

(3) M. L. Bender, F. Chloupek, and M. C. Neven, *ibid.*, 80, 5384 (1958).

(4) E. R. Garrett, *ibid.*, 79, 3401 (1957).

(5) Combining *t*-butyl salicylate-7-^{14}C with *o*-benzyloxybenzoyl chloride and subjecting the resulting ester to hydrogenolysis followed by acid yielded labeled **1**. With diazomethane, then hydroxylamine, **1** yielded methyl salicylate and salicylohydroxamic acid; the latter could be consistently obtained from unequilibrated **1** with less than 2% activity.