from various mercaptans. Their value agrees fairly well with the value of 32(±4) kcal /mole for $\Delta H_f(\text{SH})$ determined in these laboratories,[3] especially if, as pointed out by them, the heats of formation of radicals obtained by the electron impact method tend to be rather high. Since

$$D(\text{H–SH}) = D_1 = \Delta H_f(\text{H}) + \Delta H_f(\text{SH}) - \Delta H_f(\text{H}_2\text{S}) \quad (1)$$

and the values for $\Delta H_f(\text{H}) = 52$ kcal./gram atom and for $\Delta H_f(\text{H}_2\text{S}) = -4.8$ kcal./mole are well established[4a,b] it is now possible to calculate in terms of the above values for $\Delta H_f(\text{SH})$ the dissociation energy, $D(\text{H–SH})$, of the first bond in H_2S (denoted by D_1) at 95(±5) or 89(±4) kcal./mole, respectively.

Furthermore, the dissociation energy $D(\text{S–H})$ of the second bond in H_2S (denoted by D_2) can be calculated by the similar expression

$$D(\text{S–H}) = D_2 = \Delta H_f(\text{S}) + \Delta H_f(\text{H}) - \Delta H_f(\text{SH}) \quad (2)$$

Unfortunately, it is impossible at present to decide on one particular value for D_2 since in equation (2) $\Delta H_f(\text{S})$ may have one of three values 53.5, 57 or 66.5 kcal./mole[5] depending on the choice of one of the three possible values of 76, 83 or 102.5 kcal./mole for $D(\text{S–S})$ in S_2.[6] Hence, D_2 can be 67, 70.5 or 80 kcal./mole on the basis of Franklin and Lumpkin's value for $\Delta H_f(\text{SH})$ or 73.5, 77 or 86.5 kcal./mole on the basis of our value for $\Delta H_f(\text{SH})$.

By adding equations (1) and (2) it follows that the sum of the two S–H dissociation energies in H_2S can vary between 162 and 175 kcal./mole depending on whether $D(\text{S–S})$ is taken as 76 or 102.5 kcal./mole. The uncertainty in choosing a particular value for $D(\text{S–S})$ is due to the difficulty of interpreting unambiguously the spectrum of S_2. However, Gaydon[6] after analyzing all relevant data is inclined to favor the highest value. From recent interpretations of the S–H spectrum Porter[7] and Ramsay[8] deduce values of 85 and 83 kcal./mole, respectively, for D_2. These, in conjunction with the values given above for D_1 support also the highest value for $D(\text{S–S})$.

Franklin and Lumpkin disagree with Porter's value for D_2 and suggest instead a value of 67 kcal./mole. Since the sum of their values for D_1 and D_2, respectively, 95 and 67 kcal./mole, is 162 kcal./mole it appears that they tacitly assumed the lowest value for $D(\text{S–S})$. Indeed, an analysis of their results indicates that they used this value throughout their calculations. They argue that if Porter's value of 85 kcal./mole for D_2 is correct then D_1 must be 77 kcal./mole, *i.e.*, D_1 would then be smaller than D_2, which is contrary to what one would expect by comparison with the corresponding bond strengths in H_2O. It seems, therefore, that their arbitrary choice of the lowest value for $D(\text{S–S})$ is the only reason for their disagreeing with Porter's value for D_2. Surprisingly, however, in spite of their method of calculation they suggest that on general chemical grounds the highest value for $D(\text{S–S})$ appears to be the correct one.

Thus if $D(\text{S–S})$ is, indeed, 102.5 kcal./mole then the sum of the two dissociation energies in H_2S is 175 kcal./mole, and since a value of ~90 kcal./mole for D_1 is supported by both electron impact and pyrolytic methods, D_2 will be ~85 kcal./mole, which is in reasonable agreement with Porter's and Ramsay's values obtained spectroscopically. A final settlement of this point can only be reached by an unambiguous determination of $D(\text{S–S})$ or $\Delta H_f(\text{S})$.

Note: Franklin and Lumpkin give $D(\text{HS–SH}) = 80.4$ kcal./mole, a value, which was presumably obtained by them by using in their calculations $\Delta H_f(\text{H}_2\text{S}_2)_{\text{liq}} = -3.6$ kcal./mole instead of $\Delta H_f(\text{H}_2\text{S}_2)_{\text{g}}$, as required. Since the heat of vaporization of H_2S_2 is probably ~8 kcal./mole, it follows that $D(\text{HS–SH})$, based on their value for $\Delta H_f(\text{SH})$, should have actually been 72.4 kcal./mole. On the other hand on the basis of our value for $\Delta H_f(\text{SH})$ $D(\text{HS–SH})$ is 59.6 kcal./mole, a value which is comparable with $D(\text{HO–OH})$ of 54 kcal./mole.[9]

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[3] This value has been calculated by using the data of our determination of $D(\text{CH}_3\text{–SH})$ by the "toluene-carrier" technique [A. H. Sehon and B. deB. Darwent, A. C. S. Meeting, Buffalo, March, 1952. A full account will be published shortly].

[4] (a) Selected Values of Chemical and Thermodynamic Properties, N. B. S., Washington, 1947; (b) K. K. Kelley, U. S. Dept. of Interior, Bureau of Mines, Bulletin 406 (1937).

[5] Since $[\Delta H_f(\text{S}) = (\Delta H_f(\text{S}_2)_g + D(\text{S–S})]/2$ where $\Delta H_f(\text{S}_2)_g = 30.80$ kcal./mole. [W. H. Evans and D. D. Wagman, Natl., Bur. Standards, Report No. 1037, Washington, 1951.]

[6] A. G. Gaydon, "Dissociation Energies and Spectra of Diatomic Molecules," Chapman and Hall, Ltd., London, 1947.

[7] G. Porter, *Discussion Faraday Soc.*, **81**, 60 (1950).

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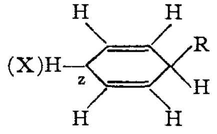
Quantum Mechanical Calculations of Orientation in Aromatic Substitution[1]

BY JOHN D. ROBERTS AND ANDREW STREITWIESER, JR.[2]

RECEIVED MARCH 11, 1952

Wheland[3] has shown definitely that the molecular orbital method makes possible a single unified treatment of electrophilic, free-radical and nucleophilic substitution reactions of aromatic molecules. His approach was based on calculations of the energies of activated complexes of type I where z is a unit positive charge, an unpaired electron or a unit negative charge depending on whether the attacking reagent (R) is an electrophilic, radical or nucleophilic species.



I

With various substituent groups (X) and reasonable assignments to appropriate parameters, he found that the pattern of aromatic substitution could be well reproduced.

In the present work, the simple molecular orbital

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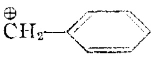
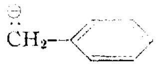
[1] Supported by the research program of the U. S. Atomic Energy Commission under Contract AT(30-1)905.

[2] U. S. Atomic Energy Commission Post-Doctoral Fellow, 1951–1952.

[3] G. W. Wheland, THIS JOURNAL, **64**, 900 (1942).

method[4,5] has been used to determine whether the pattern of some benzene substitutions could be obtained without adjustment of arbitrary parameters and, in fact, with avoidance of assumptions other than those used generally in the calculation of π-electron energies of unsaturated hydrocarbon molecules, radicals or ions. Such conditions are met if the energies are compared of the substitution activated complexes of benzene, the benzyl cation (II) and the benzyl anion (III). The $\overset{\oplus}{\mathrm{C}}\mathrm{H}_2$– group of II may be considered as an analog of nitro, carbethoxyl or comparable groups and by the usual qualitative considerations[6] should be expected to have similar directing powers. The $\overset{\ominus}{\ddot{\mathrm{C}}}\mathrm{H}_2$– group of III is analogous to the $:\overset{\ominus}{\ddot{\mathrm{O}}}$–, $\ddot{\mathrm{N}}\mathrm{H}_2$–, etc., substituents and should similarly influence benzene substitution.


II


III

Our calculations may be illustrated by the following example. The total π-electron energy of benzene computed in the usual way[4] is $(6q + 8.00\beta)$[7] while that of I for the electrophilic substitution of benzene is $(4q + 5.46\beta)$. The net electrical work (Δw) for the formation of I is then $(2q + 2.54\beta)$ which may be compared with $\Delta w(2q + 2.86\beta)$ obtained as the difference in π-electron energies for the benzyl cation $(6q + 8.72\beta)$ and I (X = $\overset{\oplus}{\mathrm{C}}\mathrm{H}_2$–) for the para electrophilic substitution of the benzyl cation $(4q + 5.86\beta)$. It is thus seen that the para-substitution of II is calculated to be energetically less favorable than that of benzene by 0.32β[8] for electrophilic reagents. Values of Δw for various substitutions of benzene, II and III are given in Table I. To save space, the q-values have been omitted from Δw since these are constant for a given type of substitution; *i.e.*, $2q$ for electrophilic, q for radical and $0q$ for nucleophilic substitutions.

The calculated values of Δw are in reasonable agreement with qualitative expectations[3,6] for substitution reactions of II and III at the meta- and para-positions based on the behavior of analogous compounds. Thus, the reactivity of the various positions (neglecting statistical factors) is predicted to be: electrophilic substitution: III > benzene ≳ meta-III ~ meta-II > para-II; radical substitution: para-II ~ para-III > benzene ≳ meta II-~ meta-III; nucleophilic substitution: para-II > benzene ≳ meta-II ~ meta-III > para-III. The only discrepancies are in the predictions of (1) a general slightly too great reactivity for benzene and (2) equivalent reactivity of the meta-positions of II and III.

TABLE I

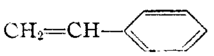
CALCULATED VALUES OF Δw FOR AROMATIC SUBSTITUTIONS

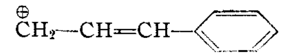
Reactant	Point of attack	Δw^a Electrophilic	Radical	Nucleophilic
Benzene	. . .	2.54	2.54	2.54
Benzyl cation (II)	Ortho	2.62	2.18	1.73
	Meta	2.56	2.56	2.56
	Para	2.86	2.34	1.82
Benzyl anion (III)	Ortho	1.73	2.18	2.62
	Meta	2.56	2.56	2.56
	Para	1.82	2.34	2.86
Styrene (IV)	Ortho	3.07	3.07	3.07
	Meta	3.09	3.09	3.09
	Para	2.97	2.97	2.97
	β	2.25	2.25	2.25
Cinnamyl cation (V)	Ortho	2.56	2.21	1.87
	Meta	2.40	2.40	2.40
	Para	2.68	2.31	1.94

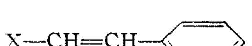
[a] In units of β, q values omitted.

The agreement for the ortho-positions is formally less satisfactory in that such positions in II or III are uniformly expected to be more reactive than the para-positions. In practice, such behavior appears to be encountered frequently only in nucleophilic substitutions.[9] It is interesting that the simple molecular orbital theory appears to predict that substitution at ortho-positions should be generally more facile than that at para-positions. The fact that facilitated ortho-substitution does not usually occur is explicable in terms of steric hindrance at these positions.

It is of considerable interest to see whether the method can be applied satisfactorily to other benzenoid systems and consequently we have investigated the substitution of styrene (IV) and the cinnamyl cation (V) (*cf.* Table I). Styrene is predicted to undergo nuclear substitution preferentially in the ortho and para-positions with all types of reagents[10] while, with V, meta-substitution is predicted with electrophilic reagents and ortho–para orientation with radical and nucleophilic species. In practice, the electrophilic substitution of substances like VI (with X = $-\mathrm{NO}_2$, $-\mathrm{CO}_2\mathrm{C}_2\mathrm{H}_5$, etc.) is well known to occur predominantly at the ortho-


IV


V


VI

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(4) For refs., see J. D. Roberts, A. Streitweiser, Jr., and C. M. Regan, *ibid.*, **74**, 4579 (1952). It is important to note that our calculations (and others of similar character) may be rather seriously in error for any of the substitutions in which the initial molecules or the intermediate complexes of type I are charged since in such circumstances the π-electron charge distributions are not "self-consistent" and the values of q and β are probably different than for neutral entities.

(5) The treatment is different from that of Wheland[3] in that the non-orthogonality integrals S between adjacent atomic orbitals are neglected.

(6) *Cf.*, G. W. Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, Chap. 8.

(7) Notation of C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc. (London)*, **A191**, 39 (1947).

(8) Equivalent to 5.5 kcal. if β is given the customary value of 17 kcal.

(9) Thus *o*-nitrobromobenzene reacts 100 times more rapidly with piperidine than *p*-nitrobromobenzene although the corresponding isomers of bromobenzonitrile react at comparable rates, W. C. Spitzer and G. W. Wheland, THIS JOURNAL, **62**, 2995 (1940). Recent studies by R. L. Dannley and E. C. Gregg, Abstracts of the Buffalo Meeting of the American Chemical Society, March, 1952, p. 1K, indicate preferential *ortho*-phenylation in the free-radical reactions of benzoyl peroxide with various substituted benzenes.

(10) Actually, non-nuclear substitution at the β-position of the double bond is predicted to yield the most stable activated complexes; *cf.* Table I.

and para-positions and it appears that V is not a good model for such compounds despite the fact that II seems to be a reasonable analog of nitrobenzene. The disparity can be resolved in the following way. The secular equation for II (and the corresponding activated complex I with X = $\overset{\oplus}{\mathrm{C}}\mathrm{H_2}$–) contains terms expressing the "resonance" integral β and the Coulombic integral q of the $\overset{\oplus}{\mathrm{C}}\mathrm{H_2}$–group. For a graded series of compounds ranging between II and benzene with various degrees of electronically deficient groups in place of $\overset{\oplus}{\mathrm{C}}\mathrm{H_2}$–, the q and β terms diminish to zero as one approaches benzene, but nonetheless, at all times, meta-substitution is predicted to be preferred. As a result, II is a good qualitative model for nitrobenzene or any similar substance where directing substituent exerts its influence by virtue of an electronically-deficient atom attached directly to the benzene ring.

On the other hand, in the transition between V and IV as β and q diminish, a changeover between prediction of meta- to ortho–para orientation must occur. Since the electronically-deficient atoms of the usual ortho-para substituting derivatives of VI (X = $-\mathrm{NO_2}$, $-\mathrm{CO_2C_2H_5}$, etc.) would be expected to have smaller q and β values than $\overset{\oplus}{\mathrm{C}}\mathrm{H_2}$–, it is possible that such groups on detailed analysis would be calculated to give different orientations from V. It will be interesting to determine whether electrophilic substitution of V or a suitable analog would actually occur in the meta-position as predicted.

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Effects of Hydrogenation upon the Microbiological Activities of N^{10}-Methylpteroylglutamic Acid, Aminopterin and A-Methopterin

BY GLYNN P. WHEELER, MARGARET A. NEWTON, JEANENNE S. MORROW AND JOYCE E. HILL

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It has been found that hydrogenated folic acid has a growth-promoting activity for *Leuconostoc citrovorum 8081* which is intermediate between that of folic acid and that of leucovorin[1-3] and also intermediate between that of N^{10}-formylfolic acid and that of leucovorin.[3] Also, a commercial sample of aminopterin (4-aminopteroylglutamic acid), which inhibits the growth of *Leuconostoc citrovorum 8081*, was converted to a growth factor for this organism by hydrogenation under pressure.[4] It was later found that this growth-promoting activity was due to an impurity, but nevertheless the inhibitory action of pure aminopterin was decreased by hydrogenation.[5] These facts indicate that the state of oxidation of these compounds has important influence upon the microbiological activity.

Since hydrogenation at elevated temperature under pressure could conceivably cause degradation of the aminopterin molecule, it seemed worthwhile to carry out the hydrogenation under milder conditions and to extend the study to include N^{10}-methylpteroylglutamic acid and A-methopterin (N^{10}-methyl-4-aminopteroylglutamic acid). Accordingly, the compound (100 mg.) to be hydrogenated was suspended, without further purification, in water (25 ml.), and the *p*H was adjusted to 7.0–8.0 by adding a solution of sodium hydroxide, whereupon a homogeneous solution was obtained. Platinum oxide (50 mg.) was added, and hydrogenation was carried out at room temperature and atmospheric pressure. After approximately two moles of hydrogen had been taken up and hydrogenation appeared to be complete, the catalyst was removed by filtration through a bed of fullers earth on a sintered glass plate. The entire filtrate was subjected to freeze-drying, and this yielded a light-colored, fluffy, solid product which was stored under nitrogen. When compared with the spectra for pteroylglutamic acid and tetrahydropteroylglutamic acid,[6] spectra for the initial materials and the products of hydrogenation indicated that hydrogenation had been accomplished.

To determine the inhibitory activities of the initial materials and of the products of hydrogenation for *Streptococcus faecalis* R. the method of Mitchell and Snell[7] was used with slight modification, and folic acid was used as the growth factor. Constant levels of folic acid were used, and the quantity of test compound was varied. The final volume of medium per tube was 10 ml. Seventeen hours following inoculation the turbidity was determined by means of a Lumitron colorimeter with a 660 mμ filter. The resulting data are given in Table I. In all instances hydrogenation caused a considerable decrease in inhibitory activity.

TABLE I

EFFECT OF HYDROGENATION UPON THE INHIBITORY PROPERTIES OF CERTAIN FOLIC ACID ANTAGONISTS WITH *Streptococcus faecalis* R.

Compound[a]	Inhibition index[b] Folic acid (μg./10 ml.) 0.002	0.02	0.2	2.0
N^{10}-Methyl PGA	25	2.5	0.44	0.28
Hydrogenated N^{10}-methyl PGA	Less than 50% inhibition at all levels			
Aminopterin	26	2.8	1.5	0.34
Hydrogenated aminopterin	Less than 50% inhibition at all levels			
A-methopterin	25.5	2.5	0.25	0.04
Hydrogenated A-methopterin	45	70	26	11

[a] All compounds were used as the sodium salts. [b] Inhibition index = weight of agent required for half maximal inhibition/weight of folic acid.

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[6] A. Pohland, E. H. Flynn, R. G. Jones and W. Shive, THIS JOURNAL, **73**, 3247 (1951).

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