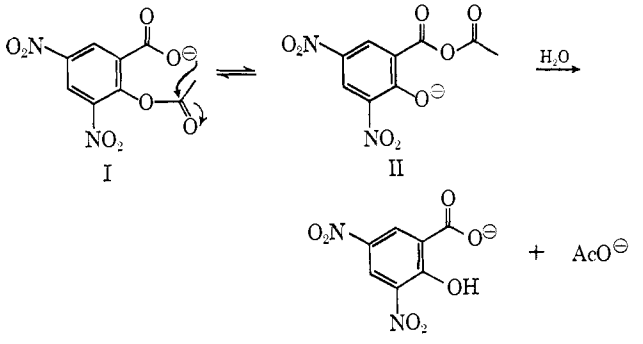
intramolecular nucleophilic catalysis in the hydrolysis of a substituted aspirin.

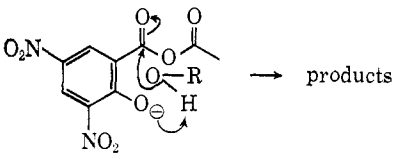
The carboxylate group of aspirin is not an effective nucleophilic catalyst because it is too weakly basic.[1] Gold has shown[2] that acetate ion does not catalyze the hydrolysis of substituted phenyl acetates by the nucleophilic mechanism if the leaving group is more than 3–4 pK units more basic than the catalyst. Other things being equal, the mechanism is determined by the difference in basicity between the nucleophile and the leaving group.

By an appropriate choice of substituents it is possible to lower the basicity of the leaving group of aspirin relative to that of the carboxyl group. The two nitro groups of 3,5-dinitro-aspirin (I), for example, would be expected to lower the pK_a of the carboxyl group by about $2\sigma_m$ = 1.4 pK units, whereas two nitro groups *ortho* and *para* to phenolic OH lower its pK_a by some 6 units. We find that the change in the relative basicities of nucleophile and leaving group is sufficient to change the mechanism to nucleophilic catalysis in the hydrolysis of 3,5-dinitro-aspirin.[3]



In the pH-independent region above pH 3[4] this ester is hydrolyzed in $H_2{}^{18}O$ at 39° with over 40% incorporation of labeled oxygen into the salicylic acid produced. On solvolysis in 50% aqueous methanol in this pH region the major product is methyl 3,5-dinitrosalicylate,[5] which is produced in 60 ± 2% yield[6] and can be isolated in 56% yield. It is evident that the anhydride II is an intermediate and lies on the major reaction pathway.

Further kinetic data suggest that the nucleophilic reaction I → II is not the slow step of the reaction. The relative rates of solvolysis in various methanol–water mixtures, and in light and heavy water (k_H/k_D = 2.0), and the entropy of activation (−20.6 eu) are all similar to those observed for the hydrolysis of aspirin anion and are not consistent with rate-determining nucleophilic attack. We consider that the reaction is best described in terms of a rapid preequilibrium formation of the anhydride anion II, in very low concentration. This is then hydrolyzed by rate-determining attack of a molecule of water on the salicyloyl carbonyl group, in a reaction which very probably involves intramolecular general base catalysis by the phenolate oxygen.[7]



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(3) Prepared by the method of G. Ciampa, *Ann. Chim.* (Rome), 54, 975 (1964).
(4) A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, **89**, 5961 (1967).
(5) The product had identical melting point, mixture melting point, and infrared spectrum as an authentic sample (mp 128–129°; T. Zincke, *J. Prakt. Chem.*, [2] **82**, 23 (1910), reports mp 129°).
(6) Estimated spectrophotometrically. No methyl salicylate is produced on solvolysis of aspirin under these conditions.
(7) Ample precedent for this mechanism exists in work on the hydrolysis of substituted phenyl salicylates, by M. L. Bender, F. J. Kézdy, and B. Zerner, *J. Am. Chem. Soc.*, **85**, 3017 (1963), and B. Capon and B. C. Ghosh, *J. Chem. Soc., Sect. B*, 472 (1966).

A. R. Fersht, A. J. Kirby
University Chemical Laboratory
Cambridge, England
Received July 27, 1967

Intramolecular General Acid Catalysis of Ester Hydrolysis by the Carboxylic Acid Group

Sir:

We have reported cases in which the carboxylate anion catalyzes the hydrolysis of a neighboring ester group by acting as a nucleophile[1] and a general base.[2] A third possible role for the carboxyl group in enzymic catalysis is that of a general acid. We report here an example of intramolecular catalysis of ester hydrolysis by the carboxylic acid group which appears to involve this mechanism.

The pH–rate profile for the hydrolysis of 3,5-dinitro-aspirin (see Figure 1) shows two pH-independent regions and differs strikingly from that of aspirin itself[3]

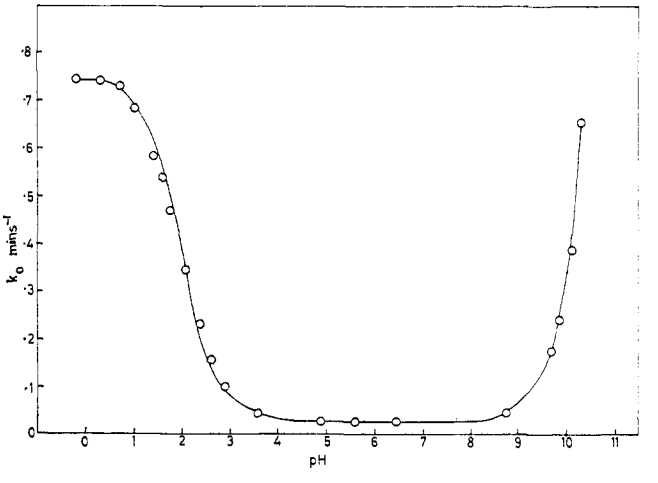

Figure 1. pH–rate profile for hydrolysis of acetyl-3,5-dinitrosalicylic acid at 39°, ionic strength 1.0.

in that the free acid is considerably more reactive (by 28 times) than the anion. The hydrolysis of the anion is subject to intramolecular nucleophilic catalysis by the carboxylate group,[1] so that the faster hydrolysis of the neutral species must be a result of catalysis also.[4] The pH–rate profile shows that this catalysis depends on a

(1) A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, **89**, 5960 (1967).
(2) A. R. Fersht and A. J. Kirby, *ibid.*, **89**, 4857 (1967).
(3) L. J. Edwards, *Trans. Faraday Soc.*, **46**, 723 (1950).
(4) Our preliminary results show that the methyl ester of 3,5-dinitro-aspirin is hydrolyzed over 200 times more slowly than the free acid.

group of apparent $pK_a = 1.95$, close to the value expected for the carboxyl group.[5]

We believe that hydrolysis of the neutral species, in the lower pH-independent region, involves general acid catalysis by the carboxyl group; probably of the attack of a molecule of water on the carbonyl carbon atom of the ester, since this is most likely the slow step in the uncatalyzed hydrolysis of esters of this type[2] and since the attack of other nucleophiles is also catalyzed. Formate ion, for example, attacks the free acid 48 times faster than the anion.[6] Mechanisms involving the salicylic–acetic anhydride can be ruled out with some confidence because solvolysis in 50% aqueous methanol produces a quantitative yield of 3,5-dinitrosalicylic acid.[7]

(5) This cannot be measured directly, because of rapid hydrolysis. The value obtained by subtracting $2\sigma_m$ from the pK of aspirin (3.36) is 1.94.
(6) A. R. Fersht and A. J. Kirby, unpublished results.
(7) Estimated spectrophotometrically.

A. R. Fersht, A. J. Kirby
University Chemical Laboratory
Cambridge, England
Received July 27, 1967

Nuclear Magnetic Resonance Spectroscopy. Carbon–Carbon Coupling in Cyclopropane Derivatives[1]

Sir:

The nature of the bonding in cyclopropane, the smallest and most highly strained carbocyclic ring system, has long been a lively and controversial topic. Walsh[2] has described the carbon–carbon bonding in cyclopropane as involving a three-center bond, while Coulson and Moffitt[3a] and Trinajstić and Randić[3b] have used quantum-mechanical treatments equivalent to bent bonds wherein the regions of highest electron density are not located along the C–C internuclear axes. Molecular orbital calculations of varying degrees of sophistication have been carried out.[4] A recent summary of the description of bonding in cyclopropanes was given by Bernett.[5]

Nuclear magnetic resonance spectroscopy has been extensively used in the structural analysis of cyclopropane derivatives because the protons directly bonded to the ring give resonances at characteristically high fields.[6] A comprehensive study of proton–proton coupling in substituted cyclopropanes has been carried out,[7] and recently Watts and Goldstein[8] have obtained accurate values of the one-bond carbon–proton coupling constant and the three proton-proton coupling constants in cyclopropane itself.

The carbon orbitals used to form the carbon–proton bonds in cyclopropane have been assigned 33% s character on the basis of the carbon–proton coupling constant.[9] Such correlations of carbon–proton coupling with the carbon orbital hybridizations seem valid in hydrocarbon systems. However, when electronegative substituents are present, the parameter which most strongly influences the coupling constant appears to be the effective nuclear charge of the carbon 2s orbital.[10] Frei and Bernstein[11] in their study of carbon–carbon couplings showed experimentally that such coupling constants are proportional to the product of the s characters of the two hybrid orbitals used in forming the bond. This approach was justified theoretically by the molecular orbital calculations of Pople and Santry.[12] Ethane, whose carbon–carbon bond is formed from two sp^3 orbitals (25% s character), has a carbon–carbon coupling constant of 34.6 Hz.[13] The coupling constant for a carbon–carbon bond formed from an sp^3- and an sp^2-hybridized orbital, as in the methyl to ring bond in toluene, is 44.2 Hz.[11]

Foote[14] in a study of carbon–proton coupling in cycloalkanes has suggested that, because the carbon orbitals forming the carbon–proton bonds have more s character than a normal hydrocarbon, the carbon–carbon bonds must have more p character. If it is assumed that each carbon has a single 2s orbital which is used in forming its bonds[15] and that the two orbitals used in forming the carbon–proton bonds have 33% s character each, this leaves 33% s character to be divided between the two orbitals forming the carbon–carbon bonds, or 17% s character in each hybrid orbital. This is roughly sp^5 hybridization.[5]

The predicted carbon–carbon coupling constant for a single bond between two 2s orbitals based on ethane as a model for an sp^3–sp^3 bond is $34.6(4)^2 = 550$ Hz. The coupling constant predicted for a bond formed between two sp^5 hybrid orbitals is $550(1/6)^2 = 15$ Hz. The carbon–carbon coupling constants which have been observed for a series of cyclopropane derivatives are given in Table I and are in striking agreement with the concept of sp^5 hybridization of the orbitals used in forming the internal bonds and sp^2 hybridization for the external orbitals. Substituent effects and the approximations inherent in the simplified description of both the coupling constant and the bonding may account for the minor variations.

Table I. ^{13}C–^{13}C Coupling Constants for Cyclopropane Derivatives

Compound	Bond	Coupling constant, Hz
Cyclopropyl bromide	1,2	13.3
Cyclopropyl iodide	1,2	12.9
1,1-Dichlorocyclopropane	1,2	15.5
Methylcyclopropane	α,1	44.0

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