TABLE IV

TYPICAL KINETIC BROMINATION DATA IN NITROMETHANE SOLUTION AT 30.0°[a]

Time, min. × 10^{-2}	$Na_2S_2O_3$, ml.	Blank corrn.[b]	Corrected titer	Reacn., %
Fluorobromomesitylene				
0	8.61	0	8.61	0
10.32	8.25	0.025	8.275	3.89
15.80	8.10	.03	8.13	5.57
25.22	7.88	.04	7.92	8.01
30.50	7.79	.045	7.835	9.00
(33.75)[c]			(7.75)[c]	10
40.97	7.60	.055	7.655	11.09
Cyanomesitylene				
0	9.07			0
1.16	8.73			3.74
3.01	8.45			6.83
4.20	8.31			8.38
5.27	8.18			9.81
(6.00)[c]	(8.10)[c]			10
13.20	7.45			17.86
15.56	7.19			20.72
Cyanodurene				
0	8.92	0	8.92	0
10.90	8.79	0.02	8.81	1.23
25.10	8.68	.04	8.72	2.24
44.80	8.52	.07	8.59	3.70
68.60	8.40	.11	8.51	4.60
102.50	8.13	.15	8.28	7.18
125.50	7.98	.18	8.16	8.52
(150.90)[c]			(8.03)[c]	10

[a] Kinetic solution (22 ml.) 0.055 *M* in both bromine and aromatic compound. Iodometric titrations with 0.025 *N* sodium thiosulfate on 2-ml. samples quenched in 5 ml. of a 4% KI solution in 70% ethanol. [b] Evaluated graphically in a separate blank experiment. [c] The values in parentheses are based upon graphic evaluation.

Nitromethane was purified according to the procedure described previously.[2] Kinetics blank experiments in this solvent showed that a slow consumption of bromine occurs in the order of about 1.6% in ten days, in the concentration range 0.03 to 0.06 *M*. These "bromine losses" are probably due to reaction with the solvent and not merely to volatility losses.

Kinetics Measurements.—The procedure used for the measurements was essentially the same as described previously except for the higher concentration of the two reactants. Allowance for the above-mentioned bromine losses was made in the case of fluorobromomesitylene and cyanodurene by running blank experiments with the same bromine concentration and evaluating the thiosulfate titer corrections graphically at any desired time. The reaction of cyanodurene was followed up to just less than 10% and the t_{10} value was obtained by extrapolation. The usual interpolation procedure[2] was used instead for the evaluation of all the other data. Typical experiments and further details are reported in Table IV. The kinetics experiments were carried out in a dark room (red lamp).

All the results are summarized in Table I. The rates, *R*, relative to durene (= 1000) were calculated from the formula $R = 20.6\ (t'_{10}/t_{10})$, where t'_{10} and t_{10} are the t_{10} values for the substance of intermediate reactivity (chloromesitylene) and for that under examination, respectively, and 20.6 is the relative rate of chloromesitylene as reported previously.[2] The reactivities k/k_0 were obtained from the formula $k/k_0 = aR/R_0$, where *a* is the ratio of the statistical factor for the parent hydrocarbon over that for the substance under examination.

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ROME, ITALY

[CONTRIBUTION FROM THE DEPARTMENT OF GENERAL CHEMISTRY OF THE UNIVERSITY OF ROME]

Relative Rates of Bromination of Some Hydroxy, Methoxy and Methylthio-substituted Polymethylbenzenes. Partial Inhibition of Resonance Effects[1]

BY GABRIELLO ILLUMINATI

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The relative rates of bromination of hydroxymesitylene and of the methoxy and methylthio derivatives of mesitylene and durene have been measured in acetic acid solution at 30.0°. The methoxy and methylthio groups have been found strongly activating in the durene series and moderately deactivating in the mesitylene series. Steric inhibition of resonance in methoxydurene appears to be a relatively minor effect, even though it involves an increase in free energy of activation by about 2 kcal./mole. For the $\sigma_m{}^+$ constant of the hydroxy group a value of −0.133 has been calculated. The relation of the present data to *m* and *p* partial rate factors for the bromination of monosubstituted benzenes is discussed.

The free energy of activation for the resonance interaction of an electron-releasing substituent with the aromatic ring is an important stabilizing factor in the transition state of electrophilic reactions. Therefore, the phenomenon of steric inhibition of resonance resulting from deviation from coplanarity with the ring in such overcrowded compounds as substituted durenes should be best illustrated with non-symmetrical groups possessing a large electron-releasing capacity. The *p*-methoxy group seemed to be most suitable to such a study both because of experimental considerations and of the availability of a sufficient amount of information about its effects on reactivity to permit a ρ-σ analysis. There seems to be only one preliminary report[2] on similar studies, one dealing with the effect of steric inhibition of resonance of the methoxy group on the aromatic bromination of 2-methoxy-*m*-xylene.

In this paper, the "polymethylbenzene approach" to orientation problems also has been extended to the *m*-hydroxy and *m*-methoxy substituents and to the next sub-group VIb analogs, the *m*- and *p*-methylthio substituents. Because of the expectedly minor importance of steric effects, con-

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(1) This paper is part IX in the series "Substitution in Polymethylbenzenes"; Part VIII, G. Illuminati, THIS JOURNAL, **80**, 4941 (1958).

(2) Quoted, as unpublished work by F. A. Whittaker, by L. A. Wiles, *Chem. Revs.*, **56**, 329 (1956).

sideration of the *m*-substituents was especially intended to give information, otherwise difficult to obtain, on the relay to the *m*-position of the electrical effects of the strongly *o*–*p* orienting substituents under study.

The fulfilment of the present plan has involved the synthesis of two new compounds, methoxy- and methylthiodurene, and the measurement of bromination rates for these compounds and for methoxy-, methylthio- and hydroxymesitylene.

Results and Discussion

The bromination rates were measured in acetic acid solution, at 30.0°, in the concentration range 0.001 to 0.01 *M*. Because of the high reactivity of the durene derivatives, a modification of Yeddanapalli and Gnanapragasam's method[3] was used for the evaluation of the times at 10% reaction in the order of seconds. Methylthiodurene was used as the compound of intermediate reactivity to assess a rate value relative to durene. The results are collected in Table I. These show that in the durene series the methoxy and methylthio groups enhance the reactivity by factors of 1.6×10^5 and *ca.* 10^3, whereas in the mesitylene series the same groups reduce the reactivity by factors of 5.2 and 39.9, respectively.

Table I

Kinetic Data on the Bromination of Some Hydroxy-, Methoxy- and Methylthio-substituted Polymethylbenzenes in Acetic Acid Solution, at 30.0°

Aromatic compound	Substituent examined	Concn., M^a	t_{10},[b] min.	R^c	$k/k_0{}^d$	(log k/k_0)
2-Hydroxymesitylene	*m*-OH	0.01	0.57	5.947×10^5	14.205	1.1524
2-Methoxymesitylene	*m*-CH_3O	.01	41.8	8.11×10^3	0.1937	−0.7128
3-Methoxydurene	*p*-CH_3O	.001	0.28	8.21×10^7	1.64×10^6	5.2156
2-Methylthiomesitylene	*m*-CH_3S	.01	322	1.053×10^3	2.515×10^{-2}	−1.5995
3-Methylthiodurene	*p*-CH_3S	.01	0.70	4.843×10^5	0.9686×10^3	2.9862
		.001	48			

[a] Molarity in both reactants. [b] Time at 10% reaction; mean from several determinations. [c] Rate relative to durene (= 1000). [d] Reactivity per position of attack, relative to the parent hydrocarbon (see ref. 4, Table I).

$\Delta F^{\ddagger}$ Changes Due to Reduced Resonance.—The data for methoxydurene show that, despite unavoidable interactions causing the unsymmetrical methoxy group to deviate from co-planarity with the ring, this group can achieve a high degree of conjugation in the transition state of reactions with electron-demanding reagents.

The ρ–σ analysis, as diagrammatically illustrated in Fig. 1, indicates that the reactivity of methoxydurene exceeds that predicted on the basis of the σ_m and σ_p constants[5] by factors of 1.6×10^6 and 7.2×10^2, respectively. Although Brown and Okamoto's $\sigma_p{}^+$ constant[6] obviously cannot be tested on a reaction of methoxydurene, the observed similarity[1] of aromatic bromination to the solvolysis of phenyldimethylcarbinyl chlorides, as to the electron requirements in the transition state, suggests that the $\sigma_p{}^+$ value of −0.764 can be used confidently for an estimation of the change in free energy of activation due to a steric inhibition of resonance effect. The $\Delta\Delta F^{\ddagger}$ thus obtained amounts to 1.99 kcal./mole. Inhibition of resonance, as the above data show, is far from being complete. Extensive destruction of the residual resonance effect would involve at least an extra 8.5 kcal./mole to lower the reactivity to the level predicted from the σ_m constant. While in the initial state the methoxy group is likely to assume least-strained positions out of the ring plane, on the approach of the electron-demanding reagent it may turn around the C_{Ar}–O bond to reach higher-strained equilibrium positions with one of the adjacent methyl groups in order to reduce its angle with the ring plane as much as possible.

The data for the *m* and *p*-methylthio group (Table I) represent the first clean-cut evidence for a strong *p*-orienting effect of this group in aromatic substitution.[7] However, the electron-releasing power displayed by the *p*-methylthio group in the bromination of the corresponding durene derivative, even though quite large, is decidedly smaller than that of the methoxy group.[8] The reactivity of methylthiodurene exceeds that predicted from the σ_m and σ_p constants[5] by factors of 1.7×10^4 and 3.8×10^2, respectively. The ρ–σ analysis in this case suffers from the lack of an independently evaluated σ^+ constant; at any rate, since the stereochemical requirements are similar to those of the methoxy group and the observed *p*-activating effect is large, any steric inhibition of resonance is but partial and moderate as for the methoxy group.[8a]

Electron Relays to the *m*-Position.—There is evidence that a relay of the electron-releasing conjugative effect of substituents to the *m*-position is not greatly modified in the transition state of electrophilic reactions. Thus, the enhancement of hyperconjugative electron-release of a *p*-methyl group ($\sigma^+ < \sigma$), as observed in both the solvolysis of phenyldimethylcarbinyl chlorides[6] and the bro-

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(3) L. M. Yeddanapalli and N. S. Gnanapragasam, *J. Chem. Soc.*, 4934 (1956).

(4) G. Illuminati and G. Marino, This Journal, **78**, 4975 (1956).

(5) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

(6) H. C. Brown and Y. Okamoto, This Journal, **79**, 1913 (1957).

(7) This strong *p*-orienting effect does not seem to have been clearly recognized previously. A recent discussion on the available data has been presented by F. G. Bordwell and P. J. Boutan, *ibid.*, **78**, 854 (1956).

(8) For a recent review on this order of conjugative electron-releasing power of the methoxy and methylthio groups in a number of physical and chemical phenomena, see H. Lumbroso and G. Dumas, *Bull. soc. chim. France*, **22**, 651 (1955). For a reverse order, as found in spectral work, see L. Chierici, H. Lumbroso and R. Passerini, *Bull. sci. fac. chi. ind. Bologna*, **12**, 127 (1954); A. Mangini and C. Zauli, *J. Chem. Soc.*, 4960 (1956), and references therefrom.

(8a) Added in Proof.—A σ^+ constant of −0.604 for the *p*-methylthio group has been evaluated lately by H. C. Brown, Y. Okamoto and T. Inukai from the solvolysis of *p*-methylthiophenyldimethylcarbinyl chloride (private communication by Professor H. C. Brown). From this value and the present data a $\Delta\Delta F^*$ of 3.1 kcal./mole is obtained, which is appreciably greater than the $\Delta\Delta F^*$ found for the *p*-methoxy group. This would imply a definitely larger steric interaction of an *o*-methyl group with a methylthio than with a methoxy group.

mination of polymethylbenzenes,[1] has no counterpart in the effect of a *m*-methyl group ($\sigma^+ = \sigma$).

In side-chain reactions, a *m*-hydroxy group has a small kinetic effect with respect to hydrogen, its σ- constant varying in a range of weakly positive to weakly negative values.[9] The present data on hydroxymesitylene (Table I) permit the evaluation of a σ^+ constant for this group as given by expression 1. This value is not particularly smaller than

$$\sigma_m{}^+(\mathrm{OH}) = -\log (k/k_0)/8.690 = -0.133 \quad (1)$$

the mean[12] σ_m value, -0.002, and the difference $(\sigma_m{}^+ - \sigma_m) = -0.131$ may be taken as a measure of the extra relay to the *m*-position, in the bromination transition state, from the powerfully electron-releasing hydroxy group.

In the case of the *m*-methoxy and *m*-methylthio groups, the data for the bromination of the related mesitylene derivatives (Table I) will not be used for an exact calculation of new or independent values of $\sigma_m{}^+$ constants because of a possible secondary steric inhibition of resonance effect and of an F-strain effect of the kind tentatively postulated for the nitro group.[1] The ρ–σ analysis (Fig. 1), however, indicates that both steric effects are small, the former being probably the more important in the case of the *m*-methoxy group and the latter in the case of the *m*-methylthio group. In particular, there is a correspondence between the kinetic effects of the methoxy group in the *m*- and *p*-positions, as in both cases the reactivity of the polymethylbenzene derivative is intermediate between those predicted from the σ^+ and σ constants. This lends support to the validity of the $\sigma_m{}^+$ constant for the methoxy group,[6] especially in view of the success in the application of Brown and Okamoto's constants for *o*-, *p*-substituents,[1,4] to aromatic bromination.

The bearing of the present data and of the above considerations on the *m*-partial rate factors for the bromination of monosubstituted benzenes is evident, a *m*-hydroxy group being moderately activating and a *m*-methylthio group moderately deactivating. As to the methoxy group, there is a general agreement with de la Mare and Vernon's conclusions[10] that the electron relay to the *m*-position is to be considered as a relatively small effect; however, it would appear that such a group is more likely to exert a weakly deactivating, rather than activating, influence with respect to hydrogen.

Experimental

The Preparation of Substituted Polymethylbenzenes[11]

Work done with the collaboration of Dr. Giuliana Grassini and Mr. Giancarlo Sleiter

2-Hydroxy- and 2-Methoxymesitylene.—The former was obtained in essential accordance with the method of Biedermann and Ledoux,[12] by diazotization of Fluka (Buchs, Switzerland) mesidine in sulfuric acid solution below +5°, then hydrolysis of the resulting mesityldiazonium salt solution at 50° for about 50 minutes and by steam distillation of the product, m.p. 71–72°. The yield was quantitative; for kinetic purposes the product was recrystallized from petroleum ether to constant melting point. For the preparation of the methyl ether,[12] the potassium salt of the phenol was prepared by adding a solution of 2-hydroxymesitylene in dry benzene to the equivalent amount of finely powdered potassium metal under benzene and gently refluxing the mixture for about a day. The equivalent amount of methyl iodide then was added and refluxing was continued for 10 more hours. After cooling, the precipitated inorganic iodide was removed by adding water, and the crude methyl ether was obtained in 70% yield from the benzene layer after washing the solution with 5% sodium hydroxide and distilled water, then drying and removing the solvent. The product was distilled twice in a semimicro column with a high reflux ratio and a median fraction, b.p. 105° (36 mm.), n_D 1.5025 at 20°, was used for the kinetic measurements. No by-product formation was detected.

2-Methylthiomesitylene.—2-Mesitylenethiol was prepared by reduction of 2-mesitylenesulfonyl chloride[13] according to the excellent procedure described in detail by Bourgeois[14] for the preparation of *p*-toluenethiol. The product was obtained as an oil by steam distillation of the reaction mixture, freed from its disulfide by extraction with 5% sodium hydroxide and recovered by treatment of the filtered extract with hydrochloric acid. The yield was 60%. Because of its low stability, the thiol was readily used for the conversion to the methylthio ether. The latter reaction was effected by adding methyl iodide to a solution containing an equivalent amount of the sodium salt of the thiol in methanol solution and refluxing the mixture for an hour or so. The crude yield in 2-methylthiomesitylene was higher than 90%; on distillation in a semi-micro column with a high reflux ratio, a median fraction, b.p. 74° (*ca.* 1 mm.), n^{20}_D 1.5543, was collected for use in the kinetic runs. No by-product formation was detected.

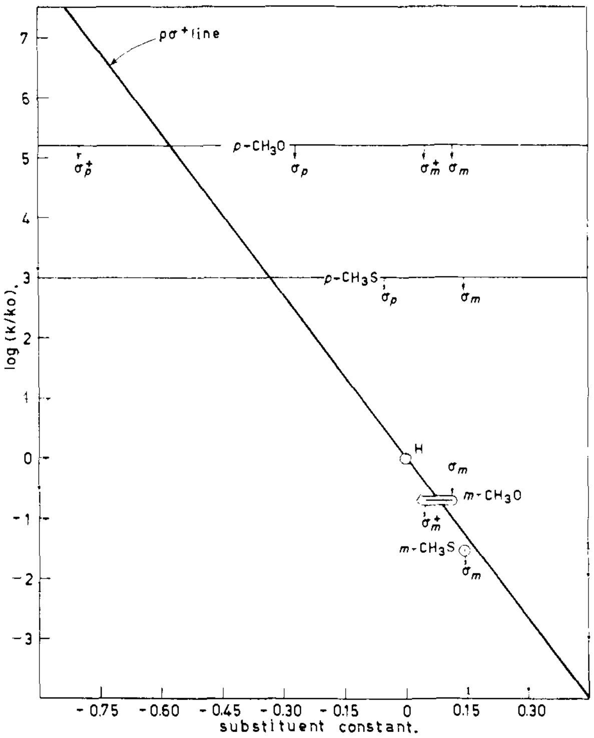

Fig. 1.—ρ–σ analysis illustrating electronic and steric effects of the methoxy and methylthio groups on the rate of bromination of substituted polymethylbenzenes. (For the $\rho\sigma^+$ line, with $\rho = -8.697$, see ref. 1).

3-Methoxydurene.—The starting 3-hydroxydurene was obtained in 79% yield from 3-aminodurene,[15] by a procedure similar to that described above for 2-hydroxymesitylene. In this case, however, the diazonium salt solution was kept for the hydrolysis at 50–60° for seven hours. Also, the

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[9] See reference 5, Table 8.

[10] P. B. D. de la Mare and C. A. Vernon, *J. Chem. Soc.*, 1764 (1951).

[11] All melting points are uncorrected.

[12] R. Biedermann and A. Ledoux, *Ber.*, **8**, 57 (1875).

[13] E. H. Huntress and F. H. Carten, THIS JOURNAL, **62**, 511 (1940); E. H. Huntress and J. S. Autenrieth, *ibid.*, **63**, 3446 (1941).

[14] E. Bourgeois, *Rec. trav. chim.*, **18**, 426 (1899).

[15] G. Illuminati, THIS JOURNAL, **74**, 4951 (1952).

steam distillation of the product was followed by extraction with 5% sodium hydroxide and the resulting extract was filtered through sintered glass and acidified with hydrochloric acid yielding the phenol, m.p. 114–115.5°, in good grade. The following is a typical experiment on the conversion to the methyl ether under optimal conditions as found by us.

To a cold solution of 1.24 g. of sodium hydroxide (0.031 mole) in the minimum amount of methanol, 4.65 g. of 3-hydroxydurene (0.031 mole) was added gradually under efficient shaking. The resulting brown-red solution was treated with 1.90 g. of methyl iodide (0.031 mole) dissolved in little methanol. A total volume of 22 ml. of methanol on mixing the reactants was used. The solution was made up in a ground-glass erlenmeyer flask and, on standing at room temperature for two days or so, it slowly turned to a crystalline mass. The material was then dissolved in diethyl ether and extracted with three or four portions of a 5% sodium hydroxide solution until the alkaline extracts became colorless. On removal of the solvent from the ether layer, 4.91 g. of a light-colored solid, m.p. 47–50°, was obtained. A solution of this solid in 40 ml. of dry petroleum ether (b.p. 30–60°) was applied on a column of 45 g. of alumina for adsorption. On elution with petroleum ether, it was found that the major and purest fraction of methoxydurene, 3.20 g. (64% yield), m.p. 56–57.5°, was contained in the first 100 ml. of eluate. On recrystallization from 95% ethanol to constant melting point, snow-white crystals, m.p. 58.8–59.8°, were obtained.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 79.45; H, 9.97.

The high elution rate with petroleum ether and the relatively low melting point of this substance are also in agreement with its structure of a simple monosubstituted durene.[16,17] A higher-melting, pale yellow side-product was left behind in the alumina column and could be eluted with chloroform. On recrystallization from ethanol, it melted at 115–116° and gave a C, H analysis distinctly different from methoxydurene. Similar, probably condensation products often have been found in the preparation of durene derivatives.[16] The substance was not examined any further for the identification.

3-Methylthiodurene.—3-Durenethiol was prepared by the method of Bourgeois[14] as mentioned above for 2-mesitylenethiol. On steam distillation of the product of reduction of durenesulfonyl chloride[13] a solid material was obtained which was extracted with a 5% sodium hydroxide solution to remove disulfide contaminations. After filtration through sintered glass, the alkaline extract was treated with acids to give the crude thiol in 46% yield, m.p. 63.5–65°. The substance decomposes on standing and turns to the disulfide, m.p. 99–100°. 3-Methylthiodurene then was obtained in 90% yield from the freshly prepared thiol by the same procedure described for the corresponding mesitylene derivative. The crude product melted at 73–75°; on recrystallization from 95% ethanol to constant melting point, white scales, m.p. 75–76°, were obtained.

Anal. Calcd. for $C_{11}H_{16}S$: S, 17.78. Found: S, 17.22.

Rate Measurements

Acetic acid was purified according to the procedure described previously[4] and the water content was determined potentiometrically with the Karl Fischer reagent and found to be 0.014% by weight.

Procedures.—The kinetics experiments in 0.01 *M* solution for the compounds showing t_{10} values higher than one minute were carried out by a procedure identical to that described previously.[4] In the case of the experiments with methylthiodurene in 0.001 *M* solution, each run was carried out with a 100-ml. sample of kinetic solution from which five 15-ml. aliquots were withdrawn at convenient time intervals and quenched into 25 ml. of a 0.2% potassium iodide aqueous solution.

A substantially different, batch-wise procedure was adopted in the case of reactions with t_{10} values lower than one minute. A standard solution of the aromatic compound in acetic acid and a complementary volume of the solvent were placed in a reactor consisting of a tall, narrow beaker provided with a small magnet and tightly adapted through a ground-glass joint into a thermostated circulating-water apparatus set over a magnetic stirrer. After thermal equilibrium was attained, a standard bromine solution was delivered, under stirring, from a 1-ml. pipet in less than 1.2 seconds and the start of delivery was counted as the zero time of the reaction. In some cases the order of addition of the reactants was reversed and the zero time was therefore based on the addition of the solution of the aromatic compound with virtually identical results. The final volume of the kinetic solution was 6 to 15 ml., depending on the concentration of the reactants. At any given time the reaction in the whole system was quenched by addition of 25 ml. of a 0.2% potassium iodide aqueous solution with a fast-delivery pipet and stirring was stopped at the end of this addition. The large volume of the potassium iodide solution used for the quenching prevented oxidation of the iodide ion by a sufficient lowering of the acetic acid concentration. For the analysis, the beaker was disconnected from the rest of the apparatus and the contents was diluted with distilled water, treated incompletely with a 0.01 *N* sodium thiosulfate solution, transferred to a titration flask just before addition of the starch–iodide indicator and finally titrated to the end-point.

Each experiment of this kind yielded a point in the plot of the titer volume *vs.* time; on carrying out a sufficiently large set of these experiments (about a dozen), a line was drawn for the evaluation of the time at 10% reaction. Experiments were performed with reaction times as short as 7 seconds; the titer at zero time was determined in blank experiments in the absence of the aromatic compound. A typical set of experiment data is reported in Table II.

TABLE II

TYPICAL SET OF EXPERIMENTS FOR THE RATE OF BROMINATION OF METHOXYDURENE IN ACETIC ACID SOLUTION, AT 30.0°[a]

Expt.	Time, sec.	$Na_2S_2O_3$, ml.	Reaction, %
1	(0)[b]	2.71	0
2	7.5	2.56	5.54
3	10	2.55	5.91
4	12.5	2.50	7.76
5	16.5	2.47	8.86
..	(17)[c]	(2.44)[c]	10
6	22.5	2.41	11.05
7	23.2	2.36	12.90
8	28	2.27	16.24
9	34	2.25	16.98

[a] Reaction in 0.001 *M* solution in both bromine and methoxydurene. [b] Blank experiment. [c] Evaluated graphically.

All rate measurements were conducted at 30.0° in a dark room and red light was used throughout the course of the experiments. The t_{10} and k/k_0 values were obtained as described previously.[1,4] The results are collected in Table I. The changes in free energy of activation were calculated from the formula $\Delta\Delta F^{\ddagger} = -2.303\ RT\ (\log(k/k_0)_f - \log(k/k_0)_i)$, where the subscripts f and i refer to "final" and "initial" states, which stand for observed and calculated reactivities, respectively.

ROME, ITALY

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(16) G. Grassini, G. Illuminati and G. Marino, *Gazz. chim. ital.*, **86**, 1138 (1956).

(17) A liquid tetramethylanisole isomeric mixture has been reported by A. J. Kolka and R. R. Vogt, THIS JOURNAL, **61**, 1463 (1939).