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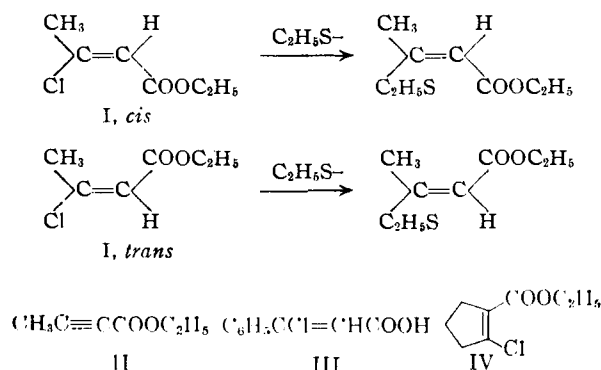
The Configurations of Some Substituted β -Haloacrylic Acids¹

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RECEIVED APRIL 1, 1961

The configurations of the β -chlorocrotonic acids have been re-examined and found to be in agreement with a recent assignment: the higher melting isomer is derived from *trans*-crotonic acid. This assignment is based on its formation from tetrolic acid, its more rapid rate of base-catalyzed elimination, n.m.r. spectra and a study of the dipole moments. The assignment is extended to the hitherto unknown bromo- and iodo-acids (the β -fluoro-acids are unstable to decarboxylation) and the β -chlorocinnamic acids. The properties of the lower melting isomers, such as volatility, solubility in polar and non-polar solvents, thermodynamic stability, infrared and n.m.r. spectra are consistent with Vernon's suggestion of intramolecular H-bonding involving the methyl and carbonyl groups; however, the infrared and n.m.r. spectra of the corresponding anions are not.

Compounds containing the group $-\text{CX}=\text{CH}-\text{CO}-$ are of interest in that the halogen atom is much more susceptible to nucleophilic displacement than in most vinyl halides; they are therefore ideally suited for stereochemical studies involving such reactions. A study of this sort² was reported recently; it was found that the *cis* and *trans* isomers of ethyl β -chlorocrotonate (I) yielded isomeric thioethers in the reaction with $\text{C}_2\text{H}_5\text{S}^-$, so that elimination of HX to form ethyl tetrolate (II) could not have preceded formation of the final product. It appeared also that the products had the same configuration as the starting materials.



Although the β -chlorocrotonic acids have been known for a long time, their configurations are still open to question. It was assumed at first that the isomer obtained in the addition of HCl to tetrolic acid was the β -chloro-*cis*-crotonic acid, though the argument used³ to support this assignment (*cis* addition) is no longer believed to be valid; indeed evidence has been published (based on n.m.r. spectra and dipole moments) that the assignment is wrong.²

The configurations of the β -chlorocinnamic acids, III, similarly appear to be in doubt. This paper presents evidence for the configurations of several substituted β -haloacrylic acids as a first step in a stereochemical study.

(1) In order to avoid ambiguity in nomenclature, it is pointed out that the methyl and carboxylic acid groups in β -halo-*trans*-crotonic acid are in *trans* positions as they are in the parent compound, *trans*-crotonic acid; a similar comment applies to the cinnamic acids.

(2) D. E. Jones, R. O. Morris, C. A. Vernon and R. F. M. White, *J. Chem. Soc.*, 2349 (1959).

(3) See, e.g., R. I. Shriner in H. Gilman, "Organic Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1953, Ch. 4, p. 460.

Results and Discussion

Only the higher melting isomer of the β -chlorocrotonic acids was found to be formed by the addition of aqueous HCl to tetrolic acid. This is considered to be evidence for the *trans* configuration; e.g., when HCl is added to acetylenedicarboxylic acid, chlorofumaric acid is formed.⁴ When dilute aqueous solutions of the anions were heated to 100° with the equivalent amount of hydroxide ion to form tetrolate ions, the higher melting isomer was found to have a $k_2 = 15 \times 10^{-4}$ l. mole⁻¹ sec.⁻¹ whereas that of the lower melting species was 2.5×10^{-4} l. mole⁻¹ sec.⁻¹; this indicates that the former has *trans* configuration (e.g., dehydrohalogenation is much faster in chlorofumaric acid than in chloromaleic acid⁵). Another method for distinguishing *cis-trans* isomers⁶ makes use of the observation that in derivatives of *cis*-crotonic acid the methyl proton resonance appears at lower applied magnetic field than in *trans*-crotonic acids. The values actually obtained (in D_2O solution with H_2O internal standard) were $\delta = +2.21$ and $+2.45$ p.p.m. (where $\delta = 10^6(\text{H}-\text{H}_{\text{H}_2\text{O}})/\text{H}_{\text{H}_2\text{O}}$), respectively. The dipole moments of the ethyl esters were reported by Vernon² as 1.43 and 2.45 debyes for the *cis* and *trans* isomers. However, no certain conclusion could be drawn since the direction of the group moment of the $-\text{COOEt}$ group is probably not along the carbon-carbonyl bond. In order to solve this problem the moments were measured again and compared with that of the model compound IV, ethyl 2-chlorocyclopent-1-enecarboxylate. The latter was found to have a moment of 2.43 D.; the *cis*- and *trans*-esters had moments of 1.50 and 2.54 D. (see also Table I, footnote *d*).

The configurations of the β -bromo- and iodo-crotonic acids are based on similarities with the chloro-acids. In both cases the higher melting isomers only are formed by the addition of HX to tetrolic acid; they are much less volatile with steam, have higher solubilities in water, lower solubilities in CS_2 and lower pK_a than their isomers as shown in Table I. Furthermore, upon prolonged heating to 130° all of them quantitatively isomerize into their lower melting isomers; their ultraviolet absorptions are less intense and in the infrared region all of them have higher $\text{C}=\text{O}$

(4) A. Michael, *J. prakt. Chem.*, **52**, 321 (1895).

(5) A. Michael, *ibid.*, **52**, 308 (1895).

(6) L. M. Jackman and R. H. Wiley, *Proc. Chem. Soc.*, 196 (1958).

TABLE I
 PROPERTIES OF β -HALOACRYLIC ACIDS

	Crotonic acids				Iodo-		Cinnamic acids	
	Chloro- High m.	Low m.	Bromo- High m.	Low m.	High m.	Low m.	Chloro- High m.	Low m.
M.p., °C.	94	59	93	55	113	66	143	133
pK_a^a	3.91	4.07	3.74	3.98	3.77	3.90	3.55	3.57
Soly. in H ₂ O ^b	3.42	2.15	4.19	2.25	1.47	0.94	0.031	0.042
Soly. in CS ₂ ^b	1.80	3.03	0.80	6.08	1.14	8.70	0.33	1.08
Voly. with steam ^c	17 ^d	95	12	75	13	65	2.5	8.8
$\epsilon_{\max} \times 10^{-3}$	18 ^e	20 ^e	14.6 ^f	17.4 ^f	7.2 ^g	10.5 ^g
$\nu_{C=O}$, cm. ⁻¹	1690	1680	1695	1680	1685	1675	1695	1700
$\nu_{C=C}$, cm. ⁻¹	1625	1615	1620	1610	1605	1600	1605	1615
Other bands in infrared	1430 } 1390 } ^w 1285w	1400m } 1300 } 1275 } ^w	1425 } 1380 } ^w 1280m	1400m } 1300 } 1275 } ^w	1420 } 1390 } ^w 1280m ₁	1390m } 1315 } 1270 } ^w		
	1210s	1225s	1210vs	1225s	1205vs	1220m		
		1090m		1070m		1065m		
		865w		865w		860w		
		780w		780w		780w		

^a At 25° in H₂O. In g./100 ml. at 25°. ^c In % when 80% of an aqueous solution containing 100 mg. acid is distilled.
^d The value for 2-chlorocyclopent-1-enecarboxylic acid in this row was 15. ^e λ_{\max} 2240 Å. ^f λ_{\max} 2340 Å. ^g λ_{\max} 2550 Å.

and C=C frequencies than the lower melting isomers. It may be concluded that all of the higher melting β -halo-acids are *trans*-crotonic acids. The β -fluoro-acids appear to be unstable; when aqueous HF was added to tetrolic acid at room temperature the infrared spectrum showed that both the acetylenic band at 2220 cm.⁻¹ and the -COOH bands at about 3000 cm.⁻¹ disappeared rapidly; no acidic product could be isolated. In the β -chlorocinnamic acids the higher melting isomer also appears to have the *trans* configuration: its dipole moment is 2.80 D. *vs.* 2.18 D. for the isomer; its k_2 in base-catalyzed elimination is 350×10^{-4} *vs.* 45×10^{-4} l. mole⁻¹ sec.⁻¹; its pK_a is slightly lower, its solubility in CS₂ is lower and its volatility with steam is lower⁷ (see footnote *c* in Table I). On the other hand, its solubility in water is also lower, the C=O and C=C stretching frequencies are lower, it is not formed exclusively by the addition of HCl to phenylpropionic acid⁸ (20 *vs.* 30% yield) and if the lower melting species is heated, it quantitatively isomerizes into its isomer.

Two possible explanations for the deviations in behavior of the cinnamic acids present themselves. First, if the pertinent properties of the *cis*-crotonic acids were due to weak H-bonding between the methyl hydrogen and the carbonyl group, it might be expected that the cinnamic acids will not resemble the crotonic acids. Although the methyl group is not ordinarily considered sufficiently polar to function as an acid in a H-bond, there are suggestions in the literature for weak interactions of this type. For instance, the relatively high acid strengths of butyric acid⁹ and of *o*-toluic acid¹⁰ have been considered a consequence of weak H-bonds between the methyl and carboxylate groups; the n.m.r. spectrum of 3-methyl-2-pyridone appears to warrant the assumption of such a bond

(7) In the distillation of the higher melting isomer, a small amount crystallized before the experiment was over, so that this value is not quite comparable to the others.

(8) T. C. James, *J. Chem. Soc.*, **99**, 1620 (1911).

(9) J. F. J. Dippy, *ibid.*, 1222 (1938).

(10) H. B. Watson, "Modern Theories of Organic Chemistry," 2nd Ed., Oxford University Press, New York, N. Y., 1941.

between the methyl group and the oxygen atom¹¹; a study of variations in the n.m.r. spectrum of propionaldehyde with temperature shows that the conformation in which the distance between methyl and carbonyl groups is at a minimum, is favored by one kcal.¹² (however, see below); finally, a weak H-bond of this type has been suggested to account for the difference in methyl hydrogen resonance of the ethyl esters of the two β -chlorocrotonic acids.^{2,13} The usual requirement for an intramolecular H-bond¹⁴ (a strain-free but relatively inflexible ring) can be met. It is pointed out that most of the properties listed in Table I, the relative stability of the isomers and the CH₃ resonances, are criteria for the existence of an intramolecular H-bond, and that the differences between the properties of the *cis* and *trans* isomers are consistent with such a bond in the *cis* configuration. If it is therefore assumed that a weak H-bond does indeed exist, it would then not be surprising if the differences in stability and infrared spectrum between the *cis*- and *trans*-cinnamic acids failed to resemble those of the crotonic acids. However, this notion is not consistent with the observation that the infrared spectra of the salts of the β -chlorocrotonic acids show no appreciable difference in either intensity or frequency of the CH₃ stretching mode. Furthermore, the difference in methyl resonance of the *cis*- and *trans*- salts, where the charge on the oxygen atom should lead to a stronger H-bond, is not appreciably greater than that of the free acids ($\delta = +2.42$ and $+2.62$ p.p.m., respectively). In any event, the criteria mentioned above are not sufficient and uncertainties in the conformation of the carboxyl group make it difficult to reach a conclusion in the absence of

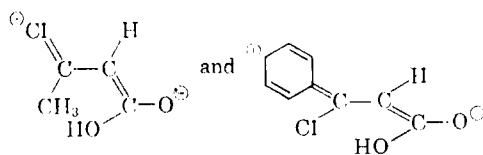
(11) J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961).

(12) R. J. Abraham and J. A. Pople, *Mol. Phys.*, **8**, 609 (1960).

(13) R. Morris, C. A. Vernon and R. F. M. White, *Proc. Chem. Soc.*, 303 (1958).

(14) (a) For general discussions of the H-bond, see G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960; (b) G. W. Wheland, "Advanced Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1960.

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. β -Chloro-*trans*-cinnamic acid was prepared from ethyl benzoylacetate and PCl_5 ; 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.⁸ 2-Chlorocyclopent-1-enecarboxylic acid was prepared from acetyl cyclopentanone-2-carboxylate.¹⁵ β -Chloro-*trans*-crotonic acid, m.p. 94° (94°¹⁵), neut. equiv. 120.9 (120.5); β -bromo-*trans*-crotonic acid, m.p. 94° (94°¹⁶), neut. equiv. 166 (165); β -iodo-*trans*-crotonic acid, m.p. 113° (113–114°¹⁷), neut. equiv. 215 (212); β -bromo-*cis*-crotonic acid, m.p. 55°, neut. equiv. 169 (165) [Anal. Calcd. for $\text{C}_4\text{H}_5\text{BrO}_2$: Br, 48.4. Found: Br, 47.1]; β -iodo-*cis*-crotonic acid, m.p. 66°, neut. equiv. 213 (212) [Anal. Calcd. for $\text{C}_4\text{H}_5\text{IO}_2$: I, 60.0. Found: I, 62.3]; β -chloro-*trans*-cinnamic acid, m.p. 143° (144°⁸); β -chloro-*cis*-cinnamic acid, m.p. 133° (133°⁸); 2-chlorocyclopent-1-enecarboxylic acid, m.p. 116° (117°¹⁵), 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 Voss¹⁸; 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_2 and CCl_4 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_2O solution with H_2O 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_2 -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 β -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_2 and measurement of the infrared spectrum; the fate of β -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 β -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).

COMMUNICATIONS TO THE EDITOR

REVERSIBLE FORMATION OF AMIDES FROM FREE CARBOXYLIC ACID AND AMINE IN AQUEOUS SOLUTION. A CASE OF NEIGHBORING GROUP FACILITATION¹

Sir:

Aside from the early work of Goldschmidt² 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 = 3.03×10^{-3} *M*, initial concentration of acid = 0.5 *M*, and the concentration of amine at equilibrium = 2.0×10^{-3} *M*.)