[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

The Difference between the Hammett Equation as Applied to *meta* and *para* Substituted Compounds[1]

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In 336 reaction series of *m*- and *p*-substituted benzene derivatives for which appropriate data were available, separate Hammett correlations for the two types of compounds have been performed. The number of series for which the ρ-values are *significantly* different is larger than expected purely by chance, although no significant differences appear for 75 to 85% of the series examined. Similarly no major differences are demonstrated in the precision with which *m*- and *p*-substituted compounds are represented by the Hammett equation.

In a recent paper, Hine[2] has outlined a theoretical analysis, suggesting that the Hammett equation cannot possibly have general validity. One of the major conclusions of Hine's arguments was that, even within the range of approximate validity of the Hammett equation, reaction constants (ρ) cannot be expected to be the same for *meta* and *para* substituents. It appeared of interest to test this conclusion. We have consequently run separate correlations on *m*- and *p*-substituted compounds[3] for the 336 reaction series for which we had available for at least 3 substituents in each of the two groups. In each series, normal σ-, σ^+- or σ^--values were used in accordance with the standard criteria for choosing the appropriate constants. In the few cases where there was serious doubt from chemical information as to which type of σ should be applicable, the choice was made so as to obtain the best fit. Polysubstituted compounds, compounds in which the substituent is a fused ring system, a heteroatom or has ionic character have been disregarded.

Two tests of differences in the correlations were made. The first test was a simple *t*-test,[4] in which ρ_p-ρ_m was tested against the mean of their standard deviations. Assuming that ρ_p and ρ_m are estimates of the same quantity, and that the same is true of their standard deviations (s_ρ) this test is valid and would be expected to lead to differences significant at the 95% level in about 5% of the cases, to difference significant at the 99% level in about 1% of the cases. The results of the application of this test are shown in Table I, where it is seen that the proportion of significant differences encountered greatly exceeds the number expected to occur by chance. The same table gives a breakdown into the groups in which the different types of σ-values are used, and the proportion of significant differences exceeds the statistically expected value in each of these groups. Consequently it must be concluded that the above assumptions are not valid, and that there are significant differences between either ρ_p and ρ_m or between their standard deviations, or more probably both.

TABLE I

THE NUMBER OF REACTION SERIES SHOWING DIFFERENCE BETWEEN ρ_m AND ρ_p

Applicable σ	Number of series	Difference significant at	Percentage showing significant difference by *t*-Test	*F*-Test
Normal σ	220	95%	26	18
		99%	17	8
σ^-	64	95%	36	11
		99%	22	5
σ^+	52	95%	15	6
		99%	13	4
All	336	95%	24	15
		99%	17	7

The second test was a standard *F*-test.[4] The sum (S) of the sum of squares of deviations from regression for the separate *meta* and *para* lines was subtracted from the corresponding value for the total regression (combining all data), and the difference, involving two degrees of freedom, was tested against S (with $n - 4$ degrees of freedom). This procedure tests whether the separate correlations produce a *significant* improvement over the single correlation. Such improvement could occur because of differences between ρ_p and ρ_m, or because of differences between intercepts ($\log k^\circ_{\text{calc}}$), and does not distinguish between these alternatives. The results, shown in Table I, again clearly indicate that significant differences occur for each of the 3 groups, far in excess of the number expected on the basis of chance.

A further observation is worthy of note. If the number of significant differences observed occurred as a matter of chance alone, one would expect the figures at the 99% level to be approximately one-fifth of those at the 95% level. This ratio is quite clearly not found, even approximately. This finding suggests that there is a small but significant number of series for which there is quite a serious difference between the two reaction constants, while there are relatively few series with an intermediate difference.

It is also apparent from Table I that the *t*-test, which simultaneously tests for differences in ρ and in s_ρ, the number of deviations, is considerably larger than in the *F*-test, which tests for differences in ρ and $\log k^\circ$. It appears likely that the *F*-test results represent mostly differences in ρ's rather than in $\log k^\circ$, and the difference between the two results is a lower limit to the number of series in which the differences in s_ρ is significant.

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(1) This work was supported by the Office of Ordnance Research, U. S. Army.

(2) J. Hine, THIS JOURNAL, **81**, 1126 (1959); the author is indebted to Dr. Hine for allowing him to see a copy of his paper prior to publication.

(3) For this purpose the unsubstituted compound has been included with the *m*-substituted compounds, both because of a matter of computational convenience, and because in some of the instances cited by Hine, in which differences between *meta* and *para* Hammett fits have previously been observed, the unsubstituted compound seemed to fit in best with the *m*-substituted groups.

(4) G. W. Snedecor, "Statistical Methods," 4th Ed., Iowa State College Press, Ames, Ia., 1946.

This finding suggests an examination of the differences in s_ρ. Accordingly the relative magnitudes of s_ρ (*i.e.*, s_ρ/ρ) were compared for the *meta* and *para* groups of each series. The number of series for which the relative value of s_ρ/ρ for the *meta* series was appreciably larger, appreciably smaller and approximately equal to the value for the *para* series were counted, and the results of these counts are presented in Table II. It is apparent that there is no significantly better overall precision in either series.

TABLE II

COMPARISON OF THE PRECISION OF THE HAMMETT EQUATION APPLIED SEPARATELY TO m- AND p-SUBSTITUTED COMPOUNDS (ENTRIES ARE NUMBERS OF SERIES)

	$s_\rho/\rho(meta)$ — $s_\rho/\rho(para)$			$r_{meta} - r_{para}$				
Applicable σ	>1	~ 1	<1	>0.15	$\sim 0.1^a$	~ 0	~ -0.1	<-0.15
Normal								
σ	93	9	118	68	31	32	28	61
σ^-	31	3	30	18	10	13	12	11
σ^+	21	1	30	22	4	9	6	11
Total	145	13	178	108	45	54	46	83

It was further tested whether, in the series showing significant differences by the t-test, a systematic difference between the two types of series could be shown. Similar counts were made for the series with significant t-tests, and those with significant t- but non-significant F-tests. Whereas it appears that the number of series for which s_ρ/ρ (*meta*) is larger than s_ρ/ρ (*para*) is slightly larger than the number of series for which this relation is the reverse, there is no drastic difference in these numbers.

A further test of the comparative precision of the two types of series is provided by a comparison of the two types of series is provided by a comparison of the correlation coefficients. Again counts for different ranges of r_{meta} - r_{para} are shown in Table II, and indicate no systematic differences in the precision attainable with *meta* or *para* compounds.

Thus it is evident that Hine's conclusion that ρ_{p} and ρ_{m} need not be measures of the same quantity is borne out statistically. This conclusion does not, however, detract greatly from the usefulness of the Hammett equation. Table I shows that, in the majority of the cases (75 to 85%, depending on the criterion chosen), *no* significant difference exists between ρ_{p} and ρ_{m} and between the intercepts. The differences that are encountered are generally quite small. Considering the approximate and empirical nature of the Hammett equation, this new limitation pointed out by Hine does not appear serious.

Calculations.—The calculations were performed on an IBM 650 MDDPM by a modification of a program now in use in this Laboratory.[5] The changes in the program consisted of successively reading the data, comparing series identification, letting the computer determine whether the substituent was a fused ring system or a heteroatom (identification number between 800 and 999, 3800 and 3999, 6800 and 6999), in which case the piece of data was by-passed, and then whether the identification number was even (*meta*) or odd (*para*). Data (σ and log k), and their squares and cross-products were accumulated separately. Since the identification number for the unsubstituted compounds is 000, they were automatically included in the *meta* series. When all data for one series were read, the computer checked whether $n \geqslant 3$ for both *meta* and *para* series. If either $n <$ 3, no further work was done, but the computer proceeded automatically to the next series. If both $n \geqslant 3$, the standard program calculated the straight lines for both the *meta* and *para* series, and punched identification, ρ, s_ρ, r, S, Sy^2 and n. Then the sums, and sums of squares and cross-products for the two partial series were added together, and the total regression was performed.

The t- and F-tests were also made by the computer, using a small separate program. This program reads 3 cards (the output from the previous program for the *meta*, *para* and total series), compares identifications to ensure that cards are in order, calculates $\rho_{\text{p}} - \rho_{\text{m}}$, the average of the two s_ρ and makes the t-test. It further computes S(*meta*) and S(*para*) − S(total), divides by Sd^2(*meta*) and Sd^2(*para*), multiples the result by [n(total)-4]/2, and makes the F-test. The tests are made by comparing the values of t and F so calculated with values stored in a table on the drum of the computer. The results of the tests are punched, with the ρ-difference, the average of s_ρ, and the calculated F on a card carrying the series identification. Beyond these calculations all counts were made by hand.

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[5] H. H. Jaffé, Technical Report No. 10 to the Office of Ordnance Research. A limited number of copies of this report are available for distribution by the author.

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p-Cyanophenylphosphonic Acid and Related Compounds[1]

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p-Cyanophenylphosphonic acid has been prepared from p-cyanobenzenediazonium fluoborate by the diazo reaction and from p-aminophenylphosphonic acid by the Sandmeyer reaction. Reduction with lithium aluminum hydride gives p-α-aminotolylphosphonic acid, the phosphonic acid analog of Marfanil. p-Amidinophenylphosphonic acid was prepared through the imino ethyl ether. Neither the amino nor amidino compounds possessed significant antibacterial activity against three species of microörganisms.

The marked activity of p-aminophenylphosphonic (phosphanilic) acid against a number of pathogenic microörganisms *in vitro*[2] has prompted us to undertake the preparation of p-α-aminotolylphosphonic acid, the phosphonic acid analog of Marfanil. Marathe, Limaye and Bhide have previously attempted the preparation of this compound.[3] They were unable to prepare the

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[1] Presented at the Southeastern Regional Meeting of the American Chemical Society, Durham, N. C., November, 1957.

[2] J. D. Thayer, H. J. Magnuson and M. S. Gravatt, *Antibiotics & Chemotherapy*, **3**, 256 (1953).

[3] K. G. Marathe, N. S. Limaye and B. V. Bhide, *J. Sci. Ind. Research (India)*, **9B**, 268 (1950).