stirring for 80 hours. The reaction complex was hydrolyzed by dropwise addition with vigorous stirring of 28.8 ml. of water, followed by 39.5 ml. of concentrated hydrochloric acid. The ether filtrate was evaporated to give 10.5 Gm. of an oily semisolid. Repeated recrystallization of this residue from mixtures of benzene and petroleum ether gave 2 Gm. of white crystals. m.p. 69–70°. Chemical analysis indicated that this compound was benzyl disulfide. Comparison to an authentic specimen showed identical infrared spectrum and no depression of melting point.

In a subsequent identical run, during the evaporation of the ether solution to dryness, the escaping gases were passed through a trap containing hydrochloric acid. Evaporation of the solution from this trap left a residue of 4.5 Gm., m.p. 95–105°. Re-

crystallization from ethanol-ether mixtures gave 2.5 Gm. (28%) of ethylamine hydrochloride, m.p. 108–109°. This is in agreement with the known melting point of 109° (5). Conversion to the benzamide derivative gave a product which melted at 68–69°, in agreement with the previously reported melting point for N-ethylbenzamide of 69° (6).

### REFERENCES

(1) McCarthy, W. C., and Ho, B. T., J. Org. Chem., 26, 4110(1961).
(2) Leonard, N. J., Leubner, C. W., and Burk, E. H., Jr., ibid., 15, 979(1950).
(3) Bhat, K. V., and McCarthy, W. C., THIS JOURNAL, in press.
(4) Heacock, R. A., Hutzinger, O., and Nerenberg, C., Can. J. Chem., 39, 1143(1961).
(5) Raiford, L. C., and Ravely, M. F., J. Org. Chem., 5, 204 (1940).
(6) Reid, E. E., Am. Chem. J., 45, 38(1911).

# Use of Hammett Graphs in Stability Programs

## By J. THURØ CARSTENSEN, E. G. SERENSON, and J. J. VANCE

HAMMETT GRAPHS have been used for many years by organic and physical chemists, primarily for elucidation of reaction mechanisms.

Research programs involving the screening of a host of related compounds may benefit from this sort of approach. By establishing a few pKa values and rate constants, rapid estimates of degradation rates of new compounds can be made simply by a pKa measurement. The advantage of this in pharmaceutical formulation is quite obvious.

The condition that a linear relationship holds (1, 8) is that the entropy of reaction is either zero or is the same for all the hydrolyses (or whatever reaction is pertinent) or that $\Delta H$ and $\Delta S$ be linearly related.

In general, the substituent parameter is referred to as $\sigma$, and the reaction parameter as $\rho$; the latter in particular is useful in deducing the actual reaction mechanism. Substituent $\sigma$ values and reaction $\rho$ values are abundantly reported in the literature (1).

The authors have exemplified the utility of this sort of approach by a study of a series of allylbarbituric acids.

The materials used in this study were obtained by suitable extraction from commercially available dosage forms in the case of talbutal and secobarbital. 5-Allyl-5(2-cyclopenten-1-yl) barbituric acid,[1] itobarbital,[2] and allobarbital[3] were obtained from suppliers. Unsubstituted allylbarbituric acid was synthesized according to the method of Arnold et al. (2) and Johnson and Hill (3).

Experimentally, samples were prepared by dissolving 250 mg. of barbiturate in form of the acid in 50 ml. of 95% ethanol. This was then diluted 1:50 with a borate buffer of the following composi-

tion: 0.97 Gm. of boric acid, 1.15 Gm. of potassium chloride, 344 ml. of 0.1 N sodium hydroxide and adjusted to 1000 ml. with distilled water, yielding a final pH of 11.8.

Ampuls of these solutions were stored at 85° and assayed at six storage times. The decrease in barbiturate was determined by a decrease in absorbance at the peak wavelength (240–242 mμ) after suitable dilution with the described borate buffer. Pseudo first-order rate constants (hours⁻¹) are denoted k in Fig. 1 and Table I.

The pKa's of the barbiturates were determined spectrophotometrically. pKa° and $k_o$ in the following refer to the unsubstituted allylbarbituric acid.

In a more formal treatment (4, 5, 7, 9, 10), the reaction constant is calculated from substituent constants based on dissociation constants in water. The $\sigma$-constants as defined here hence refer to the dissociation constants relative to the dissociation of unsubstituted allylbarbituric acid. Statistical im-
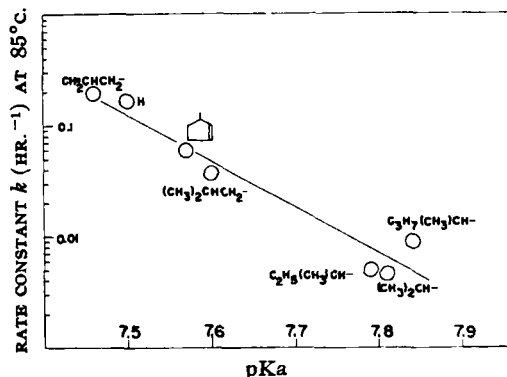
Fig. 1.—Form in which rate constants can most conveniently be calculated for an unknown substance with known pKa with previous knowledge of rate constant and pKa of compounds related to the substance in question. [Brønsted plot (11).]

### TABLE I.—HYDROLYSIS DATA AT 85° C.
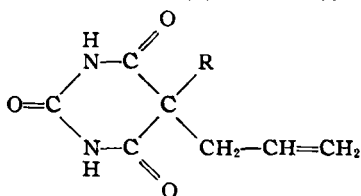


| R | 5-Substituent | Generic Name | Hydrolysis Rate Constant at 85°C. $k$ (Hr. $^{-1}$) | $k/k_o$ | pKa | pKa° − pKa |
|---|---|---|---|---|---|---|
| H | | | 0.168 | | 7.50 | |
| $C_5H_7{}^-$ | Cyclopentenyl | None[a] | 0.10 | 0.595 | 7.57 | −0.07 |
| $C_2H_5CH(CH_3)-$ | sec-Butyl | Talbutal | 0.0050 | 0.030 | 7.79 | −0.29 |
| $C_3H_7CH(CH_3)-$ | 1-Methylbutyl | Secobarbital | 0.0092 | 0.054 | 7.84 | −0.34 |
| $(CH_3)_2CH-$ | Isopropyl | Aprobarbital | 0.0046 | 0.028 | 7.81 | −0.31 |
| $CH_2=CHCH_2{}^-$ | Allyl | Allobarbital | 0.198 | 1.180 | 7.46 | +0.04 |
| $(CH_3)_2CHCH_2-$ | Isobutyl | Itobarbital | 0.037 | 0.220 | 7.60 | −0.10 |

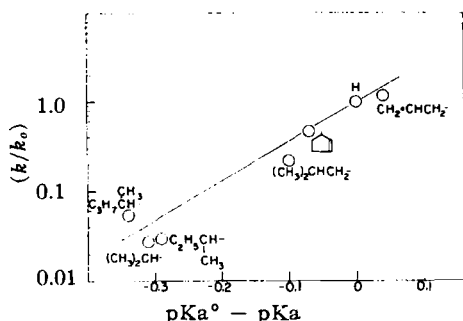[a] Chemical name: 5-allyl-5-(2-cyclopenten-l-yl) barbituric acid.



Fig. 2.—Semilogarithmic plot of $k/k_o$ vs. pKa° − pKa. (See text for notation.)

provement (7) over this is accomplished by the (confined) least-square relationship

$$\log k/k_o = 4.47 \log K_a/K_a°$$

derived from Fig. 2 and then obtaining individual $\sigma$'s from $\log k/k_o = \sigma \cdot \rho = 4.47 \ \sigma$. Values calculated in this manner are listed as $\sigma_B$ in Table II. Substituent values have been reported in the previous literature for only three of the six substituents tested here. Previously published $\sigma$ values are predominantly for substituents in aryl (10) and alkyl (10, 11) compounds in a variety of reactions, and some values are listed in Table II (with references) for comparison purposes.

Actual reaction mechanisms of the barbiturate hydrolysis have not been dealt with here; the primary scope of this report has been stability prediction.

### TABLE II.—SUBSTITUENT SIGMA VALUES

| Substituent | $\sigma_B$ | | Ref. |
|---|---|---|---|
| $(CH_3)_2CH-$ | −0.35 | $\sigma_+ = -0.151$ | (7) |
| | | $\sigma_p = -0.280$ | (6) |
| $C_5H_7-$ | −0.05 | | |
| $CH_2=CH-$ | | | |
| $CH_2-$ | +0.02 | | |
| $(CH_3)_2CHCH_2-$ | −0.15 | $\sigma = -0.115$ | (6) |
| $C_3H_7CH(CH_3)-$ | −0.28 | | |
| $C_2H_5CH(CH_3)-$ | −0.34 | $\sigma = -0.123$ | (6) |
| | | $\sigma = -0.983$ | (10) |

### REFERENCES

(1) Wells, P. R., *Chem. Rev.*, **63**, 171(1963).
(2) Arnold, R., De Moura Campos, M., and Lindsay, K., *J. Am. Chem. Soc.*, **75**, 1046(1953).
(3) Johnson, T., and Hill, A., *Am. Chem. J.*, **46**, 540 (1911).
(4) Van Bekkum, H., Verkade, P., and Wepster, B., *Rec. Trav. Chim.*, **78**, 815(1959).
(5) Okamoto, Y., and Brown, H. C., *J. Org. Chem.*, **22**, 485(1957).
(6) Jaffé, H., *Chem. Rev.*, **53**, 191(1953).
(7) Brown, H. C., and Okamoto, Y., *J. Am. Chem. Soc.*, **80**, 4979(1958).
(8) Hammett, L., *J. Chem. Phys.*, **4**, 613(1936).
(9) Garrett, E., THIS JOURNAL, **51**, 811(1962).
(10) Portoghese, P., and Malspeis, L., *ibid.*, **50**, 494(1961).
(11) Brønsted, J., and Pedersen, K., *Z. Phys. Chem.*, **108**, 185(1924).