

Advances in Heterocyclic Chemistry

By A. R. KATRITZKY

Volume 1

Advances in
HETEROCYCLIC
CHEMISTRY

Edited by

A. R. KATRITZKY

*University Chemical Laboratory
Cambridge, England*

Volume 1



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Preface

Heterocyclic chemistry is of the utmost practical and theoretical importance. Heterocyclic compounds are in use as pharmaceuticals, dyes, pesticides, herbicides, plastics, and for many other purposes; the industries producing and researching into these products provide employment for a large fraction of all chemists. On the theoretical side, heterocyclic chemistry has provided a host of interesting concepts and structures. Yet, the subject is often deprived of the importance it deserves; it is said that it is possible to complete work at graduate schools of some universities without having attended a lecture course dealing specifically with heterocyclic chemistry.

I was indeed fortunate to have grown to chemical maturity under Sir Robert Robinson, and in an environment where heterocyclic chemistry was certainly not neglected. This being so, it is natural that I feel the dissemination and rationalization of knowledge in heterocyclic chemistry to be of vital importance. Recently several good heterocyclic texts have appeared, but a need exists for a medium in which current advances in the subject can rapidly be presented to a wide audience. The present series aims to make available to graduate students and research workers in academic and industrial laboratories up-to-date reviews of a wide variety of heterocyclic topics.

For this volume, and for succeeding volumes in the series, I have been fortunate in enlisting the cooperation of distinguished heterocyclic chemists from many different countries to contribute articles on their special fields. I am much indebted to all the authors for their interest and cooperation. In this volume, the attempt has been made to cover the literature to the end of 1961, and a not inconsiderable number of 1962 references do in fact occur.

My thanks are also due to members of the Editorial Board, especially Professor Adrien Albert to whom I owe a great debt of gratitude for his kindly advice and encouragement. The cooperation of Academic Press is appreciated.

A. R. KATRITZKY

Cambridge, England
October 1962

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Recent Advances in the Chemistry of Thiophenes

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University of Uppsala, Uppsala, Sweden*

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I. Introduction

In the development of thiophene chemistry three periods can be clearly distinguished; the Victor Meyer era, the Steinkopf period,¹ and the modern development starting with the discovery of the synthesis of thiophene from butane and sulfur,² making thiophene potentially available in unlimited amounts. Hartough in his well-known monograph,³ has reviewed the intense and hectic thiophene research toward the end of the 1940's carried out mainly at the Socony-Vacuum laboratories, but also at many academic institutions. An article by Nord *et al.*⁴ appeared in 1955 in which the research work in thiophene chemistry at Fordham University, as well as progress in general up to 1954, was reviewed.

During the first two periods interest was mainly focused on the substitution reaction of thiophenes. In particular, Steinkopf *et al.*¹ carried out a great deal of work on the preparation of the different isomers of simple thiophenes. Although interest in this area continued after the discovery of the new thiophene synthesis, especially in reactions more specific for the thiophene ring, the main aim was to introduce the thiophene ring in more complex organic molecules in order to obtain pharmacologically active or otherwise practically useful compounds. The large amount of work carried out in this direction is obvious from the recent review article by Martin-Smith and Reid⁵ on biological activity in compounds possessing the thiophene ring. The conclusion of these authors is that all this work has shown small reward, if measured in terms of the number of new drugs of clearly superior clinical desirability which have been produced. However, these investigations have, in a somewhat unsystematic way, also increased our knowledge of the chemistry of thiophene.

During the last 5-6 years a new trend has been noticeable. The study of the reactivity of the thiophenic hydrogens and the influence

¹ W. Steinkopf, "Die Chemie des Thiophens." Theodor Steinkopff, Dresden und Leipzig, 1941.

² H. E. Rasmussen, R. C. Hansford, and A. N. Sachanen, *Ind. Eng. Chem.* **38**, 376 (1946).

³ H. D. Hartough, "Thiophene and Its Derivatives." Interscience, New York, 1952.

⁴ F. F. Nord, A. Vaitiekunas, and L. J. Owen, *Fortschr. chem. Forsch.* **3**, 309 (1955).

⁵ M. Martin-Smith and S. T. Reid, *J. Med. Pharm. Chem.* **1**, 507 (1959).

of the thiophene nucleus on the reactivity of substituents have been attacked again with more quantitative methods. The whole arsenal of spectroscopic and other physical methods has been utilized in order to study the aromatic character of thiophene and the substituent effects in thiophenes. Metalation and halogen-metal interconversion reactions have been shown to be of great utility in the preparation of substituted thiophenes. Finally Raney nickel desulfurization has made thiophene compounds more and more important as intermediates for the preparation of aliphatic compounds.

It is the intention of the present author to discuss the aforementioned developments and not to give a complete review of all work concerning thiophenes which has appeared during the last 7-8 years. Because of the subjectivity inherent in choosing material for such a survey, it is possible that important contributions will unintentionally be overlooked for which the author would like to apologize.

II. Molecular Structure and Physical Properties of Thiophenes

A. MOLECULAR STRUCTURE

1. Quantum Chemical Calculations

Since the time of the quantum-mechanical calculations by Longuet-Higgins,⁶ many attempts have been made to calculate π -electron densities, resonance energies, dipole moments, and optical transitions both by the LCAO-MO and the valence bond method.⁷⁻¹⁷ However, no agreement has been reached on the importance of *pd*-hybridization of the sulfur atom. This is considered by some workers an essential

⁶ H. C. Longuet-Higgins, *Trans. Faraday Soc.* **45**, 173 (1949).

⁷ J. Metzger and F. Ruffler, *J. chim. phys.* **51**, 52 (1954).

⁸ J. de Heer, *J. Am. Chem. Soc.* **76**, 4802 (1954).

⁹ K. Kikuchi, *Sci. Repts. Tôhoku Univ., First Ser.* **40**, 133 (1956).

¹⁰ K. Kikuchi, *Sci. Repts. Tôhoku Univ., First Ser.* **41**, 35 (1957).

¹¹ K. Maeda, *Sci. Repts. Tôhoku Univ., First Ser.* **43**, 203 (1959).

¹² K. Maeda, *Bull. Chem. Soc. Japan* **33**, 304 (1960).

¹³ G. De Alti and G. Milazzo, *Univ. studi Trieste, Fac. sci., Ist. chim.* No. **24**, p. 15 (1958).

¹⁴ G. Milazzo and G. De Alti, *Rend. ist. super. sanità* **22**, 787 (1959).

¹⁵ L. Melander, *Arkiv Kemi* **8**, 361 (1955).

¹⁶ M. M. Krevoy, *J. Am. Chem. Soc.* **80**, 5543 (1958).

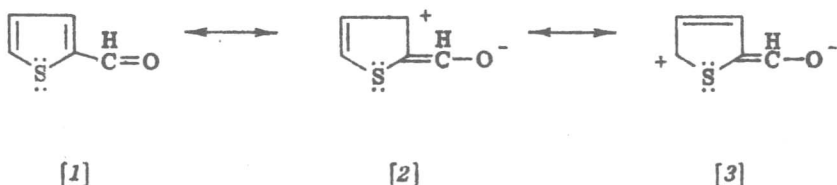
¹⁷ A. Mangini and C. Zauli, *J. Chem. Soc.* p. 2210 (1960).

feature in the electronic structure of thiophene, making the sulfur atom similar to a $\text{CH}=\text{CH}$ group, and being responsible for some of the differences between thiophene and furan and pyrrole; whereas others have suggested that most of the properties of thiophenes may be accounted for without invoking *pd*-hybridization at all,¹⁶⁻¹⁸ Mangini and Zauli¹⁷ even doubting the basic validity of the Longuet-Higgins approach. Different results have also been obtained regarding the relative π -electron densities in the α - and β -positions of thiophene,⁹⁻¹² which in the original Longuet-Higgins treatment⁵ are equal. The greater free valence^{8,18} and self-polarizability of the α -carbon,⁸ the latter being related to Ingold's electromeric effect, are in accordance with the known greater reactivity of the α -position, which is also predicted by calculations on the localization energies of the quinoid transition states in aromatic substitution.^{15,18}

Quantum-mechanical calculations on substituted thiophenes are still more difficult and localization energies and electronic charges have been calculated only for 2- and 3-nitrothiophene.^{19,20}

2. Resonance Theory

Gronowitz *et al.* have discussed the effects of substituents on chemical reactivity and on ultraviolet (UV), infrared (IR), and nuclear magnetic resonance (NMR) spectra in terms of simple resonance theory.^{21,22} They assume resonance structures (1-5) to contribute to a $-\text{I}-\text{M}$ (Ingold's terminology) 2-substituted thiophene, resonance forms (6-10) to the structure of a $\pm\text{I}+\text{M}$ 2-substituted thiophene, forms (11-16) to a $-\text{I}-\text{M}$ 3-substituted thiophene, and forms (17-22) to a $\pm\text{I}+\text{M}$ 3-substituted thiophene.



¹⁶ F. L. Pilar and J. R. Morris, *J. Chem. Phys.* **34**, 389 (1961).

¹⁷ L. Melander, *Acta Chem. Scand.* **9**, 1400 (1955).

¹⁸ L. Melander, *Arkiv Kemi* **11**, 397 (1957).

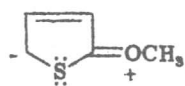
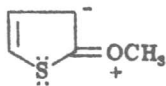
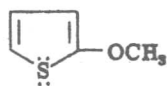
¹⁹ S. Gronowitz, *Arkiv Kemi* **13**, 295 (1958).

²⁰ S. Gronowitz and R. A. Hoffman, *Arkiv Kemi* **16**, 539 (1960).



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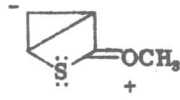
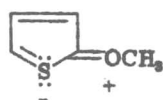
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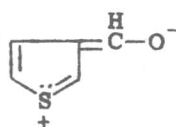
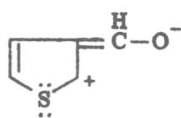
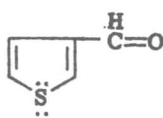
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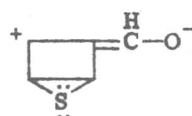
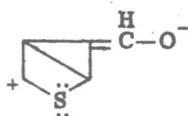
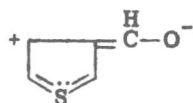
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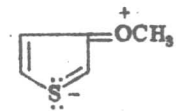
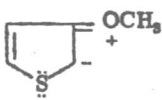
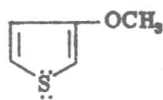
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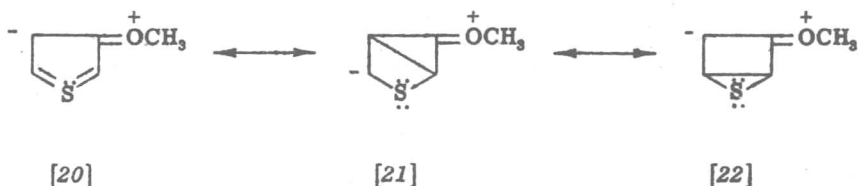
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[19]



Of these resonance forms, the classic ones (1, 6, 11, 17), although very important, give no information about the effect of substitution on the relative electron distribution. The others can be divided into four classes. Of greatest importance are those which contain only C—S single bonds and no "long bonds" (2, 3, 7, 8, 12, 18). Second in importance are those structures involving C=S double bonds and a positively charged sulfur (4, 13). Of minor weight are structures containing decets^{22a} around the sulfur (9, 14, 19, 20), whereas structures with long bonds (5, 10, 15, 16, 21, 22) are considered to be almost negligible. The effects of some of these long-bond structures are identical with those of structures containing decets (cf. 14 with 16 and 20 with 22). The order of relative importance of the various resonance structures is similar to that given by Schomaker and Pauling²³ in their classic study on the structure of thiophene itself. They suggested that the classic form should be given 70% weight, structures involving C=S double bonds and a positively charged sulfur 20%, and structures involving a decet on the sulfur were given a weight of 10%.

The foregoing resonance structures describe the influence of the substituents on the π -electron distribution in the thiophene ring. Besides this effect the inductive effect of the substituents on the σ -electron system must be considered when discussing physical and chemical properties of thiophenes.

Physical and chemical evidence supporting the theory mentioned in the foregoing will be given in the appropriate sections. Some predictions may be mentioned here. From resonance structures (2, 3, 7, 8) it is inferred that the substituent effect in 2-substituted thiophenes should be parallel to that in the corresponding benzenes, the 3- and 5-positions may be considered as *ortho* and *para* positions and the 4-position as a *meta* position. It is, however, obvious that the effect of a —M- and a +M-substituent are not simply reversed, as reso-

^{22a} Ten electrons.

²³ V. Schomaker and L. Pauling, *J. Am. Chem. Soc.* **61**, 1769 (1939).

nance structure (4) belonging to "class 2" is assumed to have a greater weight than (9). It is also expected from the low weights of structures such as (14), (20), (16), and (22), that the 4-position of 3-substituted thiophenes can hardly be expected to show the properties of an *ortho* position in the same way as in benzenes. Also for 3-substituted thiophenes differences in the effects of $-M$ and $+M$ substituents may be expected.

B. SPECTROSCOPY OF THIOPHENES

1. NMR Spectra

The study of the NMR spectra of thiophenes has attracted considerable interest,^{22,24-38b} partly because the spectra of substituted thiophenes containing only a few ring hydrogens are quite suitable for complete analysis and partly because in a series of related compounds the chemical shifts observed are related to differences in the electron distribution about chemically nonequivalent hydrogens (for review, see reference 39), especially for hydrogens far removed from the substituent.

²⁴ S. Gronowitz and R. A. Hoffman, *Arkiv Kemi* **13**, 279 (1958).

²⁵ K. Takahashi, Y. Matsuki, T. Mashiko, and G. Hazato, *Bull. Chem. Soc. Japan* **32**, 156 (1959).

²⁶ S. Fujiwara, M. Katayama, S. Hayashi, H. Shimuzu, and S. Nishimura, *Bull. Chem. Soc. Japan* **32**, 201 (1959).

²⁷ J. B. Leane and R. E. Richards, *Trans. Faraday Soc.* **55**, 518 (1959).

²⁸ R. A. Hoffman and S. Gronowitz, *Arkiv Kemi* **15**, 45 (1959).

²⁹ S. Gronowitz and R. A. Hoffman, *Acta Chem. Scand.* **13**, 1687 (1959).

³⁰ P. L. Corio and I. Weinberg, *J. Chem. Phys.* **31**, 569 (1959).

³¹ R. J. Abraham and H. J. Bernstein, *Can. J. Chem.* **37**, 2095 (1959).

³² R. A. Hoffman and S. Gronowitz, *Arkiv Kemi* **16**, 501 (1960).

³³ R. A. Hoffman and S. Gronowitz, *Arkiv Kemi* **16**, 515 (1960).

³⁴ R. A. Hoffman and S. Gronowitz, *Arkiv Kemi* **16**, 563 (1960).

³⁵ T. Isobe, *Bull. Chem. Research Inst. Non-aqueous Solutions Tôhoku Univ.* **9**, 115 (1960).

³⁶ B. Dischler and W. Maier, *Z. Naturforsch.* **16a**, 318 (1961).

³⁷ S. Gronowitz, B. Gestblom, and R. A. Hoffman, *Acta Chem. Scand.* **15**, 1201 (1961).

³⁸ S. Gronowitz and B. Gestblom, *Arkiv Kemi* **18**, 513 (1962).

^{38a} G. S. Reddy and J. H. Goldstein, *J. Am. Chem. Soc.* **83**, 5020 (1961).

^{38b} K. Takahashi, Y. Matsuki, Y. Miyake, and G. Hazato, *Bull. Chem. Soc. Japan* **34**, 1599 (1961).

³⁹ J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," pp. 271 ff. McGraw-Hill, New York, 1959.

The chemical shifts of the α - and β -hydrogens of thiophenes have been determined through a study of deuterated thiophenes²⁸ and also through complete interpretation of the complex thiophene spectrum.^{28,31,32} The chemical shifts between the α - and β -hydrogens of the five-membered heterocyclics show the order furan > pyrrole > thiophene < selenophene as being 1.05 ppm,³⁵ 0.6 ppm,^{40,41} 0.125 ppm,²⁸ and 0.57 ppm respectively.³⁵ The minimum at thiophene is in accordance with the fact that the aromatic character is greatest for this heterocycle. The fact that the resonances of the α -hydrogens occur at lower fields than those of the β -hydrogens in these heterocycles has been ascribed to lower electron density at the α -hydrogens.^{40,42}

An investigation on 36 monosubstituted^{22,33} and 65 disubstituted thiophenes³⁴ showed that the coupling constants, which are of equal sign,^{28,33} fall in four distinct regions: $J_{35} = 1.25\text{--}1.70$ c/s; $J_{25} = 3.20\text{--}3.65$ c/s; $J_{34} = 3.45\text{--}4.35$ c/s; and $J_{45} = 4.90\text{--}5.80$ c/s. This reveals the outstanding suitability of NMR as a tool for the structure determination of disubstituted thiophenes^{43,44} and also makes possible the assignment of each band in the NMR spectrum of a monosubstituted thiophene to a definite hydrogen.^{24,25,27,33}

The chemical shifts of monosubstituted thiophenes relative to the α - and β -hydrogens of thiophene at infinite dilution in cyclohexane²² are given in Table I and are discussed in the following.

The electron-withdrawing effect from the 3- and 5-positions in —I—M 2-substituted thiophenes, in accordance with resonance forms (2) and (3), is evident from the shifts toward lower field of the resonances of the 3- and 5-hydrogens. The shifts of the 5-hydrogens of COX 2-substituted thiophenes follow the mesomeric order of these substituents.⁴⁵ The chemical shifts of 2-thiocyanothiophene clearly reveal the electron-withdrawing effect of the SCN group which, although *ortho-para* directing, is strongly deactivating in electrophilic

²² R. J. Abraham and H. J. Bernstein, *Can. J. Chem.* 37, 1056 (1959).

³⁴ S. Gronowitz, A-B. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *Arkiv Kemi* 18, 133 (1961).

⁴³ E. J. Corey, G. Slomp, S. Dev, S. Tobinaga, and E. R. Glazier, *J. Am. Chem. Soc.* 80, 1204 (1958).

⁴⁴ S. Gronowitz, *Arkiv Kemi* 13, 269 (1958).

⁴⁵ S. Gronowitz, P. Moses, A-B. Hörnfeldt, and R. Håkansson, *Arkiv Kemi* 17, 165 (1961).

⁴⁶ C. K. Ingold, "Structure and Mechanism in Organic Chemistry," p. 77. Bell and Sons, London, 1949.

TABLE I
CHEMICAL SHIFTS (PPM) OF SUBSTITUTED THIOPHENES, RELATIVE
TO THE SHIFTS OF THE α - AND β -HYDROGENS IN THIOPHENE

Substituent	Character	2-Substituted thiophenes			3-Substituted thiophenes		
		δ_2	δ_4	δ_5	δ_2	δ_4	δ_6
NO ₂	-I-M	-0.82	+0.03	-0.30	-0.95	-0.60	-0.03
SO ₂ Cl	-I-M	-0.73	-0.06	-0.45	—	—	—
CN	-I-M	-0.47 ^a	0.00	-0.28 ^a	-0.63	-0.20	-0.15
CHO	-I-M	-0.65 ^a	-0.10	-0.45 ^a	-0.79	-0.45	-0.03
COCH ₃	-I-M	-0.57	0.00	-0.28	-0.68	-0.47	+0.02
COC ₂ H ₅	-I-M	-0.55	0.00	-0.28	-0.70	-0.48	+0.05
COCl	-I-M	-0.88	-0.06	-0.44	-1.05	-0.50	-0.03
CO ₂ CH ₃	-I-M	-0.70	+0.05	-0.20	-0.78	-0.47	+0.05
SCN	-I(\pm M)	-0.30	+0.05	-0.28	-0.25	-0.05	-0.05
C \equiv CH	-I-M	-0.15	+0.16	+0.12	—	—	—
I	-I+M	-0.13	+0.33	-0.01	-0.06	0.00 ^a	+0.19 ^a
Br	-I+M	+0.05	+0.27	+0.11	+0.12	+0.08	+0.10
2-Thienyl	?	-0.08	+0.11	+0.15	—	—	—
SH	-I+M	0.00	+0.20	+0.07	+0.22 ^a	+0.20 ^a	+0.10 ^a
SCH ₃	-I+M	+0.03	+0.18	+0.05	+0.33	+0.10	+0.03
CH ₃	+I+M	+0.37	+0.24	+0.28	+0.45	+0.22	+0.14
OCH ₃	-I+M	+0.94	+0.43	+0.82	+1.10	+0.38	+0.20
OC ₂ H ₅	-I+M	+0.92	+0.43	+0.81	—	—	—
OC(CH ₃) ₃	-I+M	+0.77	+0.38	+0.65	+0.78	+0.36	+0.22
NH ₂	-I+M	+0.95	+0.45	+0.85	+1.25	+0.53	+0.25

^a These resonances were not resolved.

substitution.⁴⁶ +M-Substituents cause shifts toward higher field especially of the 3- and 5-hydrogens, in accordance with resonance forms (7) and (8), the shifts of the 5-hydrogens following the known mesomeric order (NH₂ > OCH₃ > CH₃). The smaller upfield shift of the 5-hydrogen resonance in 2-*t*-butoxythiophene as compared to 2-methoxy- and 2-ethoxy-thiophene is ascribed to steric inhibition of resonance.²² The fact that -M-substituents cause no shift of the 4-hydrogen in 2-substituted thiophenes or of the 5-hydrogen in 3-substituted compounds, whereas +M-substituents cause a noticeable upfield shift, has been ascribed to a relay of the charge of the 3- and 5-position (resonance forms 7 and 8) to the 4-position in a +M-substituted compound.²² In -M-substituted compounds an alternative relay of the positive charge to the sulfur exists (resonance form 4),

⁴⁶ F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.* 78, 854 (1956).

whereas an alternative relay of negative charge to the sulfur (resonance form 9) is less important.

The much larger shift of the 2-hydrogen compared to the 4-hydrogen in 3-substituted thiophenes are in complete agreement with the assumed weight of resonance forms (12) and (14) or (18) and (20). However, it is obvious from the high-field shift of hydrogen 4 in 3-methoxythiophene that resonance form (20) cannot be neglected and that *pd*-conjugation must, therefore, be considered in a more detailed discussion of the structure of thiophenes.²²

The larger shifts of hydrogen 2 in 3-substituted thiophenes than those of hydrogen 3 in 2-substituted, have been ascribed to the greater probability of structures (12) and (18) over (2) and (7).

The SH, SCH₃, and weakly directing halogens cause small shifts, which to a large extent are determined by magnetic anisotropy effects, especially in the case of the halogens. Attempts have been made to estimate these effects for the other thiophenes.²² Except for ortho-hydrogens, these effects are usually very small.

As can be seen from the present discussion, the electron distribution inferred from the chemical shifts of monosubstituted thiophenes is in good agreement with that expected on the basis of simple resonance theory.

In the benzene series, an approximately linear relationship has been obtained between the chemical shifts of the *para*-hydrogen in substituted benzenes⁴⁷⁻⁴⁹ and Hammett's σ -values of the substituents. Attempts have been made, especially by Taft,^{50,51} to use the chemical shifts as a quantitative characteristic of the substituent. It is more difficult to correlate the chemical shifts of thiophenes with chemical reactivity data since few quantitative chemical data are available (cf. Section VI,A). Comparing the chemical shifts of the 5-hydrogen in 2-substituted thiophenes and the parahydrogens in substituted benzenes, it is evident that although $-I-M$ -substituents cause similar shifts, large differences are obtained for $+M$ -substituents indicating that such substituents may have different effects on the reactivity of the two aromatic systems in question. Differences also

⁴⁷ P. Diehl, *Helv. Chim. Acta* p. 829 (1961).

⁴⁸ R. R. Fraser, *Can. J. Chem.* **38**, 2226 (1960).

⁴⁹ H. Spiesscke and W. G. Schneider, *J. Chem. Phys.* **35**, 731 (1961).

⁵⁰ R. W. Taft, Jr., *J. Am. Chem. Soc.* **79**, 1045 (1957).

⁵¹ R. W. Taft, Jr., S. Ehrenson, I. C. Lewis, and R. E. Glick, *J. Am. Chem. Soc.* **81**, 5352 (1959).