Tetrahedron Letters No.57, pp. 4959-4962, 1970. Pergamon Press. Printed in Great Britain.

STERIC ACCELERATIONS OF NUCLEOPHILIC DISPLACEMENT AND ADDITION REACTIONS BY 2-t-BUTYLBENZENTHIOLATE ANION

Dorothy Semenow Garwood (1) and Donald C. Garwood
Molecular Biology Institute and The Department of Chemistry,
University of California, Los Angeles, California 90024

(Received in USA 4 November 1970; received in UK for publication 9 November 1970)

Steric crowding in electrically neutral nucleophiles such as amines and phosphines generally causes a decrease in the rates of nucleophilic attack on carbon-carbon double bonds (2) and of S_N2 reactions (3). Similar steric effects have been reported for alkylmercaptide anions as nucleophiles. For example, in a kinetic study of the base catalyzed nucleophilic additions of cysteine and β,β-dimethylcysteine derivatives to the double bond of acrylonitrile, the β,β-dimethyl compounds showed rate decelerations interpreted as due to steric effects (4). We now report rate accelerations in a nucleophilic addition reaction and in an S_N2 displacement reaction at sulfur which originate from steric effects in the nucleophile, 2-t-butylbenzenethiolate anion.

The reactions investigated were: the nucleophilic addition of arenethiols to the olefinic bond of N-ethylmaleimide (NEM) to give α-arylthio-N-ethylsuccinimide derivatives (I); and the displacement of 2,4-dinitrobenzenethiolate anion by arenethiolates from ethyl 2,4-dinitrophenyl disulfide (DIS) to form the new ethyl aryl disulfides (II) where aryl designates phenyl, 2-t-butylphenyl or 4-t-butylphenyl.

The data for the acid dissociation constants of the arenethiols (ArSH) and the reactions of the corresponding thiolate anions (ArS^-) with NEM and DIS in 95% ethanol at 25° are summarized in Table I. The acid dissociation constants (K_a) for the thiols were determined

ArSH	ACID DISSOC CONST		NEM REACTION		DIS REACTION	
	pK_a [c] Av. ± S.D.	$\frac{K_a, PhSH}{K_a, ArSH}$	$k_{anion} \times 10^{-4}$ $\underline{M}^{-1}\ sec^{-1}$ Av. ± S.D.	$\frac{k_{anion}, ArS^-}{k_{anion}, PhS^-}$	$k_{anion} \times 10^{-4}$ $\underline{M}^{-1}\ sec^{-1}$ Av. ± S.D.	$\frac{k_{anion}, ArS^-}{k_{anion}, PhS^-}$
PhSH [1]	9.58 ± 0.06[d,e]	1.0	1.90 ± 0.14[g,h]	1.0	7.05 ± 0.03[j,k]	1.0
4-*t*-BuPhSH [1]	9.90 ± 0.02[d,f]	2.1	3.83 ± 0.23[g,h]	2.0	11.6 ± 0.25[j,k]	1.6
2-*t*-BuPhSH [1]	11.64 ± 0.13[d,e]	115.	33.5 ± 1.14[h,i,j]	17.5	60.5 ± 0.93[j,k]	8.5

Table I. Acid Dissociation Constants for Arenethiols (ArSH)[a] and Second Order Rate Constants[b] for Reactions of Arenethiolate Anions with N-Ethylmaleimide (NEM) and with Ethyl 2,4-Dinitrophenyl Disulfide (DIS) at 25.0 ± 0.2°C.

(a) All measurements were done in 95% (azeotropic) ethanol; KOH used for neutralization. (b) All rates were measured in 0.01 $\underline{M}$ acetic acid-potassium acetate buffers in 95% ethanol. (c) All pH values were measured using a Copenhagen Radiometer pH meter No. 26 with a glass-aqueous calomel electrode pair standardized with aqueous buffers. (d) Values obtained at 30% and 50% neutralization agreed within 0.04 pK unit. (e) Average of 8 determinations. (f) Average of 4 determinations. (g) **Duplicate runs at each** pH = 5.43, 6.24 and 6.91. (h) Kinetic data measured for 60-83% reaction. (i) Since NEM and this product had nearly identical extinction coefficients at 302 nm, a method of quenching the unreacted NEM with β-mercaptoethanol was used. (j) Average of 4 runs at pH = 6.91. (k) Kinetic data measured for 75-99% reaction. (1) Thiols and NEM addition products gave satisfactory elemental analyses.

from the pH at half-neutralization. The contribution of the electrode aqueous-non-aqueous junction potential to pH measurements in 95% ethanol is reflected in the absolute magnitudes for the ionization constants, but the values obtained represent a reasonable approximation to the relative acid strengths. Corrections for hydrolyses (protonations by water) of the anions from weak acids have not been applied, but such corrections would slightly increase the reported differences in pK_a's.

The rates were followed spectrophotometrically by decrease in the 302 nm absorption of NEM and the increase in the 425 nm absorption of 2,4-dinitrobenzenethiolate anion, respectively. The NEM addition products (I) were formed in >95% yields. The equilibria for the DIS reactions lie 88-93% toward the substitution products (II); the rate constants include a correction for back reaction.

Second order kinetics with thiolate anion as the reactive species were established for the addition to NEM by the constancy of the specific rate constant k_{anion} (defined by equation (1) and calculated according to equation (2)) over a range of pH.

$$(1)\quad \text{Rate} = k(\text{substrate})\,(\text{ArSH}) = k_{anion}(\text{substrate})\,(\text{ArS}^-)$$

$$(2)\quad k_{anion} = \frac{k(H^+)}{K_a}$$

Second order kinetics, first order in disulfide and first order in thiolate anion, have been previously established for the DIS reaction (5). The values calculated for k_{anion} should be free from junction potential errors since any such errors in measurements of buffer pH and thiol pK_a cancel each other.

The 55-fold weaker acidity of ortho- compared to para-t-butylbenzenethiol is attributed to steric inhibition of solvation (for which the term "sterinsol" is suggested) in the ortho-t-butylbenzenethiolate anion. A comparable interpretation has been advanced for the decreased acidity of hindered phenols (6) and aliphatic carboxylic acids (7).

In the present instance, alternate explanations of the decreased acidity which invoke a greater inductive electron release or steric inhibition of resonance for the ortho-t-butyl compound are untenable on the following bases. A recent assessment of the electronic effects (apparently free from steric effects) of the ortho- and para-t-butyl substituents from nmr chemical shift data showed the ortho group to be less electron-releasing than the para (8). Steric inhibition of resonance in the ortho-t-butylbenzenethiolate anion would require that the sulfur be bent out of the aromatic plane. Consideration of CPK space-filling molecular models strongly suggests that non-bonding repulsions are insufficient to compel such a distortion. If necessary, the distance between the sulfur and the adjacent *t*-butyl group can be increased by an in-plane bending without loss of resonance stabilization.

The reactivity data reported in Table I reveal that these very rapid reactions (k_{anion} values of the order of 10^4 $M^{-1}sec^{-1}$) are accelerated by a sterinsol effect. The rate enhancement due to increased ground state energy of the reactant *ortho*-*t*-butylbenzenethiolate anion relative to the *para*-isomer exceeds any rate-diminishing effects due to steric restrictions in the *ortho*- compound transition states. The net result is that the *ortho*-isomer is more reactive than the *para*-isomer by an order of magnitude.

Undoubtedly, the sterinsol effect, which increases thiolate nucleophilicity, overshadows but is accompanied by steric inhibition of the nucleophilic reactions. A comparison of the rates for *ortho*-*t*-butylbenzenethiolate with an unhindered thiolate anion of the same basicity would reveal the magnitudes of the steric retarding effects for the two reactions. We are continuing investigations in this area.

Acknowledgements: The authors wish to thank Dr. Paul D. Boyer for financial support and helpful discussions. The technical assistance of Mr. Darryl Benson was most helpful.

This research was supported in part by Grant No. GM 11094 from the Institute of General Medical Sciences, U. S. Public Health Service; P. D. Boyer, Principal Investigator.

References

1. To whom inquiries should be sent.

2. Z. Rappoport, C. Degani, and S. Patai, *J. Chem. Soc.*, 4513 (1963).
3. a. E. L. Eliel, "Substitution at Saturated Carbon Atoms," Chapter 2 in "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp 157-161. b. R. U. Pagilagan and W. E. McEwen, *Chem. Comm.*, 652 (1966).
4. M. Friedman, J. F. Cavins, and J. S. Wall, *J. Amer. Chem. Soc.*, **87**, 3672 (1965).
5. A. Fava, A. Iliceto, and E. Camera, *ibid.*, **79**, 833 (1957).
6. a. P. D. Bartlett, *J. Chem. Ed.*, **30**, 22 (1953). b. P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Amer. Chem. Soc.*, **76**, 2349 (1954).
7. G. S. Hammond and D. H. Hogle, *ibid.*, **77**, 338 (1955).
8. M. J. Tribble and J. G. Traynham, *ibid.*, **91**, 379 (1969).