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]

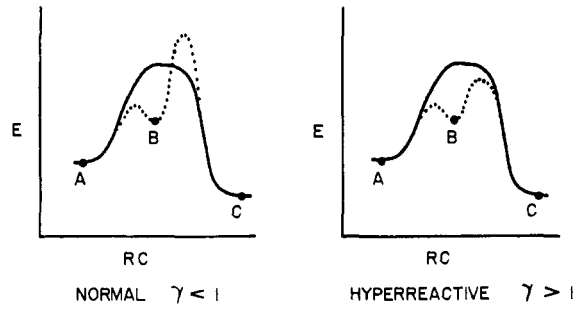

Figure 1.

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.

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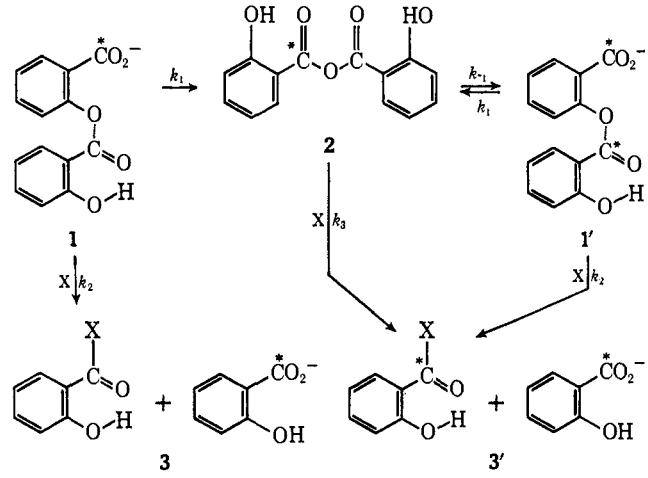
The Hydrazinolysis of Salicyloylsalicylic Acid. The Irrelevance of an Anhydride Intermediate

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

(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.

(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.

functions.[5] Addition of sodium salicylate fails to accelerate the equilibration or to dilute the isotopic concentration; equilibration consequently must occur intramolecularly *via* **2**.

At 30° in water, pH 8.2, $\mu = 0.5$, the half-life of the equilibration of **1** to **1′** is 15 sec, and similarly rapid exchange occurs in organic solvents—in ethyl acetate at 0° in the presence of 1 equiv of triethylamine a first-order half-life of 7.5 min was observed. The insensitivity of the exchange process to solvent supports a simple mechanism involving equilibration among isomeric anions.

For water, reaction with **1** occurs *ca.* 10^4 times more slowly than equilibration of label, and direct information concerning product origin is inaccessible. However, with a nucleophile which can react with **1** at a rate which approximates k_1, measurement of equilibration of **1** with **1′** and labeling of **3** will allow direct calculation of k_2 if reaction occurs predominantly from **1**, or of k_{-1}/k_3 if from **2**.

$$\mathbf{1} + \mathbf{1'} \rightarrow \mathbf{3} + \mathbf{3'}$$

$$\ln\left(\frac{[\mathbf{1}]_0}{[\mathbf{1}] + [\mathbf{1'}]}\right) = \left(\frac{k_1}{\frac{k_{-1}}{k_3} + 1} + k_2\right)t = k_{obsd}t \qquad (1)$$

Disappearance of **1**

$$\ln\left(\frac{[\mathbf{1}]_0}{[\mathbf{1}]}\right) = (k_1 + k_2)t \qquad (2)$$

$$\mathbf{1} \rightarrow \mathbf{1'}$$

$$\ln\left(\frac{[\mathbf{1}] + [\mathbf{1'}]}{[\mathbf{1}]}\right) = \left(\frac{k_1}{\frac{k_3}{k_{-1}} + 1}\right)t \qquad (3)$$

Label fraction in products

$$\frac{[\mathbf{3}]}{[\mathbf{1'}] + [\mathbf{3'}]} = \frac{k_2}{k_1} \qquad (4)$$

The three pertinent experimental ratios, measured for a series of reactions of **1** with aqueous hydrazine, are given in Table I, along with values for k_{obsd}, k_1, and k_2 calculated from eq 1–4.

Table I. Reaction of **1** with Aqueous Hydrazine[a]

$[N_2H_4]$, *M*	A	B	C	k_{obsd}, min^{-1}	k_2, min^{-1}	k_1, min^{-1}
0.021	0.97	0.51	0.91	0.034	0.045	2.5
0.046	0.91	0.58	0.92	0.088	0.099	2.5
0.071	0.86	0.63	0.90	0.15	0.14	2.4
0.095	0.79	0.67	0.92	0.24	0.21	2.6
0.144	0.63	0.65	0.92	0.46	0.40	2.6
0.193	0.48	0.65	0.93	0.73	0.64	2.8
0.292	0.25	0.60	0.91	1.38	1.16	2.6
0.341	0.16	0.57	0.91	1.82	1.56	2.7

[a] t = 1.0 min, 30°, pH 8.15, μ = 0.5. A = ([I] + [1′])/[1]$_0$; B = [3′]/([3] + [3′]); C = [1′]/([1] + [1′]).

The constancy of the ratio [1′]/([1′] + [1]) indicates that k_3/k_{-1}, which should increase at least as rapidly as $[N_2H_4]$, must be markedly less than unity over this concentration range. Moreover, the equivalence of k_2, calculated from eq 2 and 4, with k_{obsd} establishes direct attack of hydrazine on **1** as the mechanism of hydrazinolysis. The kinetic irrelevance of salicylic anhydride (**2**), established under conditions in which **2** approaches its equilibrium concentration with respect to **1**, requires that **2** be regarded as a *normal* intermediate in the sense of the accompanying communication; for **2**, intrinsic reactivity fails to compensate inferior concentration.

Two generalizations arise from this work. (1) Aside from its symmetry, **1** is a normal representative of its class, and similarly rapid equilibrations with anhydride isomers are expected for other acylsalicylic acids. (2) With hydrazine, **1** appears to be exactly as reactive as a simple phenolic ester;[6] however, because of hydrogen bonding and the likelihood of intramolecular catalysis, **2** is anticipated both to be present at higher concentration and to be more reactive than expected for the intrinsic stability of an aromatic anhydride. As models for the relative reactivity of equilibrated phenolic esters and anhydrides, **1** and **2** appear to offer a choice particularly weighted toward **2**. The failure to observe reactions *via* anhydrides in this and in related systems implies that carboxylates cannot serve as nucleophilic catalysts for ester hydrolysis, even with the assistance of an agent which allows the intermediary anhydride to reach its limiting concentration. This conclusion is in harmony with the results of Gold,[8] for all but highly activated phenolic esters, and with the thermodynamic and kinetic data of Jencks.[9,9a]

(6) The term k_{obsd} may be represented as $(1.4 + 12[N_2H_4])[N_2H_4]$, in good agreement with more accurate data obtained by a uv method. These coefficients may be compared with the values 0.65 M^{-1} min^{-1} and 19.0 M^{-2} min^{-1} observed by Bruice and Benkovic[7] for hydrazinolysis of phenyl acetate under comparable conditions. See also ref 2 for a discussion of pertinent issues.

(7) T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, **86**, 418 (1964).

(8) A. R. Butler and V. Gold, *J. Chem. Soc.*, 1334 (1962); D. G. Oakenfull, T. Riley, and V. Gold, *Chem. Commun.*, 385 (1966).

(9) J. F. Kirsh and W. P. Jencks, *J. Amer. Chem. Soc.*, **86**, 833, 837 (1964).

(9a) NOTE ADDED IN PROOF. Data concerning the contrary case of cyclic anhydrides have been summarized by T. C. Bruice and W. C. Bradbury, *J. Amer. Chem. Soc.*, **90**, 3808 (1968). The main conclusions of this study have been established independently by Fersht and Kirby [A. R. Fersht and A. J. Kirby, *ibid.*, **90**, 5818, 5826, 5833 (1968)].

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Electron Spin Resonance of Aliphatic Hydrocarbon Radicals in Solution

Sir:

We wish to report a convenient and versatile technique for examining the esr spectra of a variety of short-lived free radicals in solution. The method is particularly useful for the study of alkyl and other organic free radicals in nonaqueous systems, where the more conventional flow techniques are difficult to apply.

Radicals (R·) are generated by ultraviolet irradiation of a static solution of di-*t*-butyl peroxide in the presence of a hydrogen donor (RH). The thoroughly degassed sample is contained in a small fused silica tube (4-mm