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THE FAILURE OF REACTIVITY INDICES AS QUANTITATIVE MEASURES OF THE SUSCEPTIBILITY OF HETEROCYCLIC COMPOUNDS TO ELECTROPHILIC SUBSTITUTION[1]

Sergio Clementi,[2] Alan R. Katritzky* and H. Okan Tarhan[3]

School of Chemical Sciences, University of East Anglia, Norwich, England

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Summary: The effects of poly-substitution and heteroatom substitution in benzene on the hydrogen-exchange rate are so different to the effects of the same substitutions on the nitration rate as to preclude any universal index of the susceptibility of an individual ring position towards electrophilic substitution.

We have recently described a procedure to obtain standard $\underline{k}_o$ rate constants for acid-catalysed hydrogen-exchange at pH 0 and 100°C and listed $\underline{k}_o$ for numerous benzenoid and heterocyclic compounds.[4] A similar procedure has been developed[5] for nitration rate constants at 25°C and in 75% H_2SO_4 as solvent. Thus, two measures for the susceptibility to electrophilic attack are now available for a wide variety of heteroaromatic compounds. We now wish to report that there is no simple relation between these two measures (see Figure). Although, for both hydrogen-exchange[6] and nitration,[7] linear free energy relations hold for limited series of compounds in which only a single structural parameter is changed (e.g. for monosubstituted benzenes), the differences in the effects of the mutual interaction of substituents in poly-substituted and heteroaromatic compounds on hydrogen exchange and on nitration is vividly indicated by the scatter apparent in the Figure. Two possible reasons for the scatter (a) differential steric effects greater in nitration and (b) the possible inversion of nitration _via_ NO^+ attack can be eliminated by examination of the detailed results.[7] It is clear that there is no unique order of the susceptibility of individual ring positions towards electrophilic attack and in particular that no single reactivity index can be used as such a measure.

The failure[8, 9] of quantum chemical calculations to provide any general measure for predicting qualitatively the relative rates of electrophilic substitution from one compound to another is now more easily understood: no such calculation can possibly succeed unless it considers explicitly the reagent. The role of the solvent must also be vital in any quantitative prediction: our work with both hydrogen-exchange[4] and nitration[5] has indicated that the biggest effect of substitution on reaction rates manifests itself in changes in $\Delta \underline{S}^{\ddagger}$ rather than $\Delta \underline{H}^{\ddagger}$.

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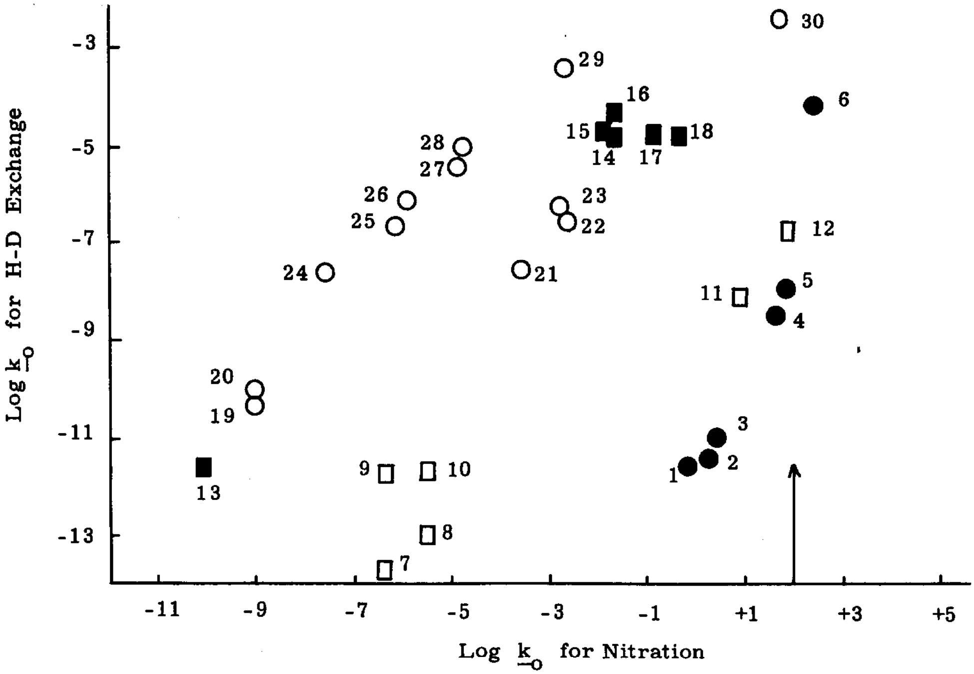

FIGURE. Plot of reaction rates for H-exchange vs. nitration for

● Substituted benzenes (1 : C_6H_5Br at p; 2 : C_6H_5Me at m; 3 : C_6H_6; 4 : p-$C_6H_4Me_2$ at 2; 5 : C_6H_5Me at p; 6 : C_6H_5OMe at p).

□ Bicyclic compounds (7 : quinolium cation at 8; 8 : isoquinolinium cation at 8; 9 : quinolinium cation at 5; 10 : isoquinolinium cation at 5; 11 : naphthalene at 2; 12 : naphthalene at 1).

■ Heteroaromatics with six-membered rings (13 : 2,4,6-trimethylpyridinium cation at 3; 14 : 4-pyridone at 3; 15 : 5-methyl-2-pyridone at 3; 16 : 3-methyl-2-pyridone at 5; 17 : 2-pyridone at 5; 18 : 2-pyridone at 3).

○ Heteroaromatic compounds with five-membered rings (19 : 2,3,5-trimethylisothiazolium cation at 4; 20 : 3,5-dimethylisothiazolium cation at 4; 21 : isothiazole at 4; 22 : 3-methylisothiazole at 4; 23 : 5-methylisothiazole at 4; 24 : 1-methylpyrazolium cation at 4; 25 : 1,5-dimethylpyrazolium cation at 4; 26 : 1,3-dimethylpyrazolium cation at 4; 27 : 1,2,3,5-tetramethylpyrazolium cation at 4; 28 : 1,3,5-trimethylpyrazolium cation at 4; 29 : 3,5-dimethylisoxazole at 4; 30 : thiophene at 2.

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2 Permanent address: Istituto di Chimica Organica, Università di Perugia, Perugia, Italy

3 Permanent address: Department of Chemistry, Middle East Technical University, Ankara, Turkey

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