Substituent Effects in the Ionization of *trans*-2-Substituted Cyclopropanecarboxylic Acids

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The ionization constants of *trans*-2-substituted cyclopropanecarboxylic acids were determined in water and 50% aqueous ethanol at 25 °C. The substituent effects thus obtained were interpreted by the use of the four parameter equations presented by Yukawa and Tsuno. The transmitting resonance effect of *trans*-cyclopropylene is about a quarter that of *trans*-vinylene and a half that of *p*-phenylene.

There have been a number of reports on the analogy between a cyclopropane ring and a double bond. Previous investigations based on linear free-energy relationships (LFER) have suggested almost exclusively the possibility of the transmission of a resonance effect through a cyclopropane ring.[1] However, the degree of transmission of the resonance effect is still uncertain because of the use of limited data and the variety of treatments of the LFER. In connection with the previous study of the estimation of the electronic effects of the cyclopropane ring,[2] a definite answer has been sought concerning the degree of the transmission of conjugation through a *trans*-cyclopropylene. The ionization constants of *trans*-2-substituted cyclopropanecarboxylic acids have been determined in water and in 50% ethanol at 25 °C, and the substituent effects thus obtained have been interpreted in terms of the LFER reported by Yukawa and Tsuno.[3]

Results and Discussion

The pK_a values measured are listed in Table 1. The effects of the substituents in the two solvents were in the usual order and were correlated with each other, as is illustrated in the figure. The plot of the ΔpK_a values against the substituent constants, σ', σ^0, σ_p, σ^-, or σ^+, fails to give a linear relationship. The correlation coefficients proved to be from 0.885 to 0.94. However, an excellent correlation with a ρ value of 1.99 was obtained by means of σ_m with the correlation coefficient of 0.999 (in water), while the ionization of acrylic acids was correlated with the σ_p constants.[4] In the case of ionization in 50% ethanol, ρ and the correlation coefficient for σ_m were 2.92 and 0.998 respectively.

Yukawa and Tsuno successfully separated the polar effects of the substituent into inductive and resonance effects,[3] they expressed σ_m and σ_p as $0.87\sigma'+0.21\Delta\bar{\sigma}_R$ and $0.74\sigma'+0.685\Delta\bar{\sigma}_R$ respectively, where σ' is a polar substituent constant presented by Roberts[5] and where $\Delta\bar{\sigma}_R$ measures the capacities of the substituents to supply electrons by resonance.[3] Thus, the substituent effects (ΔpK_a) for the ionization of *trans*-2-substituted cyclopropanecarboxylic, *trans*-β-substituted acrylic, β-substituted propionic, and *p*-substituted benzoic acids are expressed by the equations given in Table 2. In the sets of the same structural type, such as XZCOOH, it seemed reasonable to assume that the ratio (*fr*) of the coefficient of $\Delta\bar{\sigma}_R$ to that of $\Delta\bar{\sigma}_R$ of the reference system is a measure of the ability of the Z group to transmit the resonance effect to the reaction site, *i.e.*, COOH, under the same reaction conditions. The *fr* values of (1) and (2) to (4) were 0.62 and 2.7 respectively. Thus,

Table 1. pK_a Values of *trans*-2-substituted cyclopropane carboxylic acids in water at 25°.

Substituent	pK_a (±0.01)	
	In water	In 50% ethanol
H	4.84, 4.83[a]	6.44
CH_3	4.98	6.62
Br	4.09	5.41
C_2H_5O	4.46	
CH_3O		5.76
CH_3CO	4.08	5.36
C_2H_5OCO	4.10	5.35
CH_3OCO	4.09	
CN	3.73	4.63

a) M. Kilpatric and J. O. Morse, *J. Am. Chem. Soc.*, **75**, 1854 (1953).

Table 2. Substituent effects for the dissociation of carboxylic acids in water(a) and in 50% ethanol(b)

				fi	*fr*
(a)					
	(1)	*trans*-2-XC_3H_4COOH	$1.73\sigma'+0.42\Delta\bar{\sigma}_R$	1.08	0.62
	(2)	*trans*-β-XC_2H_2COOH	$1.63\sigma'+1.86\Delta\bar{\sigma}_R$[a]	1.02	2.71
	(3)	XC_2H_4COOH	$1.60\sigma'$[b]	1.00	0.00
	(4)	*p*-XC_6H_4COOH	$0.743\sigma'+0.685\Delta\bar{\sigma}_R$		1.00
(b)					
	(1)	*trans*-2-XC_3H_4COOH	$2.54\sigma'+0.61\Delta\bar{\sigma}_R$		0.57
	(4)	*p*-XC_6H_4COOH	$1.06\sigma'+1.08\Delta\bar{\sigma}_R$		1.00

a) ρ value is 2.19: K. Bowden, *Can. J. Chem.*, **43**, 3354 (1965). b) ρ was calculated by the ionization constants appeared in "Lange's Handbook of Chemistry," ed. by J.A. Dean, eleventh edition, Mcgraw-Hill (1973).

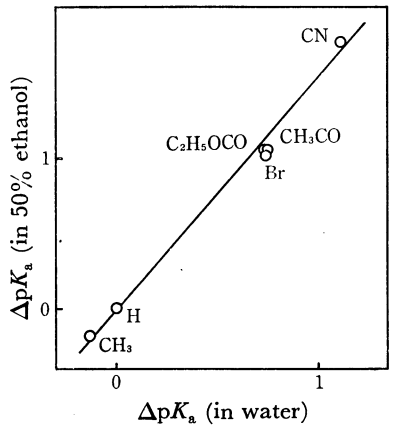

Fig. 1. Linear free energy relation for dissociation of *trans*-2-substituted cyclopropanecarboxylic acids at 25 °C.

the transmitting-resonance effect of *trans*-cyclopropylene is about a quarter that of *trans*-vinylene and a half that of *p*-phenylene.[6] Three models (a trigonally hybridized model,[7] a bent-bond model,[8] and a molecular orbital model[9]) for the bonding in cyclopropane, previously presented, have led to a prediction of the *p* orbital character of C–C bonds. Since there is no steric interaction between the substituent and the carboxy group in *trans*-2-substituted cyclopropanecarboxylic acids, the substituent and the carboxy group can both overlap with the cyclopropane ring. Thus, it is revealed that cyclopropylene is a transmitter of the resonance effect, although its action is rather poor.

The ratios(f_i) of the coefficients of σ' of (1) and (2) to that of σ' of (3) were 1.0 and 1.1 respectively, indicating that the transmission of the inductive effect was practically equal in all three series.

Experimental

The materials were identified on the basis of spectroscopic and gas-chromatographic measurements and elemental analysis. The NMR spectra were measured on a JEOL JNM-C-60HL (60 MHz) spectrometer, with tetramethylsilane employed as the internal standard. The structure assignments for the geometrical isomers were made by means of the NMR spectra of ring protons by means of shift reagents based on a generalization that the tendency of the shift of the signal of the *cis* proton to ethoxycarbonyl is larger than that of the shift of the *trans* protons.[10] Unsubstituted,[11] *trans*-2-methyl,[12] ethoxycarbonyl,[13] methoxycarbonyl[13] and bromocyclopropanecarboxylic[13] acids were synthesized by the methods described in the literature. The syntheses of other substituted cyclopropanecarboxylic acids will be described below.

Ethyl trans-2-*Ethoxycyclopropanecarboxylate.* To a mixture of commercial ethyl vinyl ether (100 g) and an anhydrous copper (I) sulfate catalyst (1 g), ethyl diazoacetate was added over a period of 1 h with rapid stirring. The mixture was then cooled to room temperature, and the catalyst was removed by filtration. The remaining ethyl vinyl ether was removed *in vacuo*, and the residue was distilled to give a main fraction boiling at 95—105 °C at 35 mmHg. Yield, 75 g. Pure ethyl *trans*-2-ethoxycyclopropanecarboxylate was obtained by fractional distillation; bp 66 °C/9 mmHg. NMR (CCl_4) δ 0.72—1.86 (3H, m, ring), 1.24 (3H, t, J=7 Hz, CH_3), 1.16 (3H, t, J=7 Hz, CH_3), 3.16—3.5 (1H, m, ring), 3.54 (2H, q, J=7 Hz, $COCH_2$), 4.06 (2H, q, J=7 Hz, ester CO_2CH_2), Found: C, 59.56; H, 9.04%. Calcd: C, 60.74; H, 8.92%.

trans-2-*Ethoxycyclopropanecarboxylic Acid.* Ethyl *trans*-2-ethoxycyclopropanecarboxylate (20 g) was saponified by refluxing with 6 g of sodium hydroxide in 40% ethanol to yield, after acidification, extraction with 50 ml of ether, and distillation *in vacuo*, 13 g of *trans*-2-ethoxycyclopropanecarboxylic acid; bp 119 °C/10 mmHg. NMR (CCl_4) δ 1.0—1.4 (2H, m, ring), 1.16 (3H, t, J=7 Hz, CH_3), 1.49—1.82 (1H, m, ring), 3.35—3.6 (1H, m, ring), 3.35—3.75 (2H, q, (J=7 Hz); neut. equiv. Found 132, Calcd 130.

Ethyl trans-2-*Methoxycyclopropanecarboxylate.* To a stirred mixture of 100 g of methyl vinyl ether and 1 g of anhydrous copper (I) sulfate in 100 ml of hexane at 35 °C, we added, drop by drop, 110 g of ethyl diazoacetate. After the reaction has been completed, the catalyst was removed by filtration. The solvent and unreacted methyl vinyl ether were removed *in vacuo*, and the residue was distilled to give 65 g of crude products; bp 75—100 °C/15 mmHg. The fractional distillation afforded 5 g of pure ethyl *trans*-2-methoxycyclopropanecarboxylate; bp 61—63 °C/15 mmHg. NMR (CCl_4) δ 0.80—1.80 (3H, m, ring), 1.23 (3H, t, J=7 Hz, CCH_3), 3.32 (3H, s, OCH_3), 4.6 (2H, q, J=7 Hz, CO_2CH_2C). Found: C, 56.36; H, 8.40%. Calcd: C, 58.31; H, 8.39%.

trans-2-*Methoxycyclopropanecarboxylic Acid.* Ethyl *trans*-2-methoxycyclopropanecarboxylate (6 g) was hydrolyzed by refluxing with sodium hydroxide (2.6 g) in 70 ml of water to yield, after a routine treatment, *trans*-2-methoxy-cyclopropanecarboxylic acid (2 g); bp 116 °C/16 mmHg. NMR ($CDCl_3$) δ 1.16—1.45 (2H, m, ring), 1.60—1.90 (1H, m, ring), 3.41 (3H, s, CH_3), 3.3—3.8 (1H, m, ring). neut. equiv: Found 117, Calcd 116.

trans-2-*Cyanocyclopropanecarboxylic Acid.* The saponification of ethyl *trans*-2-cyanocyclopropanecarboxylate (8 g)[14] with potassium carbonate (4 g) in water (20 ml) gave crude *trans*-2-cyanocyclopropanecarboxylic acid (1.5 g). Pure acid was obtained by recrystalization from benzene; mp 127—128 °C. NMR ($CDCl_3$) δ 1.80—2.45 (2H, m), 0.92—1.70 (2H, m). neut. equiv: Found 112, Calcd 111.

Ethyl trans-2-*Acetylcyclopropanecarboxylate.* This ester was obtained by the reaction of *trans*-2-ethoxycarbonylcyclopropanecarbonyl chloride (25 g) with dimethyl cadmium in benzene prepared by the treatment of methyl magnesium bromide (about 0.17 mol) with cadmium chloride (20 g); bp 105 °C/19 mmHg. IR (in CS_2) 1730 cm^{-1} (C=O, ketone), 1710 cm^{-1} (C=O, ester), NMR (CCl_4) δ 1.25 (3H, t, J=7 Hz, $OCCH_3$), 1.25—1.45 (2H, m, ring), 1.8—2.15 (1H, m, ring), 2.16—2.6 (1H, m, ring), 2.23 (3H, s, $COCH_3$), 4.05 (2H, q, J=7 Hz, CO_2CH_2C). Found: C, 60.72; H, 8.07%, Calcd: C, 61.51; H, 7.74%.

trans-2-*Acetylcyclopropanecarboxylic Acid.* Ethyl *trans*-2-acetylcyclopropanecarboxylate (6.2 g) was hydrolyzed with sodium hydroxide (1.6 g) in 80% ethanol (35 ml) to yield *trans*-2-acetylcyclopropanecarboxylic acid (4 g); bp 122—124 °C/3 mmHg, mp 56—57 °C. NMR (CCl_4) δ 1.88—2.60 (2H, m, ring), 1.20—1.55 (2H, t, J=6 Hz, ring), 2.26 (3H, s, CH_3). neut. equiv: Found 128, Calcd 128.

The ionization constants were determined by a potentiometric titration of substituted cyclopropanecarboxylic acids (0.005 M) with sodium hydroxide (0.02 M) according to the previously outlined procedure.[2]

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