TABLE VI

VALUES OF $\gamma$

| G | Dipole moments of XGH[a] | Ionization constants of $XGCO_2H$[b] |
|---|---|---|
| *p*-Phenylene | 1 | 1 |
| *trans*-Vinylene | 0.87 | 2.23 |
| Acetylene | 0.94 | 1.89 |
| Cyclopropylidene | 1.05 | 5.36 |

[a] This work. [b] Ref. 11.

show that, for correlations of dipole moments, $\rho$ is independent of G. The result is surprising. A dipole moment may be defined as the product of the distance between two charges and the magnitude of one of them. Thus, $\rho$ would be expected to be a function of the distance separating the charges. Then, as all values of $\rho$ obtained are about the same, the distance must be the same in all of the systems studied. This can be rationalized if the distance involved is the carbon–substituent bond length, which would have about the same average value for the systems considered.

**The Variation of $\rho$ with Y.**—We have shown for equilibrium and rate data that for sets XGY where Y is a constant substituent, eq. 14 is obeyed.[18] Correlation

$$\rho_Y = m\sigma_Y + c \qquad (14)$$

of $\rho$ for sets 1b, 2b, 3b, 4, 5b, and 7 with $\sigma_p$ gave $r$ = 0.464, $s$ = 0.487, $t$ = 1.047, and $m$ = 0.783. Thus $\rho$-values for dipole moment correlations of *trans*-vinylene sets do not appear to follow eq. 14. Due to the uncertainty regarding sets 15 and 16, and the lack of correlation in set 17, no conclusion can be reached concerning the applicability of eq. 14 to acetylenic sets.

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[18] M. Charton, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1963, p. 46T.

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# Application of the Hammett Equation to Nonaromatic Unsaturated Systems. IV. Vinylidene and Heterovinylidene Sets

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The Hammett equation has been extended to the correlation of p$K_a$ values of vinylidene (C=C<) and heterovinylidene (Z=C<) sets, including 2-substituted acrylic acids, 2′-substituted *cis*-cinnamic acids, 2′-substituted *trans*-cinnamic acids, substituted carbonylacetic acids, substituted carbonylpropanoic acids, and *anti*-substituted oximinocarboxylic acids. The $\sigma_m$-constants are preferred for correlation. The electrical effect of a vinylidene substituent is largely a localized electrostatic effect with a small but apparently significant resonance contribution. Sets bearing a constant *cis*-vinylene ( ∖C=C/ ) substituent are more sensitive to vinylidene substituent effects than those bearing a constant *trans*-vinylene substituent. Vinylidene sets are very much more sensitive to substituent effects than are *trans*-vinylene sets.

We have for some time been interested in structure–reactivity relationships among nonaromatic $\pi$-bonded systems. In particular, we have considered the extension of the Hammett equation[1] to these systems.

$$Q_X = \rho\sigma_X + Q_H \qquad (1)$$

*trans*-Vinylene,[2,3] acetylene,[4] and cyclopropylidene[5] sets have been reported to be correlated by eq. 1 using the $\sigma_p$-constants. *trans*-Cyclopropylene sets are said to be correlated by the $\sigma_m$-constants.[5] It seemed of interest to extend those observations to vinylidene sets, I. Data from the literature for four vinylidene sets have therefore been correlated with the Hammett equation as described by Jaffé.[1] The correlations were made with the $\sigma_I$-, $\sigma_m$-, and $\sigma_p$-substituent constants in order to determine the nature of the electrical effect of vinylidene substituents. The sets studied are 2-substituted acrylic acids (1) (I, $R^1 = R^2 = H$); *cis*-2′-substituted cinnamic acids (2) (I, $R^1 = H, R^2 = Ph$); *trans*-2′-substituted cinnamic acids (3) (I, $R^1 = Ph, R^2 = H$); and 2-substituted 3,3-dimethylacrylic acids (4) (I, $R^1 = R^2 = Me$). Data used in the correlations are given in Table I. The $\sigma_m$- and $\sigma_p$-constants used are generally from the compilations of McDaniel and Brown[6]; the $\sigma_I$-constants are from our recent compilation.[7] Substituent constants from sources other than those cited above are given in Table II.

We have also examined several heterovinylidene sets in which the $CR^1R^2$ group in I is replaced by O (II) or NOH (III). These sets include substituted carbonylacetic acids (5) (II, $n$ = 1); substituted carbonylpropanoic acids (6) (II, $n$ = 2); substituted carbonylbutanoic acids (7) (II, $n$ = 3); substituted carbonylpentanoic acids (8) (II, $n$ = 4); and substituted oximinocarboxylic acids (9) (III). Data for these sets are also given in Table I. Data for all sets are taken from

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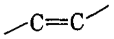
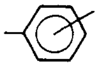
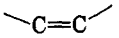
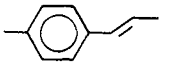
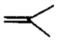
[1] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940; H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953); V. Palm, *Russ. Chem. Rev.*, **31**, 471 (1961); P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).

[2] We will find it convenient to define the following names of diradical groups.

| | | | |
|---|---|---|---|
| *trans*-vinylene |  | phenylene |  |
| *cis*-vinylene |  | styrylene |  |
| vinylidene |  | *trans*-cyclopropylene |  |
| acetylene | —C≡C— | cyclopropylidene |  |

[3] M. Charton and H. Meislich, *J. Am. Chem. Soc.*, **80**, 5940 (1958); J. Hine and W. C. Bailey, Jr., *ibid.*, **81**, 2075 (1959); J. Hine and W. C. Bailey, Jr., *J. Org. Chem.*, **26**, 2098 (1961).

[4] M. Charton, *ibid.*, **26**, 735 (1961).

[5] M. Charton, *J. Chem. Soc.*, 1205 (1964).

[6] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

[7] M. Charton, *ibid.*, **29**, 1222 (1964).

TABLE I

p$K_a$ VALUES USED IN CORRELATIONS

| X | Set[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| H | 4.26[b] | 3.88[b] | 4.44[b] | 5.12[b] | | | | |
| F | 2.55[b] | | 3.71[c] | | | | | |
| Br | | 1.84[d] | 3.03[d] | | | | | |
| Cl | | 1.97[d] | 3.02[d] | | | | | |
| I | | 2.24[d] | 3.30[d] | | | | | |
| Me | 4.65[e] | 3.62[f] | 4.82[f] | 4.42[g] | 3.58[h] | 4.60[h] | 4.67[h] | 4.72[h] |
| Et | | | | | | | | |
| *i*-Pr | | | | | | | | |
| Ph | 3.84[i] | 3.74[j] | 4.71[j] | | | 4.65[k] | | |
| Bu | 4.80[l] | | | | | | | |
| $AsO_3H^-$ | 4.225[b,m] | | | | | | | |
| SCN | 1.896[n] | | | | | | | |
| CN | | | | 3.04[o] | | | | |
| $CO_2Et$ | | | | 3.36[o] | | | | |
| $CONH_2$ | | | | 3.45[p] | | | | |
| OH | | | | | 3.14769[q,r] | 4.52[q,s] | 4.64[q,s] | 4.74[q,s] |
| OEt | | | | | 3.25[h] | 4.52[h] | | 4.60[h] |
| OMe | | | | | 3.35[t] | 4.49[u] | | |
| $O^-$ | | | | | 5.39573[v] | 5.40[v,s] | 5.12[v,s] | 5.14[v,s] |
| $NH_2$ | | | | | 3.64[b] | 4.54[b] | 4.60[b] | 4.63[b] |
| PhNH | | | | | 3.717[i] | 4.701[i] | | |
| HCNOH | | | | | | | | |

| | Set | | |
|---|---|---|---|
| | 9 | 10 | 11 |
| H | 3.00[w] | 4.44[x] | 4.70[x] |
| Cl | | 2.80[x] | 3.22[x] |
| Me | 3.38[w] | 4.29[b,y] | 4.96[b,y] |
| Et | 3.20[w] | | |
| *i*-Pr | 3.05[w] | | |
| Ph | 2.82[w] | | |
| HCNOH | 2.55[w] | | |

[a] 1, 2-Substituted acrylic acids; 2, *cis*-2′-substituted cinnamic acids; 3, *trans*-2′-substituted cinnamic acids; 4, 2-substituted 3,3-dimethylacrylic acids; 5, substituted carbonylacetic acids; 6, substituted carbonylpropanoic acids; 7, substituted carbonylbutanoic acids; 8, substituted carbonylpentanoic acids; 9, *anti*-substituted oximinocarboxylic acids; 10, *cis*-2-substituted crotonic acids; and 11, *trans*-2-substituted crotonic acids. [b] G. Kortum, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution," Butterworth and Co. Ltd., London, 1961. [c] F. Swartz, *Bull. soc. chim. France*, **25**, 325 (1919). [d] T. C. James, *J. Chem. Soc.*, **103**, II, 1368 (1913). [e] T. Alfrey and H. Morawetz, *J. Am. Chem. Soc.*, **74**, 436 (1952). [f] Estimated from $K_a$ in 40% MeAc–$H_2O$ at 25° reported by R. D. Kleene, F. H. Westheimer, and G. W. Wheland [*J. Am. Chem. Soc.*, **63**, 791 (1941)]. [g] B. Szyszkowski, *Z. physik. Chem.* (Leipzig), **22**, 173 (1897). [h] H. C. Brown, D. H. McDaniel, and O. Hafliger in "Determination of Organic Structures by Physical Methods," Academic Press Inc., New York, N. Y., 1955, p. 567. [i] W. Ostwald, *Z. physik. Chem.* (Leipzig), **3**, 241 (1889). [j] Estimated from p$K_a$ in 60% EtOH–$H_2O$ reported by L. F. Fieser [*J. Chem. Educ.*, **31**, 291 (1954)]. [k] A. Hantzsch and A. Miolati, *Z. physik. Chem.* (Leipzig), **10**, 1 (1892). [l] J. Cason and M. J. Kalm, *J. Org. Chem.*, **19**, 1947 (1954). [m] p$K_2$ for 2-arson acrylic acid. [n] A. Fredga, *Svensk Kem. Tidskr.*, **42**, 155 (1930). [o] E. J. Corey, *J. Am. Chem. Soc.*, **75**, 1172 (1953). [p] E. J. Corey, *ibid.*, **75**, 1163 (1953). [q] Includes statistical factor of 0.5. [r] S. N. Das and D. J. G. Ives, *Proc. Chem. Soc.*, 373 (1961). [s] R. H. Jones and D. I. Stock, *J. Chem. Soc.*, 102 (1960). [t] W. D. Treadwell and E. Wettstein, *Helv. Chim. Acta*, **18**, 204 (1935). [u] W. A. Bone, J. J. Sudburough, and G. H. G. Spranklong, *J. Chem. Soc.*, **85**, 534 (1904) [v] Includes statistical factor of 2. [w] Ref. 9. [x] M.-L. Dondon and M. T. Paris, *J. Chim. Phys.*, **58**, 222 (1961). [y] At 18°.

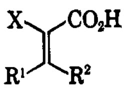
TABLE II

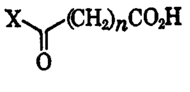
SUBSTITUENT CONSTANTS[a]

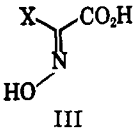
| X | $\sigma_I$ | $\sigma_m$ | $\sigma_p$ |
|---|---|---|---|
| $AsO_3H^-$ | | 0[b] | −0.019[c] |
| SeCN | | 0.61[b] | 0.664[c] |
| $CONH_2$ | | | 0.36[d] |
| PhNH | 0.02[e] | −0.12[f] | −0.40[f] |
| CN | | 0.615[e] | |
| HCNOH | 0.27[e] | 0.216[g] | 0.103[g] |
| $O^-$ | 0.12[h] | −0.47[i] | −0.81[i] |

[a] From sources other than ref. 6 and 7. [b] Calculated from $\sigma_m = (2\sigma_I + \sigma_p)/3$. [c] H. H. Jaffé, ref. 1. [d] See ref. 11. [e] Calculated from $\sigma_I = (3\sigma_m - \sigma_p)/2$. [f] Calculated as described in ref. 11. [g] P. Cecchi, *Ric. Sci.*, **28**, 2526 (1958). [h] R. W. Taft, Jr., private communication to P. R. Wells, ref. 1. [i] J. Hine, *J. Am. Chem. Soc.*, **82**, 4880 (1960).

the literature; results of the correlations for all sets are given in Table III.


I


II


III

In set 1, p$K_2$ of 2-arsonoacrylic acid has been assigned to the carboxyl group, by comparison with 4-arsonobenzoic acid. In sets 5–8, statistical factors of 0.5 for X = OH and 2 for X = $O^-$ were used in the correlations.

## Results

**Vinylidene Sets.**—The $\sigma_I$- and $\sigma_m$-constants give best correlation with 2-substituted acrylic acids (1), *cis*-2′-substituted cinnamic acids (2), and 2-substituted 3,3-dimethylacrylic acids (4). The results obtained show no significant difference between $\sigma_I$ and $\sigma_m$ for these sets. In the case of the *trans*-2′-substituted cinnamic

TABLE III

RESULTS OF CORRELATIONS

| Set | | $\rho^a$ | $r^b$ | $s^c$ | $t^d$ | $Q_H$ | $n^e$ |
|---|---|---|---|---|---|---|---|
| 1 | I | −4.013 | 0.984 | 0.215 | 12.37$^f$ | 4.39 | 7 |
| | *m* | −4.247 | 0.984 | 0.212 | 12.53$^f$ | 4.27 | |
| | *p* | −3.402 | 0.874 | 0.586 | 4.024$^g$ | 3.92 | |
| 2 | I | −3.927 | 0.968 | 0.270 | 7.685$^g$ | 3.77 | 6 |
| | *m* | −4.420 | 0.966 | 0.277 | 7.486$^g$ | 3.70 | |
| | *p* | −4.814 | 0.889 | 0.492 | 3.880$^h$ | 3.32 | |
| 3 | I | −2.915 | 0.900 | 0.376 | 4.607$^g$ | 4.64 | 7 |
| | *m* | −3.762 | 0.957 | 0.251 | 7.349$^f$ | 4.64 | |
| | *p* | −4.54 | 0.936 | 0.303 | 5.954$^g$ | 4.26 | |
| 4 | I | −2.930 | 0.912 | 0.394 | 3.849$^i$ | 4.65 | 5 |
| | *m* | −2.703 | 0.909 | 0.400 | 3.771$^i$ | 4.62 | |
| | *p* | −2.142 | 0.873 | 0.468 | 3.098$^j$ | 4.53 | |
| 5 | I | −3.652 | 0.766 | 0.532 | 2.669$^i$ | 4.12 | 7 |
| | *m* | −3.344 | 0.939 | 0.286 | 6.082$^g$ | 3.51 | |
| | *p* | −2.484 | 0.771 | 0.527 | 2.707$^i$ | 2.70 | |
| 6 | I | −1.507 | 0.736 | 0.220 | 2.665$^i$ | 4.83 | 8 |
| | *m* | −1.310 | 0.879 | 0.155 | 4.506$^g$ | 4.61 | |
| | *p* | −0.723 | 0.627 | 0.253 | 1.970$^j$ | 4.41 | |
| 7 | I | −0.536 | 0.399 | 0.260 | 0.616$^k$ | 4.75 | 4 |
| | *m* | −0.791 | 0.841 | 0.154 | 2.195$^k$ | 4.64 | |
| | *p* | −0.500 | 0.620 | 0.223 | 1.117$^k$ | 4.50 | |
| 8 | I | −0.883 | 0.709 | 0.177 | 1.742$^k$ | 4.85 | 5 |
| | *m* | −0.741 | 0.818 | 0.144 | 2.467$^j$ | 4.70 | |
| | *p* | −0.515 | 0.652 | 0.190 | 1.491$^k$ | 4.53 | |
| 9a | I | −2.120 | 0.942 | 0.126 | 4.843$^h$ | 3.11 | 5 |
| | *m* | −2.374 | 0.924 | 0.143 | 4.185$^i$ | 3.03 | |
| | *p* | −2.601 | 0.952 | 0.115 | 5.370$^h$ | 2.80 | |
| 9b | I | −2.146 | 0.930 | 0.119 | 5.065$^g$ | 3.09 | 6 |
| | *m* | −2.368 | 0.923 | 0.125 | 4.795$^g$ | 3.03 | |
| | *p* | −2.398 | 0.914 | 0.132 | 4.499$^h$ | 2.85 | |
| 10 | I | −3.115 | 0.986 | 0.217 | 5.823$^k$ | 4.28 | 3 |
| | *m* | −4.435 | 0.977 | 0.326 | 4.576$^k$ | 4.19 | |
| | *p* | −3.942 | 0.866 | 0.641 | 1.732$^k$ | 3.92 | |
| 11a | I | −3.267 | 0.99866 | 0.0686 | 19.32$^i$ | 4.75 | 3 |
| | *m* | −3.947 | 0.99998 | 0.00887 | 149.7$^g$ | 4.69 | |
| | *p* | −4.499 | 0.955 | 0.395 | 3.211$^k$ | 4.34 | |
| 11b | I | −3.208 | 0.996 | 0.0801 | 16.86$^g$ | 4.72 | 4 |
| | *m* | −3.895 | 0.999 | 0.0498 | 27.21$^g$ | 4.67 | |
| | *p* | −4.551 | 0.952 | 0.293 | 4.407$^i$ | 4.42 | |

[a] The negative sign of these $\rho$-values is due to the correlations being made with the p$K_a$ values. For comparison with other $\rho$-values, the signs should be changed. [b] Correlation coefficient. [c] Standard deviation. [d] "Student t" test. [e] Number of points in the set. [f] 99.9% significance level (s.l.). [g] 99% s.l. [h] 98% s.l. [i] 95% s.l. [j] 90% s.l. [k] Less than 90% s.l.

acids (3) the results obtained with $\sigma_m$ are significantly better than those obtained with $\sigma_I$. For the correlations with $\sigma_m$, sets 1 and 3 give results significant at the 99.9% confidence level, set 2 at the 99% confidence level, and set 4 at the 95% confidence level.

It is possible on the basis of sets 10 and 11 to make a tentative assignment of configuration to the $\alpha$-arsonocrotonic acid reported by Backer and Van Oosten.[8] Calculation of the p$K_a$ for the *cis* and *trans* acids using $\sigma_m$ gives 4.19 and 4.69, respectively, for p$K_2$. The reported value of p$K_2$ is 4.61. Thus it seems likely that this compound has the *trans* configuration. Inclusion of this p$K_a$ in the correlation gives set 11b of Table III. The correlation with $\sigma_m$ is significant at the 99% confidence level.

**Heterovinylidene Sets.**—All of the substituted carbonyl sets (5–8) give best correlation with $\sigma_m$. The substituted oximino set (9) is well correlated by both $\sigma_I$ and $\sigma_m$. For the correlations with $\sigma_m$, sets 5 and 6 give results significant at the 99% confidence level; 9b, at the 99% confidence level. Sets 6, 7 and 8 give poor correlation. This is probably due to the low sensitivity of these sets to substituent effects. With the exception of the value for X = O$^-$, the p$K_a$ values in these sets are all within a range of 0.2 p$K_a$ units; they are probably not known to better than ±0.1 p$K_a$ unit. Thus, no conclusion can be drawn from these sets.

The configuration of the oximinocarboxylic acids are those given by Ahmad and Spenser[9] with the exception of oximinoacetic acid (X = H). The assignment of the *anti* configuration to oximinoacetic acid is based on the fact that correlation of this set with the exclusion (9a) and inclusion (9b) of the p$K_a$ or X = H (for the acid, m.p. 137–140°) gave essentially the same results. The *syn* acid should have a significantly different p$K_a$ from that of the *trans* acid. Inclusion of its p$K_a$ in the correlation should therefore result in significantly decreased correlation. Furthermore, the p$K_{a,H}$ values calculated for series 9a are in good agreement with the p$K_a$ measured for oximinoacetic acid (m.p. 137–140°).

## Discussion

**Nature of the Electrical Effect.**—The $\sigma_m$-constants give significantly better results than $\sigma_I$ in sets 3, 5, and 6 and results which are not significantly different from those obtained with $\sigma_I$ in sets 1, 2, 4, and 9. They are therefore preferred for the correlation of vinylidene and heterovinylidene sets. This is in accord with the observation that dipole moments of vinylidene sets are best correlated by $\sigma_m$.[10] Furthermore, in the correlation of $\sigma_m$-cox and $\sigma_p$-cox with eq. 2,[11] best results were

$$\sigma_{\mathrm{COX}} = m\sigma_{\mathrm{X}} + c \qquad (2)$$

obtained with $\sigma_{m\text{-X}}$. These results suggest that there is a small but significant resonance contribution to the electrical effect of a vinylidene substituent. The overall electrical effect of a substituent may be represented as eq. 3,[12] where $\lambda$ is the coefficient of the localized

$$\sigma_{\mathrm{T}} = \lambda\sigma_{\mathrm{I}} + \delta\sigma_{\mathrm{R}} \qquad (3)$$

electrical effect represented by $\sigma_I$ and $\delta$ is the coefficient of the delocalized electrical effect represented by $\sigma_R$. We may define [13]

$$\epsilon = \frac{\delta}{\lambda} \qquad (4)$$

where $\epsilon$ is the ratio of localized to delocalized effects and is therefore characteristic of the nature of the electrical effect of a substituent. Values of $\epsilon$ are given in Table IV.

TABLE IV

VALUES OF $\epsilon$

| Substituent constant | $\epsilon^a$ |
|---|---|
| $\sigma_I$ | 0 |
| $\sigma_m$ | 0.3 to 0.5 |
| $\sigma_p$ | 1 |
| $\sigma_0$ | 1 |
| $\sigma_p^+$ | 1.73$^b$ |

[a] See ref. 13. [b] From $\sigma_{R^+} = 1.73\sigma_R - 0.04$; see also C. N. R. Rao and G. K. Goldman, *Can. J. Chem.*, **36**, 1596 (1958).

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(8) H. J. Backer and R. P. VanOosten, *Rec. trav. chim.*, **59**, 41 (1940).

(9) A. Ahmad and I. D. Spenser, *Can. J. Chem.*, **39**, 1340 (1961).

(10) M. Charton, Abstracts, 141st National Meeting of the American Chemical Society, Washington, D. C., March 1962, p. 47R.

(11) M. Charton, *J. Org. Chem.*, **28**, 3121 (1963).

(12) R. W. Taft, Jr., and I. C. Lewis, *J. Am. Chem. Soc.*, **80**, 2436 (1958).

(13) M. Charton, *ibid.*, **86**, 2033 (1964).

**Transmission of Substituent Effect.**—We may write the structure of any set in the form XGY where X is the substituent, Y, the reaction site (if any), and G, the group to which X and Y are attached. The transmission of substituent effects may now be described by eq. 5[4,5] where $\rho_G$ is the reaction constant for the group

$$\gamma = \frac{\rho_G}{\rho_{G^\circ}} \qquad (5)$$

G under consideration, undergoing some reaction under specified conditions, and $\rho_{G^\circ}$ is the reaction constant for the reference group G° undergoing the same reaction under the same conditions. Some values of $\gamma$ for groups G requiring the use of $\sigma_m$ in correlations are given in Table V.

TABLE V

VALUES OF $\gamma$

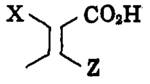
| G | $\gamma$ | G | $\gamma$ |
|---|---|---|---|
| *m*-Phenylene | 1.00[a] | Carbonylmethyl | 3.34[c] |
| *trans*-Cyclopropylene | 1.97[b] | *trans*-Vinylene | 2.23[b] |
| Vinylidene | 4.25[c] | Ethynylene | 1.89[b] |
| Oximino | 2.37[c] | Cyclopropylidene | 5.36[b] |

[a] $\rho_{G^\circ}$ is for the ionization of benzoic acids in water at 25°. [b] See ref. 5. [c] This work.

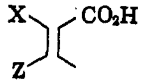
The value of $\gamma$ for the oximino group is strikingly less than that for the vinylidene group. Unfortunately, no direct comparison can be made with the carbonyl group, as hydration of the carbonyl group in substituted carbonyl carboxylic acids apparently is quite extensive. Thus in these compounds the measured ionization constant is a composite. Presumably, however, $\gamma$ of the carbonyl group will be greater than or at least the same magnitude as the value of $\gamma$ for the carbonylmethyl group.

The vinylidene group is very much more sensitive to substituent effects than is the *trans*-vinylene group as is shown by their $\gamma$-values of 4.25 and 2.23, respectively. This is in accord with the molecular geometry of the two groups.

**Effect of Constant Substituents.**—A comparison of $\rho$-values for sets bearing the same constant substituent but differing in configuration (IVa,b) is of interest.



IVa



IVb

We may compare the sensitivity of the two configurations to substituent effects by means of the ratio below.

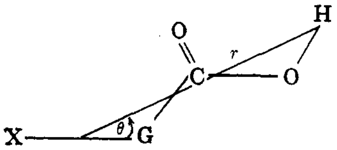
$$q = \frac{\rho_{cis}}{\rho_{trans}} \qquad (6)$$

Values of $q$ are given in Table VI. To provide an additional value of $q$, $\rho$-values for the short sets *cis*- and *trans*-2-substituted crotonic acids (10, 11) were evaluated. The data used are given in Table I; the results are in Table III. The available values of $q$ both show the *cis* configuration to be more sensitive to vinylidene substituent effects. This may be due to a decrease in the X-C-1-C-2 bond angle and/or a rotation of the $CO_2H$ group out of the plane of the double bond. Either or both of these phenomena would affect the distance $r$ and angle $\theta$ which determine the magnitude of $\rho$(V).[14]

TABLE VI

VALUES OF $q$

| Z | $\rho_{cis}$ | $\rho_{trans}$ | $q$ |
|---|---|---|---|
| Ph | −4.42 | −3.76 | 1.2 |
| Me | −4.43 | −3.95 | 1.1 |



V

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[14] M. Charton, Abstracts, 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April 1960, p. 92O; Abstracts, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 961, p. 57T.

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# Studies on Methylglyoxal Bis(guanylhydrazone)[1] Analogs. IV. Acetylation Studies[2]

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Acetylation of methylglyoxal bis(guanylhydrazone) (I) has been studied. The diacetylated derivative was prepared by the reaction of ketene with I. The structure of this product was confirmed by an alternate and unambiguous synthetic method using methylglyoxal dihydrazone and S-methylacetylthiourea hydroiodide. The tetraacetylated derivative of I was prepared by the reaction of I with either acetic anhydride or ketene, and its structure was substantiated with the aid of n.m.r. studies.

Since the discovery of the antileukemia activity of methylglyoxal bis(guanylhydrazone)[3] (I), a systematic investigation of compounds related to I has been undertaken in our laboratories.[4] One phase of the study centered about the preparation of acylated derivatives of I, which by alteration of the polarity of the molecule

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[1] The *Chemical Abstracts* name for this compound is 1,1′-[(methyl)-ethanediylidenedinitrilo]diguanidine.

[2] This investigation is supported by the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service, Contract SA-43-ph-3025.

[3] (a) B. L. Freedlander and F. A. French, *Cancer Res.*, **18**, 360 (1958); (b) F. Freireich and E. Frei, III, *Proc. Am. Assoc. Cancer Res.*, **3**, 319 (1962).

[4] (a) E. G. Podrebarac, W. H. Nyberg, F. A. French, and C. C. Cheng, *J. Med. Chem.*, **6**, 283 (1963); (b) F. Baiocchi, C. C. Cheng, W. J. Haggerty, Jr., L. R. Lewis, T. K. Liao, W. H. Nyberg, D. E. O'Brien, and E. G, Podrebarac, *ibid.*, **6**, 431 (1963); (c) E. G. Podrebarac and C. C. Cheng. *ibid.*, **7**, 806 (1964).