Role of Structure, Medium and Pathway in Electrophilic Aromatic Substitutions. Part 3.[1] Influence of Isotope and Solvent Effects on Electron Release from Phenolic O–H σ-Bonds

Osman M. E. El-Dusouqui *,† and Mohamed N. Mousa
Chemistry Department, University of Kuwait, PO Box 5969 Safat, 13060 Safat, Kuwait

The rate of molecular bromination of phenol at 25 °C in $CH_3CO_2{}^1H$ as solvent exceeds the rate of the corresponding reaction in $CH_3CO_2{}^2H$ by a factor of 1.5. Correction for substrate–solvent interaction brings the rate ratio to *ca.* 4.5, further confirmed by competitive bromination in the two media. A solvent isotope effect of this magnitude is indicative of substantial contribution to electrophilic reactivity from phenolic O–H σ-bonds.

The nature of contribution to aromatic reactivity from both σ-bonded and lone-pair electrons of the hydroxy function in phenols has been discussed in a recent review on hyperconjugation.[2] Two modes have been advanced to account for possible electron release from the O–H σ-bond: a hyperconjugative effect and $H^{\delta+}$–$O^{\delta-}$ bond polarization which results in augmented mesomeric release of the lone-pair electrons on the hydroxy oxygen. Of particular relevance is the observation that rate enhancement due to hyperconjugation involving an O–H bond that is only half-broken in the transition state of the reaction would be considerable.[2]

Values of the Hammett σ^+ substituent constants of the OH and OCH_3 groups of phenol and anisole estimated under different reaction conditions, together with relative rates of electrophilic reactions in media of variable acidities were used to emphasize the susceptibility of oxygen-containing aromatics to hydrogen bonding.[2,3] Besides, hydrogen-bond donor acidities of solvents have now been recognized as factors of considerable importance when effects of solvents on reaction rates are being rationalized.[4]

The present work describes results obtained for the molecular bromination of phenol, anisole and some of their alkyl derivatives in protio- and deuterio-acetic acid media. Two important considerations have to be addressed on investigating bromination reactions of phenols: (*a*) the complexity of the kinetic rate equation for molecular brominations; and (*b*) the possible formation of dienone intermediates and their subsequent rearrangement to final substitution products. The kinetics of these reactions could be reduced to a second-order rate term, first-order with respect to both bromine and substrate, by conducting the reactions at very low bromine concentrations and in the presence of a large excess of bromine ion at constant ionic strength.[5] The dienone formation step is considered to be a bimolecular process essentially similar to the transition state of electrophilic aromatic substitution leading to the arenonium σ-complex intermediate. Hence, evaluation of the rate constant early in the reaction would provide acceptable k_2 values for the second-order bromination reaction.[2,6] Since the bromination reactions are conducted in acidic media, the highly reactive phenoxide ion is excluded from the reaction pathway.

Results and Discussion

Observed second-order rate constants are converted into specific rate constants using the procedure described by Butler.[5]

† *Present address:* Institut für Physikalische Chemie, Technische Universität Wien, Getreidemarkt 9/156, A-1060 Wien, Austria.

Table 1 Specific second-order rate constants for molecular bromination of phenol, anisole and alkyl derivatives at 25.0 °C

Substrate	k_2/dm^3 mol^{-1} s^{-1}	
	$CH_3CO_2{}^1H$[a]	$CH_3CO_2{}^2H$[b]
Phenol	17.5	11.7
Anisole	0.20	0.60
2-Methylphenol	90	
2-Methylanisole	1.23	
2-*tert*-Butylphenol	18.3	
4-*tert*-Butylphenol	5.5	
2,4-Di-*tert*-butylphenol	24.2	
2,6-Dimethylphenol	110	
2,6-Dimethylanisole	0.078	
2,4,6-Tri-*tert*-butylphenol	0.75	

[a] $pK_a = 4.75$. [b] $pK_a = 5.25$.

The results by de la Mare[7] and those obtained in the present study for the specific second-order rate constants of molecular bromination of the systems under discussion are summarized in Table 1. The rate of bromination of phenol in protioacetic acid (k_2/dm^3 mol^{-1} s^{-1} = 17.5) is faster than its rate in deuterioacetic acid (11.7) by a factor of 1.5. This rate ratio is reversed for anisole: 0.20 dm^3 mol^{-1} s^{-1} in $CH_3CO_2{}^1H$ and 0.60 dm^3 mol^{-1} s^{-1} in $CH_3CO_2{}^2H$. The solvent isotope rate factor of 1.5 for phenol could be explained in terms of a hyperconjugative effect predominant in PhO–^{1}H as compared to PhO–^{2}H. However, it seems that this rate factor has to be adjusted to take into consideration a substrate–solvent interaction involving $CH_3CO_2{}^1H$ and $CH_3CO_2{}^2H$ as hydrogen-bond donor acids with the oxygen of the hydroxy and methoxy groups in phenol and anisole acting as hydrogen-bond acceptor bases.[3,4] In the case of anisole the hydrogen-bond donor/acceptor interaction results in rate reduction by a factor of 3 on going from the weaker $CH_3CO_2{}^2H$ acid ($pK_a = 5.25$) solvent to the stronger $CH_3CO_2{}^1H$ acid ($pK_a = 4.75$) solvent.[8] An effect of comparable magnitude should also apply to the phenolic system. For phenol to be more reactive in the stronger acid, contribution to reactivity from the O–H σ-bond has to offset and then supersede the adverse hydrogen-bond acidity effect of the protium solvent. If the rate factor of 3 is now used to correct and upgrade contribution to reactivity from the O–^{1}H σ-bond, the solvent isotope effect for phenol would be 4.5.

A corroborative rate factor of 3.7 was obtained indirectly using a novel application of the competition method, and, for reasons elaborated elsewhere, 2-chlorophenol was used instead of phenol; the competition method seems to give more satisfactory rate ratios when the reactivity of the competing

Table 2 Typical data for competitive bromination of 1.0×10^{-3} mol of 2-chlorophenol and of anisole: (*a*) in $CH_3CO_2{}^2H$; (*b*) in $CH_3CO_2{}^1H$

	Initial mass of substrate/g	Mass of reacted substrate material/g	Mass of unreacted substrate material[a]/g
(*a*) $CH_3CO_2{}^2H$ solvent			
Anisole	0.1081	0.0323	0.0758
2-Chlorophenol	0.1374	0.0161	0.1213
(*b*) $CH_3CO_2{}^1H$ solvent			
Anisole	0.1207	0.0416	0.079 06
2-Chlorophenol	0.1407	0.0591	0.081 58

[a] Weights of unreacted substrates are estimated using chromatographic response factors obtained for synthetic mixtures of competing substrates and *p*-xylene as internal standard (ref. 11).

substrates are close.[9] The analytical results used in estimating the competitive relative reactivities are given in Table 2. 2-Chlorophenol and anisole were allowed to compete for bromine first in acetic acid, and then in deuterioacetic acid. The rate ratio of anisole/phenol in the deuteriated reaction medium is used to correct the rate ratio of phenol/anisole in protioacetic acid; hence the rate factor of 3.7. A deuterium solvent isotope effect of the order of 3.7–4.5 would demand substantial polarization of the O–H σ-bond to either neutralize in part the positive charge being developed following the mesomeric electron release of the lone-pair electrons on the hydroxy oxygen, or to completely transfer the positive charge to the proton of the O–H group in a hyperconjugative effect.

The results of Table 1 further confirm the susceptibility of the aryl hydroxy and methoxy substituents to steric inhibition of mesomerism. This would presumably increase the demand for contribution to reactivity (at least through bond polarization) from the O–H σ-bond. A second alkyl group introduced *ortho* to the OH function in 2-alkylphenol reduces the rate of molecular bromination involving phenol by a factor of *ca.* 4 from projected reactivity; for anisole this rate factor is 97. The first *ortho* methyl group enhances the reactivity of parent phenol by a factor of 5.14: $k_2/dm^3\ mol^{-1}\ s^{-1} = 17.5$ and 90 for phenol and 2-methylphenol, respectively. Using this factor to calculate the rate expected for 2,6-dimethylphenol following the introduction of two *ortho* methyl groups gives 2,6-dimethylphenol an estimated rate constant of 462.3 $dm^3\ mol^{-1}\ s^{-1}$ ($17.5 \times 5.14 \times 5.14$). The ratio of the estimated rate constant to the experimental rate constant (110 $dm^3\ mol^{-1}\ s^{-1}$) is then the factor of 4 (4.20) given above. The parallel rate reduction factor based on the data (Table 1) obtained for the bromination of anisole, 2-methylanisole and 2,6-dimethylanisole is 97.0. The relative magnitude of steric inhibition of mesomerism involving the hydroxy and the methoxy functions is also reflected in an overall 6.3-fold rate enhancement by the two *ortho* methyl groups for phenol, and a corresponding overall 2.6-fold rate reduction for the anisole system. An even larger steric effect associated with the bulkier Bu^t group is observed when the rates of molecular bromination ($k_2/dm^3\ mol^{-1}\ s^{-1}$) of 4-*tert*-butylphenol (5.5), 2,4-di-*tert*-butylphenol (24.2), and 2,4,6-tri-*tert*-butylphenol (0.75) are similarly analysed: the analogous rate-reduction factors are estimated to be 142 and 7.3, respectively. It is to be noted, however, that the treatment of the kinetic data on the *tert*-butylphenol system neglects the effect on reactivity resulting from blockage of the particularly reactive site *para* to the hydroxy group. An alternative assessment of the influence of adjacent *tert*-butyl groups on the substituent effect of the OH function could be provided by analysing the factors relating to reactivity *meta* to the hydroxy group in 2,4,6-tri-*tert*-butylphenol. From relative rates of bromination of methyl phenols and anisoles, Illuminati concluded that *ortho* methyl groups flanking the methoxy and the hydroxy functions converted the former moiety into a deactivating substituent, while the hydroxy group remained essentially activating; the relative rate *meta* to the hydroxy group and the OH *meta* substituent constant were given as 14.2 and $\sigma^+ = -0.131$, respectively.[10] The rate of bromination of 1,3,5-tri-*tert*-butylbenzene relative to benzene is available only for the reaction catalysed by zinc chloride, and reported[11] to be 7.7. On the basis of the available data, an estimate for the overall relative reactivity of positions 3 and 5 in 2,4,6-tri-*tert*-butylphenol would be: $(7.7/3) \times 14.2 \times 2 = 73$. Projected molecular reactivity based on this estimate would presumably represent only a lower limit of expected reactivity, if only because it involves use of relative rates in lieu of rate constants to be compared with the rate of reaction (0.75 $dm^3\ mol^{-1}\ s^{-1}$) obtained for 2,4,6-tri-*tert*-butylphenol. Hence, the actual rate-reduction factor is most probably substantially in excess of $73/0.75 = 98$. It is worth emphasizing that the true rate-reduction factor would be a reflection of contribution from the primary steric effect of the bulky *tert*-butyl groups, as well as steric inhibition of mesomerism involving the OH function. The present results also seem to indicate that the Bu^t-group reduces phenolic reactivity when substituted at the *para*-position and promotes reactivity from the *ortho*-position, as evidenced by the rates of molecular bromination of 2- and 4-*tert*-butylphenol.

Experimental

Substrates and Solvents.—The methods of preparation and purification of deuterioacetic acid and of purifying acetic acid have been described.[12] These acids were carefully dried and kept so for all kinetic work. The anisole and phenol compounds were commercial samples of analytical grade. The purity of these compounds was established and confirmed prior to use.

Kinetic and Competitive Rates Measurements.—The procedure for the measurement of specific second-order rate constants of molecular bromination reactions is available.[5,7] Rates were measured at 25.0 ± 0.1 °C, and the rate constants were calculated from the kinetic data obtained for the earlier parts of the reaction.[6] Relative reactivities obtained by the competition method involved pairs of the substrates being allowed to compete for molecular bromine in the reaction medium. The substrates were of equal initial molar concentrations; their combined concentraton being kept at *ca.* ten times that of bromine. The weights of unreacted substrates were estimated using GLC techniques. For this purpose synthetic mixtures from known weights of the substrates with added internal standard were prepared and analysed on a Pye Unicam Chromatograph Series 204 coupled with a Spectra Physics microprocessor for control of the analytical variables. The response factors obtained from the synthetic mixtures were then used to estimate weights of unreacted substrates in the reaction mixtures.[13] The equation used to calculate the relative reactivity of a pair of substrates (k_A and k_B) is:[14]

$$k_A/k_B = (\log A_0 - \log A)/(\log B_0 - \log B)$$

where A_0 and B_0 are the initial weights, and A and B are the weights of unreacted substrates.

Acknowledgements

Research grant no. SC006 received from the University of Kuwait is gratefully acknowledged. Thanks are also due to Professor Johannes Lercher and the family of the Institute of Physical Chemistry, Technical University of Vienna, for their courtesy and help.

References

1 Part 2, O. M. E. El-Dusouqui, K. A. M. Mahmud and Y. Sulfab, *J. Chem. Soc., Perkin Trans. 2*, preceding paper.
2 P. B. D. de la Mare, *Pure Appl. Chem.*, 1984, **56**, 1755.
3 W. J. Archer and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1982, 295; 301.
4 M. H. Abraham, R. M. Doherty, M. J. Kamlet and R. W. Taft, *Chem. Br.*, 1986, 559.
5 A. R. Butler and J. B. Hendry, *J. Chem. Soc. B*, 1970, 170.
6 E. Baciocchi and G. Illuminati, *J. Am. Chem. Soc.*, 1967, **89**, 4017.
7 P. B. D. de la Mare, O. M. E. El-Dusouqui, J. G. Tillett and M. Zeltner, *J. Chem. Soc. B*, 1964, 5306.
8 *CRC Handbook of Chemistry and Physics*, eds. R. C. Weast and M. J. Astle, CRC Press, Boca Raton, 1981, p. D-142.
9 O. M. E. El-Dusouqui and K. A. M. Mahmud, unpublished work.
10 G. Illuminati and G. Marino, *J. Am. Chem. Soc.*, 1956, **78**, 4975; G. Illuminati, *J. Am. Chem. Soc.*, 1958, **80**, 4945.
11 L. M. Stock and H. C. Brown, *J. Am. Chem. Soc.*, 1959, **81**, 5615.
12 P. B. D. de la Mare and O. M. E. El-Dusouqui, *J. Chem. Soc. B*, 1967, 251.
13 G. W. Klumpp, *Reactivity in Organic Chemistry*, John Wiley, New York, 1982.
14 C. K. Ingold and F. R. Shaw, *J. Chem. Soc.*, 1927, 2918.

Paper 1/00389E
Received 28*th January* 1991
Accepted 1*st May* 1991