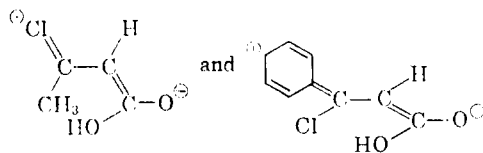


further data. Alternatively, the relative stabilities and C=O and C=C frequencies may be related to contributions from such structures as



since molecules containing conjugated double bonds are most stable in *s-trans* conformations. In either case, it must be expected that van der Waals repulsions between the carboxyl group and the halogen or phenyl group are important.

### Experimental

**Materials.**—The *trans*-crotonic acids were prepared by heating an excess of concentrated aqueous HX with tetrolic acid in sealed tubes at 100° for 12 hours. The tubes were then cooled and opened and the crystals removed by suction filtration through a sintered glass disk. The product was recrystallized several times in water and finally dried *in vacuo* over solid KOH. The *cis*-acids were obtained by heating the *trans*-acids at 135° in sealed tubes for 12–36 hours (see below, Isomerizations). The bromo- and iodoacids were obtained in high yields; large losses in several recrystallizations in water were accepted.  $\beta$ -Chloro-*trans*-cinnamic acid was prepared from ethyl benzoylacetate and PCl<sub>5</sub><sup>15</sup>; the *cis*-acid by the addition of concentrated aqueous HCl to phenylpropionic acid as above, separation of the isomers being effected through the difference in solubility of the Ba salts.<sup>8</sup> 2-Chlorocyclopent-1-enecarboxylic acid was prepared from acetyl cyclopentanone-2-carboxylate.<sup>16</sup>  $\beta$ -Chloro-*trans*-crotonic acid, m.p. 94° (94°<sup>15</sup>), neut. equiv. 120.9 (120.5);  $\beta$ -bromo-*trans*-crotonic acid, m.p. 94° (94°<sup>16</sup>), neut. equiv. 166 (165);  $\beta$ -iodo-*trans*-crotonic acid, m.p. 113° (113–114°<sup>17</sup>), neut. equiv. 215 (212);  $\beta$ -bromo-*cis*-crotonic acid, m.p. 55°, neut. equiv. 169 (165) [Anal. Calcd. for C<sub>4</sub>H<sub>5</sub>BrO<sub>2</sub>: Br, 48.4. Found: Br, 47.1];  $\beta$ -iodo-*cis*-crotonic acid, m.p. 66°, neut. equiv. 213 (212) [Anal. Calcd. for C<sub>4</sub>H<sub>5</sub>I<sub>2</sub>O<sub>2</sub>: I, 60.0. Found: I, 62.3];  $\beta$ -chloro-*trans*-cinnamic acid, m.p. 143° (144°<sup>18</sup>);  $\beta$ -chloro-*cis*-cinnamic acid, m.p. 133° (133°<sup>18</sup>); 2-chlorocyclopent-1-enecarboxylic acid, m.p. 116° (117°<sup>16</sup>), neut. equiv. 146.8 (146.6). Melting points are not corrected. The ethyl esters were prepared by the method of Scheibler

(15) M. Mousseron and R. Jacquier. *Compt. rend.*, **226**, 256 (1948).

(16) A. Michael, *J. Org. Chem.*, **4**, 128 (1939).

(17) E. Masuda, *J. Pharm. Soc. Japan*, **55**, 619 (1935); *C. A.*, **33**, 131 (1939).

and Voss<sup>18</sup>; they were purified by vacuum fractionations in a spinning band column. Boiling points and refractive indices agreed with reported values in every case.

**Measurements.**—Ultraviolet spectra were measured by means of the Cary-14 instrument; infrared spectra were taken in CS<sub>2</sub> and CCl<sub>4</sub> solvents and KBr pellets by means of an Infracord, solvent and polystyrene film being used to determine frequencies within 2–3 wave numbers; n.m.r. spectra were measured with a Varian V4300B high resolution spectrometer at 60 Mc. in D<sub>2</sub>O solution with H<sub>2</sub>O internal standard, NaCl being used to give all solutions the same ionic strength. Dipole moments were measured by means of DM 01 Dipolemeter with DFL 1 cell in benzene solution; the reproducibility was about 0.01 D.  $pK_a$ 's were determined by titrating samples in distilled water with CO<sub>2</sub>-free base and measuring the pH by means of a Beckman Zeromatic pH meter at small intervals; measurements in the buffer region only were used in the calculations. Since the solutions were quite dilute (0.01 M), the activity coefficient of the anion was assumed to be unity. That this assumption was justified was demonstrated by determining the  $pK_a$ 's of several acids whose thermodynamic  $pK_a$ 's are known, agreement being within 0.01  $pK_a$  unit. Solubilities were measured by titration of solutions saturated while warm, cooled to 25° and held there for 24 hours. Volatilities were determined with steam by distilling 40 ml. from a solution of 100 mg. of the acid in 50 ml. of water and titrating the distillate (these values have of course only comparative meaning). Isomerizations of the  $\beta$ -halo-*trans*-crotonic acids were followed by heating 1/10 mmole in sealed melting point capillary tubes at 135° for various lengths of time, dissolution of the product in 1 ml. of CS<sub>2</sub> and measurement of the infrared spectrum; the fate of  $\beta$ -chloro-*cis*-cinnamic acid was similarly followed at 170°. The infrared spectra allowed detection of 2% of each isomer in admixture with the other in each case. Rates of elimination were studied by sealing 3-ml. samples, 0.01 M in the anion and hydroxide ion, and heating them to 100° for various lengths of time. The contents were then titrated to yield a titration curve. Second-order rate constants generally remained constant within 5–10% during the first 75% of reaction except in the case of  $\beta$ -chloro-*cis*-cinnamic acid, the titration curve showing that decarboxylation was competing with elimination in that case.

**Acknowledgment.**—The author gratefully acknowledges support from the Research Foundation of State University of New York. He also wishes to thank Mr. B. Groten of Purdue University for the measurements of the dipole moments and Mr. L. Gortler of Harvard University for the n.m.r. spectra.

(18) H. Scheibler and J. Voss, *Ber.*, **53**, 382 (1920).

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## COMMUNICATIONS TO THE EDITOR

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### REVERSIBLE FORMATION OF AMIDES FROM FREE CARBOXYLIC ACID AND AMINE IN AQUEOUS SOLUTION. A CASE OF NEIGHBORING GROUP FACILITATION<sup>1</sup>

Sir:

Aside from the early work of Goldschmidt<sup>2</sup> with formic acid, it is generally believed that the rate of intermolecular formation of amides through direct interaction of a carboxylic acid group and an amine

(1) These studies are being supported in part by the National Institutes of Health under grant no. A 3437, by the U. S. Army Research and Development Laboratories under contract no. DA 18-108-405-CML-265, and by Parke Davis and Company, Detroit, Michigan.

(2) H. Goldschmidt and C. Wachs, *Z. physik. Chem.*, **24**, 353 (1897); and H. Goldschmidt and C. Wachs, *Ber.*, **39**, 97 (1906).

is extremely low. It now has been shown that with certain dicarboxylic or polycarboxylic acids the reaction occurs in relatively dilute aqueous solution at a surprisingly fast rate.

A typical case is that of the reaction between benzocaine and citric acid in an aqueous system. The residual concentration of the amine as followed at 95° spectrophotometrically and by extraction analysis is shown in Fig. 1. The amine disappeared relatively rapidly but soon reached an equilibrium concentration. (Initial concentration of amine =  $3.03 \times 10^{-3}$  M, initial concentration of acid = 0.5 M, and the concentration of amine at equilibrium =  $2.0 \times 10^{-3}$  M.)

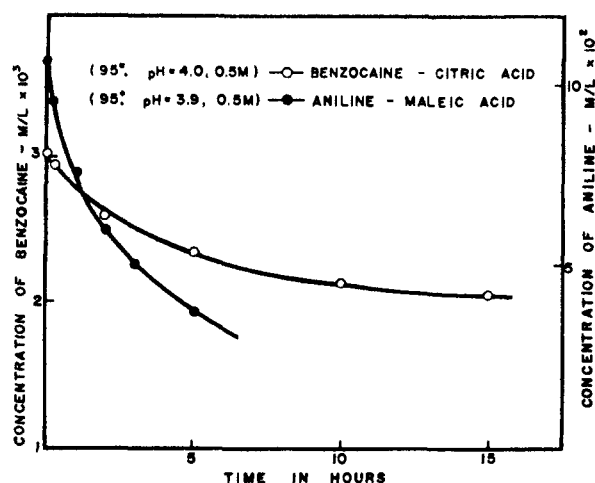


Fig. 1.—Residual concentration of amines in aqueous solutions of carboxylic acids.

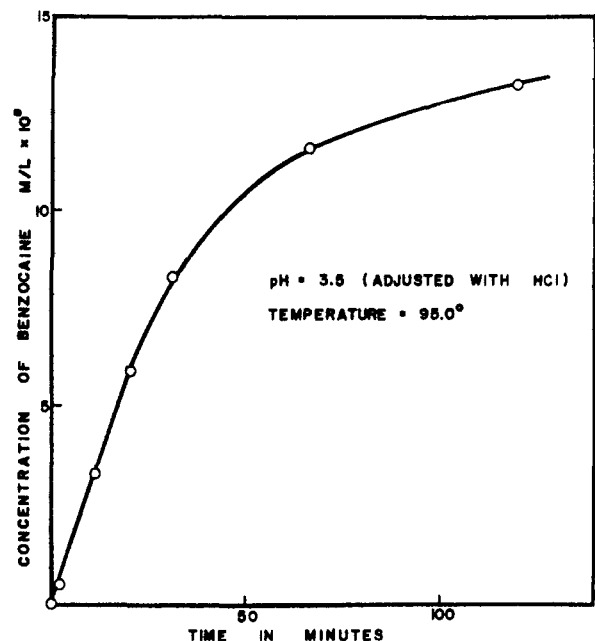


Fig. 2.—Regeneration in aqueous solution of benzocaine from its monoamide with citric acid.

The properties of the isolated product of the reaction (m.p. 184–186°) correspond to those of the monoamide of the tribasic acid. *Anal.* Calcd.: C, 53.09; H, 5.02; N, 4.13; O, 37.7; neut. equiv., 169. Found: C, 53.11; H, 5.04; N, 4.19; O, 38.26; neut. equiv., 161. This compound on heating at 95° in water rapidly reverted to the free acid and benzocaine, as shown in Fig. 2.

Similar kinetic behavior was noted for the citric acid–aniline, tartaric acid–aniline, maleic acid–aniline, and fumaric acid–aniline systems. Only the dianilide of citric acid was isolable in any large quantity from the citric acid–aniline system. Fumaric acid and maleic acid yielded an identical amide.

The pH–initial rate profiles for these systems exhibited maxima as shown in Fig. 3. The runs shown were carried out at 95° and at total concen-

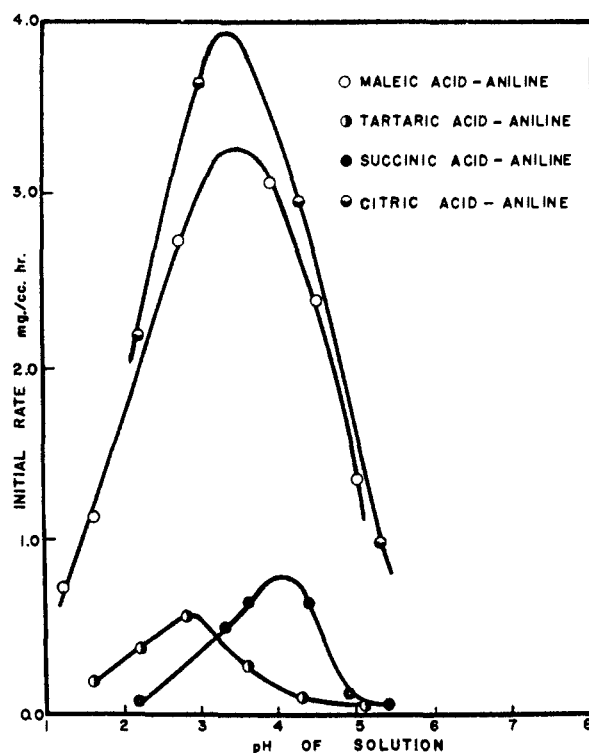


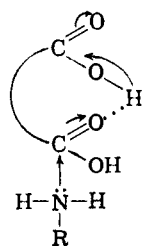
Fig. 3.—pH vs. initial rate profile.

tration of 0.50 *M* for all species of the organic acid. The results are kinetically in agreement with the formulation  $AH_2 + NH_2R \rightleftharpoons$  Amide. It can be shown mathematically that if only the un-ionized species react as shown, the initial rate will depend on pH as to yield a bell-shaped profile with maxima at approximately  $pH = \frac{1}{2}(pk_w - pk_b + pk_a)$ . According to Hall<sup>3</sup> the conjugate acid strength of aniline at 95° corresponds to  $pk_a' = 3.68$ . Although  $pk_a$  values for the organic acids at 95° have not been determined it seems reasonable in these instances to use the 50° values as first approximations. When this is done the observed maxima are in excellent agreement with the predicted pH values for the maximum rates. Moreover, any other kinetically different formulation, such as reaction of the singly ionized acid with the un-ionized amine, does not yield profiles even closely approximating the observed relationship. There is, of course, always the possibility that the singly ionized acid may react with the protonated amine since the observed kinetic relationship would still be followed, but this seems unacceptable from the mechanistic standpoint.

Since the observed rates were at least two or three orders of magnitude faster than the reaction, for example, of acetic acid with the same amines, it is suggested as an explanation that the presence of a second carboxyl group facilitates the nucleophilic attack by the amine, possibly through formation of an intermediate of the type shown.

These observations, although also involving diprotic acid species, are presumed to involve basically different mechanisms from the catalysis of amide hydrolysis. In the latter case the catalytic

(3) N. F. Hall, *J. Am. Chem. Soc.*, **54**, 3469 (1932).



activity has been found to be associated with the singly charged species<sup>4</sup> rather than with the unionized acid as in the present instance.

**Acknowledgment.**—We wish to express our appreciation to Professors Myron L. Bender and Harlan L. Goering for their comments and suggestions.

(4) T. Higuchi and H. N. Wolkoff, personal communication; T. Higuchi, A. D. Marcus and C. D. Bias, *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 129 (1954); M. L. Bender, *Chem. Revs.*, **60**, 85 (1960).

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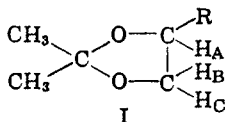
TAKERU HIGUCHI  
TOMONORI MIKI

RECEIVED JUNE 28, 1961

#### OPPOSITE RELATIVE SIGNS OF GEMINAL AND VICINAL PROTON-PROTON COUPLING CONSTANTS IN SATURATED ORGANIC MOLECULES<sup>1</sup>

Sir:

Relatively few analyses of nuclear magnetic resonance spectra of the ABC classification have been reported.<sup>2-6</sup> Though the method of analysis is lengthy, it is a particularly sensitive means of obtaining the relative signs of coupling constants. We have analyzed the spectra of a series of substituted dioxolanes (I) (R =  $-\text{COO}^- \text{K}^+$ ,  $-\text{COOCH}_3$ ,  $-\text{CD}_2\text{OH}$ ,  $-\text{C}_6\text{H}_5$ ,  $-\text{C}(\text{C}_6\text{H}_5)_2\text{OH}$ ,  $\text{C}(\text{CH}_3)_2-\text{OCO}-\text{C}_6\text{H}_4-p-\text{NO}_2$ ) for the purpose of obtaining information on the conformation of the dioxolane



ring.<sup>7</sup> During this work we have found that the analyses require the geminal coupling constant to be of opposite sign to the vicinal coupling constants. This is a direct contradiction of the theoretical calculations of Gutowsky, Karplus and Grant,<sup>4</sup> and Karplus<sup>8</sup> unless it is assumed that the H-C-H angle in our compound is greater than  $130^\circ$ . The results of their calculations using valence-bond theory predicted vicinal coupling constants would be of the same sign as geminal coupling constants

(1) This research was supported by a grant to R. U. L. by the Corn Industries Research Foundation, Washington, and the calculations were performed by R. R. F. with the cooperation of the University of Ottawa Computing Center. We wish to thank W. G. Schneider for valuable discussions and M. Welnberger for aid in obtaining the spectrum at 24.3 Mcps.

(2) R. W. Fessenden and J. S. Waugh, *J. Chem. Phys.*, **31**, 996 (1959).

(3) C. A. Reilly and J. D. Swalen, *ibid.*, **32**, 1378 (1960).

(4) H. S. Gutowsky, M. Karplus and D. M. Grant, *ibid.*, **31**, 1278 (1959).

(5) S. Castellano and J. S. Waugh, *ibid.*, **34**, 295 (1961).

(6) C. N. Banwell and N. Sheppard, *Mol. Phys.*, **3**, 351 (1960).

(7) R. U. Lemieux, R. R. Fraser and J. D. Stevens, in preparation.

(8) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

when the H-C-H bond angle  $\theta$  is less than  $125^\circ$ . This discrepancy points out the need for caution in assuming, as one might do on the basis of the theoretical work that all coupling constants are positive in saturated organic molecules and also in relating coupling constants to molecular wave functions.<sup>9</sup>

Throughout the series of compounds studied, estimated chemical shifts and coupling constants were adjusted by the iterative method as outlined by Banwell and Sheppard<sup>6</sup> using an IBM 650 computer until agreement was obtained in line positions with spectra measured on a Varian V-4302 spectrometer operating at 60 Mcps. Although there are, in theory, forty assignments possible for each ABC spectrum, each of the above compounds produced a spectrum with sufficient chemical shift between protons to make the combination bands relatively weak and easily identifiable. Thus, the number of alternative assignments was reduced to four. Of these, one is for the case where all three coupling constants,  $A_{AB}$ ,  $A_{BC}$  and  $A_{AC}$ , are of the same sign. The other three assignments involve the cases where one of the three coupling constants is of opposite sign. Since absolute signs cannot be determined, the two vicinal coupling constants will be arbitrarily assigned a positive value for ease of discussion. The alternative possibility that in the dioxolanes the geminal coupling constant is positive and the vicinal coupling constants are negative is equally compatible with our data. For the spectrum of I with R =  $\text{COO}^- \text{K}^+$ , three sets of chemical shifts and coupling constants were found to give agreement in line position to within 0.15 cps. Unfortunately, convergence by the iterative procedure was not obtained for the set with  $A_{AC}$  negative. Nevertheless, only when  $A_{BC}$  had a negative value did the intensities of the calculated spectrum agree with the observed intensities to within ten per cent. (the limit of accuracy for peak height measurements). The parameters in this case were  $\Delta\nu_B = 13.6$ ,<sup>10</sup>  $\Delta\nu_C = 35.5$ ,  $A_{AB} = 7.6$ ,  $A_{BC} = -8.3$ ,  $A_{AC} = 6.8$ . With all coupling constants positive agreement required  $A_{BC}$  to be 7.4 cps. The assignment of protons B and C to the same carbon atom was established by exchange deuteration of the methyl ester using sodium ethoxide in O-deuterated ethanol followed by alkaline hydrolysis. The signal at low field was not present in the spectrum of the potassium salt of the 2-C-deuterated acid and the spectrum was a pair of doublets with spacing  $8.2 \pm 0.2$  cps. This result obviously indicated that  $A_{BC}$  has a negative value. Confirmatory evidence that the vicinal and geminal hydrogens have coupling constants of opposite sign was obtained by measuring the spectrum of the compound at 24.3 Mcps. This spectrum is compared in Fig. 1 with the spectra calculated from the three sets of parameters which fit the 60 Mcps. spectrum except that the chemical shifts were reduced accordingly. Only with  $A_{BC}$  negative did all the line positions of the calculated spectrum agree within 0.2 cps. with those of the measured spectrum. It is therefore concluded that  $A_{BC}$  is negative.

The diphenylcarbinol derivative, R =  $\text{C}(\text{C}_6\text{H}_5)_2\text{OH}$ , whose 60 Mcps. spectrum differs greatly from

(9) M. Karplus, *J. Phys. Chem.*, **64**, 1793 (1960).

(10)  $\Delta\nu_B = \nu_B - \nu_A$  is the chemical shift in c.p.s.