tion a synthetic mixture of authentic ethyl ethylmalonate and ethyl ethylidenemalonate were completely resolved.

Reduction of Ethyl Ethylidenemalonate with Sodium Borohydride and Lithium Bromide.—To a solution of 3.78 g. (0.10 mole) of sodium borohydride in 100 ml. of diglyme was added 8.7 g. (0.10 mole) of anhydrous lithium bromide (prepared by the addition of bromine to a slurry of lithium in ether, followed by the evaporation of the ether). After the mixture had been stirred for 30 min., 14.8 g. (0.08 mole) of ethyl ethylidenemalonate was added dropwise. Spontaneous heating was noted during the addition. After the mixture had been stirred for 1 hr. without external heating and 1.5 hr. on a steam bath, 24 g. (0.40 mole) of acetic acid was added to decompose the excess hydride and alkoxide complexes. The reaction mixture was then heated at 120° for 18 hr. with 24 g. (0.24 mole) of acetic anhydride. After the salts were removed by filtration, the filtrate was poured into 300 ml. of a 5% sodium carbonate solution. The oily layer was dried over anhydrous magnesium sulfate and fractionally distilled through a 6-in. Vigreux column to yield 4.5 g. (30%) of ethyl ethylmalonate, b.p. 62° (1.0 mm.), $n^{25}D$ 1.4165; and 9.0 g. of a higher boiling residue.

Intramolecular Participation of the Amide Group in Ester Hydrolysis[1]

MARGARET T. BEHME AND E. H. CORDES

Department of Chemistry, Indiana University, Bloomington, Indiana

Received October 14, 1963

Numerous hydrolytic reactions are known to occur with intramolecular nucleophilic participation of an amide function.[2] Considerable evidence exists which suggests that, in suitable instances, the intramolecular participation of the amide group in ester hydrolysis results in very large rate increases over the uncatalyzed reaction.[2a,b] Particularly striking is the observation of Bernhard, *et al.*, that properly constituted β-benzyl esters of aspartyl peptides are cleaved, with amide participation, more than one-millionfold more rapidly than similar substrates not possessing a neighboring amide function.[2a] Results of this type have led several authors to suggest that amide groups present in protein or substrate molecules may be directly involved in the catalytic process of some enzymatic reactions. This suggestion is particularly appealing in light of the usual exchange reactions observed by Katchalski, *et al.*,[3] and by Fruton, *et al.*,[4] in the course of pepsin-catalyzed cleavage of peptide substrates. These reactions may be rationalized in terms of the intermediate formation of imides resulting from the attack of an amide group of a substrate molecule on the carboxyl group of a second substrate molecule.

We have examined the kinetics of amide group participation in ester hydrolysis employing substrates derived from salicylamide and phthalamic acid. These substrates were chosen to provide a basis for quantitative comparison of the catalytic efficiency of the amide group with other nucleophilic catalysts, previously studied in similar systems, for ester hydrolysis. While these studies were in progress, Shafer and Morawetz reported similar results on amide group participation in ester and amide hydrolysis in substrates derived from phthalamic acid.[2b]

The first-order rate constants for imide formation from O-acetylsalicylamide and methyl phthalamate increase linearly with hydroxide ion concentration in the pH range 6.2 to 8.8. The calculated second-order rate constants for these reactions are 1.2×10^6 and 1.8×10^5 M^{-1} min.$^{-1}$, respectively, at 25° and ionic strength 0.50. The latter value is in excellent agreement with the figure of 1.86×10^5 M^{-1} min.$^{-1}$ obtained by Shafer and Morawetz for this reaction at 25.9° and ionic strength 0.12.[2b] That imide formation was, in fact, the reaction being followed was established from the identity of the ultraviolet spectra and rate of hydrolysis of the initial reaction products with the corresponding properties of authentic samples of the imides. These results, together with those of Shafer and Morawetz,[2b] demonstrate that, for systems of these types in neutral or basic aqueous solutions, the amide group is several orders of magnitude more effective as an intramolecular nucleophilic reagent toward ester or amide linkages than either the imidazolyl[5] or the carboxylate[6] functions. The neighboring formyl group is similar to the neighboring amide group in terms of nucleophilic reactivity toward methyl esters.[7] On the other hand, the intermediate product (imide) obtained from amide group participation is somewhat more resistant to hydrolysis, completing the catalytic process, than corresponding intermediates for reactions involving the nucleophilic reagents indicated above.[2b]

Imide formation from O-acetylsalicylamide was found not to be detectably subject to general acid–base catalysis by 1.0 M N-methylmorpholine at pH 7.5.

Imide formation from O-acetylsalicylamide was not subject to detectable acid catalysis in hydrochloric acid solutions ranging in concentration from 1 to 5 M.

The reaction of acetamide with *p*-nitrophenyl acetate, an intermolecular analog for imide formation from O-acetylsalicylamide, was studied at 25° and pH 10.2. Under these conditions, the rate of *p*-nitrophenolate release was not detectably increased over the background hydrolysis rate, $k_{obsd} = 0.047$ min.$^{-1}$, by the presence of 2 M acetamide. Assuming that a 10% increase in this first-order rate constant might have been overlooked, this data indicates that the intramolecular reaction is at least 60,000 times more rapid than the intermolecular reaction in the presence of 1 M acetamide.[8] This is a minimum value since *p*-nitrophenyl acetate is almost certainly more reactive toward nucleophilic reagents than O-acetylsalicylamide. The observation of Shafer and Morawetz[2b] that the reactivity of amides in systems of this type is largely independent

(1) Contribution No. 1191 of the Department of Chemistry, Indiana University. Supported by Grant No. GB 431 from the National Science Foundation.

(2) (a) S. A. Bernhard, A. Berger, J. H. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *J. Am. Chem. Soc.*, **84**, 2421 (1962); (b) J. A. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1899 (1963); (c) L. Benoiton and H. N. Rydon, *J. Chem. Soc.*, 3328 (1960); (d) P. E. Zimmering, E. W. Westhead, Jr., and H. Morawetz, *Biochim. Biophys. Acta*, **25**, 376 (1957); (e) E. Sondheimer and R. W. Holley, *J. Am. Chem. Soc.*, **76**, 2467 (1954); (f) A. R. Battersby and J. C. Robinson, *J. Chem. Soc.*, 259 (1955); (g) M. Brenner, *J. Cellular Comp. Physiol.*, **54**, 221 (1959).

(3) H. Neumann, Y. Levin, A. Berger, and E. Katchalski, *Biochem. J.*, **73**, 33 (1959).

(4) J. S. Fruton, S. Fujii, and M. H. Knappenberger, *Proc. Natl. Acad. Sci. U. S.*, **47**, 759 (1961).

(5) (a) G. Schmir and T. C. Bruice, *J. Am. Chem. Soc.*, **80**, 1173 (1958); (b) U. K. Pandit and T. C. Bruice, *ibid.*, **82**, 3386 (1960).

(6) (a) E. R. Garrett, *ibid.*, **79**, 3401 (1957); (b) M. L. Bender, F. Chloupek, and M. C. Neveu, *ibid.*, **80**, 5384 (1958); (c) M. L. Bender, Y. Chow, and F. Chloupek, *ibid.*, **80**, 5380 (1958).

(7) M. L. Bender and M. Silver, *ibid.*, **84**, 4589 (1962).

(8) For a discussion of similar comparisons in related systems, see M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

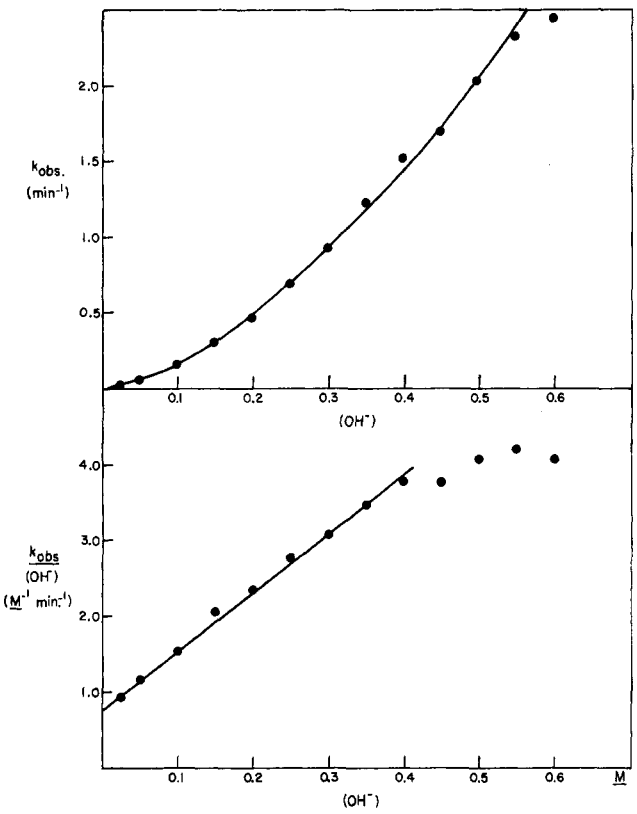


Fig. 1.—Upper half: First-order rate constants for the hydrolysis of N-acetylsalicylamide plotted against hydroxide ion concentration. The curve is a calculated line based on eq. 1 (see text). Lower half: Second-order rate constants [$k_{obs}/(OH)^-$] for the hydrolysis of N-acetylsalicylamide plotted against hydroxide ion concentration. Reactions were followed at 258 mμ at 25° and ionic strength 0.50.

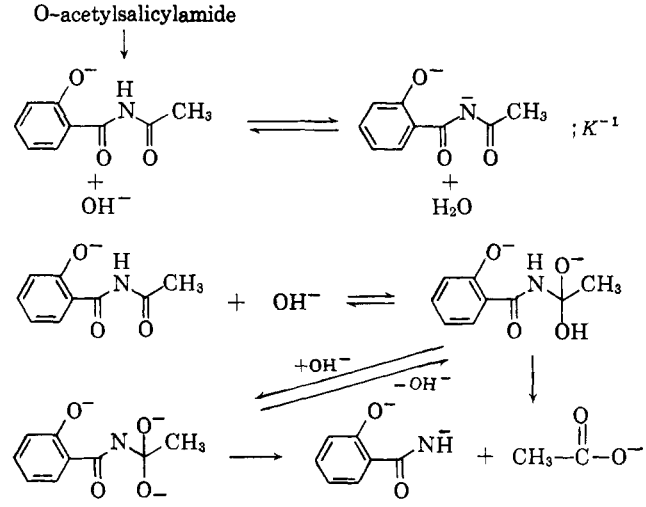
of the acid dissociation constant of the amide suggests that acetamide is a suitable model for the amide group of O-acetylsalicylamide.

The first-order rate constants for the hydrolysis of N-acetylsalicylamide, the initial product of the intramolecular amide reaction with O-acetylsalicylamide, exhibit a very interesting dependence on hydroxide ion concentration. First-order rate constants for this reaction are shown as a function of hydroxide ion concentration in the top half of Fig. 1. A plot of $k_{obs}/(OH^-)$ against (OH^-) is linear from 0.025 to 0.40 M hydroxide ion concentration (Fig. 1, lower half). At higher hydroxide ion concentrations, the second-order rate constants are less than predicted from the behavior in less alkaline solutions. Although, on the basis of the present data, a definitive explanation for these results cannot be given, the data is consistent with the reasonable mechanism shown in Scheme I.

A spectrophotometric titration of N-acetylsalicylamide at 25° and ionic strength 0.50 yielded a pK_a of 6.8 for the first dissociation constant of this substrate, so that the substrate is essentially completely converted to the monoanion under the conditions of these experiments. A spectral analysis of the reaction products from the hydrolysis of N-acetylsalicylamide indicated that at least 95% of the reaction yielded salicylamide as product.[9] The rate expression for the mechanism indicated above is shown in eq. 1 following.

$$k_{obsd}\ (\text{min.}^{-}) = \frac{K}{(OH^-) + K}\,[k_1\,(OH^-) + k_2\,(OH^-)^2] \quad (1)$$

SCHEME I



k_1 and k_2 were calculated from the intercept and slope, respectively, of the plot shown in the lower half of Fig. 1 under conditions in which this plot is linear. K = (monoanion) (OH^-)/(dianion) was chosen as 3.70 M^{-1} to give the best fit of the experimental data to eq. 1. The line drawn in the upper half of Fig. 1 is a calculated line based on eq. 1 with k_1 = 0.75 M^{-1} min.$^{-1}$ and k_2 = 7.76 M^{-2} min.$^{-1}$. Several additional reactions exhibit a term in the rate law proportional to the second power of hydroxide ion concentration which may also be interpreted in terms of pre-equilibrium hydroxide ion addition.[10]

On the other hand, the hydrolysis of related imides, such as phthalimide or succinimide, does not exhibit a second-order reaction in hydroxide ion.[11] However, the undissociated species of these substrates are much more reactive toward hydroxide ion than is the monoanion of N-acetylsalicylamide. The second-order rate constants for the attack of hydroxide ion on phthalimide[11a] and succinimide[11b] at 25° are approximately 700 and 200 M^{-1} min.$^{-1}$, respectively, compared with a corresponding value of 0.75 M^{-1} min.$^{-1}$ for the N-acetylsalicylamide monoanion. Thus, a second-order hydroxide ion term having a rate constant considerably larger than that observed for the present reaction would not have been detected for these substrates. The relatively large ratio of the rate constants for the second-order compared to the first-order term in hydroxide ion concentration for the present reaction may be rationalized in terms of the suggested mechanism, since the expulsion of the amide as the dianion should require considerably more driving force than in cases in which the amide departs as a monoanion.

Experimental

Materials.—O-Acetylsalicylamide was prepared according to the method of McConnan and Titherely.[12] Methyl phthalamate

(9) A similar result has been obtained for the hydroxaminolysis of acetyl benzoic anhydride [T. Wieland and D. Stimming, *Ann.*, **579**, 97 (1953)].

(10) (a) R. G. Pearson and E. A. Mayerle, *J. Am. Chem. Soc.*, **73**, 926 (1951); (b) S. S. Biechler and R. W. Taft, Jr., *ibid.*, **79**, 4927 (1957); (c) M. Zanger, C. A. VanderWerf, and W. E. McEwen, *ibid.*, **81**, 3806 (1959); (d) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 350.

(11) (a) J. T. Edward and K. A. Terry, *J. Chem. Soc.*, 3527 (1957), and references therein; (b) J. Tirouflet and E. L. Trouil, *Compt. rend.*, **241**, 1053 (1955).

(12) J. McConnan and J. A. Titherely, *J. Chem. Soc.*, **89**, 1318 (1906).

was prepared as follows. Methyl hydrogen phthalate[13] (18 g.) was converted to the acyl chloride with thionyl chloride.[13] The acyl chloride was dissolved in 100 ml. of anhydrous ether and dry ammonia was bubbled through the solution for 1 hr. at 0°. The white precipitate was recovered by filtration and dissolved in 50 ml. of chloroform. After discarding the insoluble material, the chloroform was removed by evaporation under reduced pressure. The resulting residue was recrystallized from ether to yield methyl phthalamate, m.p. 102–104°, lit.[11] m.p. 98–99°.

Anal. Calcd.: C, 59.88; H, 5.06; N, 7.90. Found: C, 60.33; H, 5.06; N, 7.82.

Infrared analysis ($CHCl_3$) revealed strong bands at 1680 and 1700 cm.$^{-1}$; n.m.r. spectrum (Varian A 60, deuterioacetone, tetramethylsilane as internal standard) revealed a complex multiplet centered at 7.05, a broad band near 6.6, and a sharp singlet at 3.3 p.p.m. (approximate integrated intensities are in the ratio 4:2:3, respectively).[13] Other materials were obtained commercially and recrystallized or redistilled before use. Distilled water was employed throughout.

Kinetic measurements were carried out spectrophotometrically with a Zeiss PMQ II spectrophotometer equipped with a thermostatted cell carriage as previously described.[14] All reactions were carried out at 25° in aqueous solution at ionic strength 0.5 (adjusted with potassium chloride). Dilute phosphate, borate, or carbonate buffers were employed in appropriate pH regions. For the studies of imide formation from methyl phthalamate, infinite time readings were determined artificially by immediately neutralizing strongly basic solutions of this substrate with hydrochloric acid. This procedure was necessary since the hydrolysis of the imide product was sufficiently rapid to introduce appreciable errors into the observed infinite time readings.[2b] Measurements of pH were obtained with the glass electrode and a Radiometer PHM 4c pH meter.

(13) We are indebted to Mr. D. P. Cords for recording the n.m.r. spectrum.
(14) W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959).

The Acetylation of Biferrocenyl[1,2]

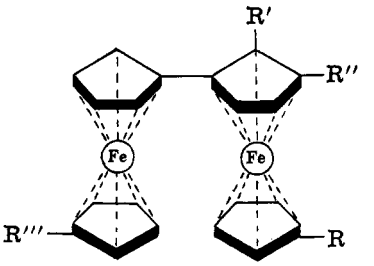
M. D. RAUSCH

Monsanto Chemical Company, Central Research Department, St. Louis, Missouri, and the Department of Chemistry, University of Massachusetts, Amherst, Massachusetts

Received August 12, 1963

The development of suitable synthetic procedures for biferrocenyl (I)[3–5] has enabled a general study concerning various ring-substitution reactions of this metallocene to be undertaken. The ability of biferrocenyl to undergo acylation and metalation reactions, as well as the isomerism of substituted biferrocenyls, has been discussed in previous communications.[1,6,7] In this paper, details concerning the acetylation of biferrocenyl and the configuration of various acetylated biferrocenyls are presented.

Three positional isomers are possible for a monoacetylated biferrocenyl: (1) isomer II, in which the acetyl group is attached to a cyclopentadienyl ring opposite the two rings joining the two ferrocenyl nuclei; (2) isomer III, in which the acetyl group is located at a position α to a bridging carbon atom; (3) isomer IV, in which the acetyl group is similarly β disposed.



I, R, R′, R″, R‴ = H
II, R′ = CO–CH_3; R, R″, R‴ = H
III, R″ = CO–CH_3; R, R′, R‴ = H
IV, R‴ = CO–CH_3; R, R′, R″ = H
V, R, R‴ = CO–CH_3; R′, R″ = H

Treatment of biferrocenyl with equimolar amounts of acetyl chloride and aluminum chloride in methylene chloride solution produced a mixture of products which could be separated by chromatography on alumina. The major product from the reaction, isolated in 14% yield, was a monoacetylbiferrocenyl of m.p. 143°. This product is assigned as acetylbiferrocenyl II on the basis of its proton nuclear magnetic resonance spectrum (Fig. 1).[8] A resonance peak at τ 7.85 representing three protons is noted in the region where the proton peak of an acetyl group attached to ferrocene is known to occur.[2] A singlet representing five protons is present at τ 6.03. The chemical shift of this peak is similar to chemical shifts of peaks representing protons of unsubstituted cyclopentadienyl rings in ferrocene (τ 5.86)[2] and biferrocenyl (τ 6.02).[9] A triplet due to two protons is noted somewhat upfield (τ 5.42) from the triplet representing the α protons in acetylferrocene (τ 5.23).[2] It is known, however, that the two directly bonded ferrocene nuclei in biferrocenyl exert a mutual shielding effect on all protons present.[9] The differential shift ($\Delta\tau$) of the triplet representing the α protons in acetylbiferrocenyl II compared to the unsubstituted ring protons in biferrocenyl is τ 0.60. This value is in good agreement with a $\Delta\tau$ value of τ 0.63 for the corresponding α protons of acetylferrocene compared to ferrocene.[2] Complex absorption in the region centered around *ca.* τ 5.71 accounts for the remaining ten protons in acetylbiferrocenyl II.

A second isomeric acetylbiferrocenyl of melting point 158–159° was isolated in *ca.* 1% yield from the reaction products. The proton n.m.r. spectrum of this product exhibited a singlet at τ 7.59 attributable to three acetyl protons, an apparent singlet at τ 5.98 attributable to ten protons on unsubstituted cyclopentadienyl rings, and complex absorption between τ 5.0 and 5.9 due to seven additional ring protons. Using an expanded (50 c.p.s.) scale, the resonance peak at τ 5.98 was further resolved into two peaks of approximately equal

(1) Presented in part at the 138th National Meeting of the American Chemical Society, New York, N. Y., Sept. 11, 1960; see Abstracts of Papers, p. 54P.
(2) Part IX of a series "Organometallic π-Complexes."
(3) M. D. Rausch, *ibid.*, **26**, 1802 (1961).
(4) E. G. Perevalova and O. A. Nesmeyanova, *Doklady Akad. Nauk SSSR*, **132**, 1093 (1960).
(5) M. D. Rausch, *Inorg. Chem.*, **1**, 414 (1962).
(6) M. D. Rausch, *J. Am. Chem. Soc.*, **82**, 2080 (1960).
(7) Electrophilic aromatic substitution reactions of biferrocenyl since have been described by other investigators: S. I. Goldberg, J. S. Crowell, and R. L. Matteson, XIX International Congress of Pure and Applied Chemistry, London, England, July 10, 1963; see Abstracts A, p. 184.
(8) Acetylbiferrocenyl II also has been synthesized recently by means of an unambiguous route, *viz.*, mixed Ullmann-type coupling of bromoferrocene and 1-bromo-1′-acetylferrocene [S. I. Goldberg and R. L. Matteson, *J. Org. Chem.*, **29**, 323 (1964)]. These investigators have likewise shown that Ullmann-type coupling of the latter derivative gives rise to diacetylbiferrocenyl V. The proton n.m.r. spectra of acetylbiferrocenyl II and diacetylbiferrocenyl V produced in this manner are identical with the spectra of the corresponding products isolated in the present study.
(9) Analogous results concerning the proton n.m.r. spectrum of biferrocenyl in chloroform solution have been reported previously: S. I. Goldberg, D. W. Mayo, and J. A. Alford, *J. Org. Chem.*, **28**, 1708 (1963).