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The Reactivity-Selectivity Principle and the Electrophilic Substitution of Aromatic Compounds

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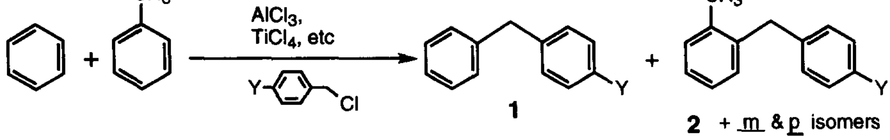
Abstract. The application of the Reactivity-Selectivity principle (RSP) to the Friedel-Crafts alkylation reaction has been reinvestigated using the N-nitrosoamide decomposition as the source of electrophiles. Plots of p_f *vs* σ^+ for 4-methylbenzyl, benzyl, 4-chlorobenzyl, and 4-nitrobenzyl cations] yielded ρ values of -3.4, -2.5, -2.4, and -1.2, resp. The data indicate that the Reactivity-Selectivity Principle is applicable to the electrophilic substitution of aromatic compounds contrary to a claim in the literature. A claim that a reactivity reversal should occur in Friedel-Crafts benzylation is also shown to be in question. © 1997 Elsevier Science Ltd.

That the reactivity of a reagent should be in proportion to its selectivity in chemical reactions, as a general principle, has been hotly debated.[1-4] Whatever the ultimate resolution of this issue turns out to be, it is crucial, obviously, that reactions be identified correctly as following, or not following, the Reactivity-Selectivity Principle (RSP). In this Communication it will be shown that the benzylation of aromatic compounds (Friedel-Crafts alkylation)[5] does obey the RSP, and that an earlier claim that the Principle was disobeyed[3,4] was based on improper assumptions. In this connection, so many examples of reactions that violate the Reactivity-Selectivity Principle (RSP) have been reported that some authors have concluded that the principle is not reliably useful.[6] Thus, it is important that *bona fide* examples of reactions that do follow the RSP be noted as an aid in determining the variables that determine whether a reaction does or does not follow that relationship.

Data obtained by Olah, *et al.*,[7] for the 4-R-benzylation of benzene/toluene mixtures (Chart 1, Y=OCH_3 and NO_2) have been analyzed by Johnson and Schofield.[3,4] The ratio of the yields of alkylated toluene and alkylated benzene ($[\mathbf{2}]/[\mathbf{1}] = k_T/k_B$) is a component of the intermolecular selectivity of the electrophile. The term p_f, a quantitative measure of the intermolecular selectivity, is defined as: (k_T/k_B)(% p isomer/100)(6).[8] P_f is the rate of para substitution of toluene relative to the rate of substitution at one site on benzene;[8] it is a specific example of the general expression k_X/k_H, where X=CH_3 or H in the example in hand. The data can be examined in terms of the Hammett equation,[4] $\log (k_X/k_H) = \rho\sigma^+$, which is apparently the basis of equations utilized by Johnson and Schofield (**1**, *e.g.*) in connection with their study.

Chart 1. The Friedel-Crafts Reaction.



Johnson and Schofield calculated ρ values from Olah's data using eq 1,[3] an equation based on

$$\rho=\log[(k_{toluene}/k_{benzene})(\%para/100)(6)]/-0.31 \qquad (1)$$

a log p_f *vs* σ^+ plot (presumably as in Fig. 1), where X=CH_3 or H refers to the toluene or benzene used; they defined ρ as a measure of the reactivity of the benzyl cationic intermediates,[9] two of which were emphasized (Chart 1, Y=CH_3O and Y=NO_2). To reach their conclusions about the non-operation of the RSP Johnson and Schofield made two assumptions without supporting evidence: (1) that Olah's data followed a linear free energy relationship (thus essentially pre-judging their conclusion).[10] In fact, each line (or calculation of ρ) was based on only two points (Fig 1); further, our extension of the series to anisole (*vide infra*) shows that the plot of σ^+ *vs* log p_f is curved, and thus the calculated ρ values are approximations relating to low values only of σ^+. (2) although the ρ values were calculated to be -8.4 (OCH_3) and -2.3 (NO_2), Johnson and Scholfield *assumed* that these rather different numbers (from a log, log relationship) did "not differ greatly".[3]

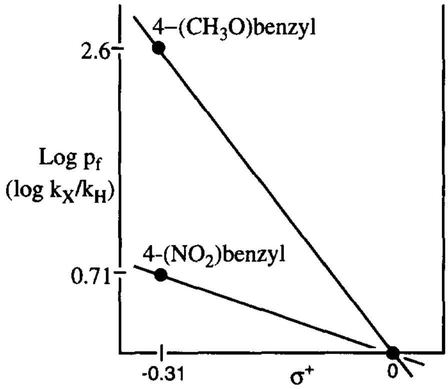
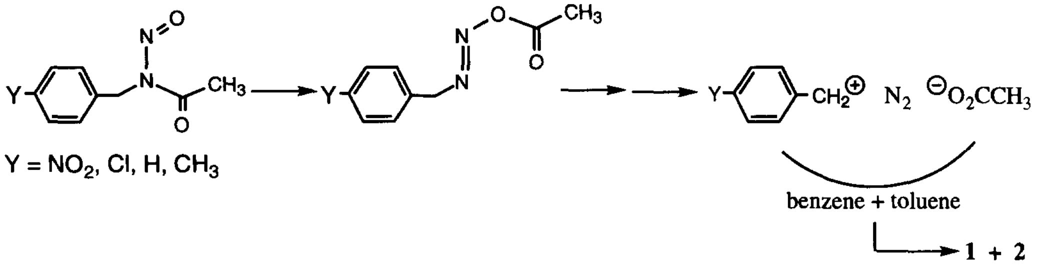


Fig 1. Multiple Reactivity-Selectivity Plot for the Benzylation of Benzene-Toluene Mixtures (Linearity of line assumed).

The two assumptions allowed Johnson and Schofield to claim that Olah's data were consistent with their general view about reactions that did not follow the RSP: ". . .for the reactions of a series of reagents whose reactivity is altered by substituents removed from steric interaction with the reaction site, operating under the same conditions, values of ρ, properly observed, should not differ greatly."[3] They interpreted their treatment of Olah's data in the following way: "The correct deduction might be that ρ is similar for all the benzylations . . . but the rates of reaction *differ markedly*, producing the variation in $k_{toluene}/k_{benzene}$ due to diffusion control with the faster reacting electrophiles in the competitive reactions. . ."[4] And: "The apparently widely differing selectivities reported by Olah may well be produced by increasing inexactitude of competitive experiments with increasing speed of reaction."[3] Such conclusions would, in reality, be meaningful only for reactions that follow, or are pre-judged to follow, a linear free energy relationship.

We have examined the benzylations of benzene-toluene mixtures utilizing an approach that is free of the difficulties outlined by Johnson and Schofield: N-nitrosoamides were used to benzylate toluene-benzene mixtures (Chart 2). By this approach essentially free cations[11] are introduced into a homogeneous medium by a

Chart 2. The Nitrosoamide Approach to Alkylation



first order process; thus, rates of mixing are not a variable. The solvent consists of an equimolar mixture of benzene and toluene, and thus "diffusion control" cannot be an issue. The reactions, which do not utilize catalysts, are straightforward, free of side reactions, and produce data with excellent precision of measurement.[11] Treating our data by the approach of Johnson and Schofield (initial slope over the σ+ range 0 to -0.31) gives ρ(4-nitrobenzyl) = -1.2, ρ(4-chlorobenzyl) = -2.4, ρ(benzyl) = -2.5, and ρ(4-methylbenzyl) = -3.4.[12,13] That is, benzyl cations of different reactivity yield different ρ values (in an inverse relationship and for low values of σ^+) under conditions whereby the rate of mixing, diffusion control and precision of analysis[14] cannot be variables; thus, a relationship exists between the reactivity of electrophiles and their selectivity in the Friedel-Crafts alkylation of aromatic compounds. Finally, we have extended the standard 2-point benzene/toluene series to the benzylation of anisole[11] (σ^+_{OCH3} = -0.78; k_A/k_B = 5.22; % p = 42.3) and find that over the total σ^+ range of 0 to -0.78 the plot of log p_f *vs* σ^+ is curved; it appears that ρ values of 0 will occur at σ^+ values more negative than ~ -1 (representing constant, intermolecular selectivity by the electrophile). Thus, for the Friedel-Crafts alkylation, the multiple reactivity-selectivity plots relating to the solvent-nucleophiles, at least, are curved, consistent for a reaction series that follows the RSP.[10]

In summary, data for the electrophilic substitution of aromatic compounds by benzyl cations are consistent with the operation of the Reactivity-Selectivity Principle. Many cases where the RSP apparently does not operate[1-4] involve the alteration of several chemical bonds. The subject of this article is a reaction that consists solely of the formation of one carbon-carbon bond, and that in non-polar solvents, and perhaps the RSP is followed for those reasons.

Reversal of Reactivity. Johnson and Schofield also pursued the issue that at a certain value of σ^+ for the substituents on the benzene substrates the reactivities of the 4-nitrobenzyl and 4-methoxybenzyl cations should reverse. Their claim was based on two assumptions: (1) that the Friedel-Crafts alkylation followed a linear free energy relationship (with *different* ρ values for the cations in this case!), and (2) that, in fact, $k_{(OCH3)}$ could equal $k_{(NO2)}$ with a particular substituted benzene under accessible reaction conditions.[15] The first assumption is in error, as demonstrated in the previous section, and the second is a pure assumption, unlikely to be true except at the diffusion-controlled limit. We conclude that no evidence exists at present to support the claim that the reactivities of benzyl cations in Friedel-Crafts type alkylation reactions will reverse in an accessible experimental range.

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(9) We omit here analogous data and conclusions for benzoylation.[3,4]

(10) The central core of the RSP issue for reactions that follow the RSP has been stated thusly:[1a] "Qualitatively, the principle means therefore that log k-log K relationships such as embodied in the Hammett or Brønsted treatments of data will be curved, approaching a zero slope as k becomes larger; in the limit, zero selectivity as denoted by zero slopes (ρ, α or ß) of such plots is produced by reagents of infinite reactivity, coincident with diffusion control."

(11) White, E. H.; Darbeau, R. W.; Darbeau, N. R.; Chen, Y.; Chen S.; Chen, D. *J. Org. Chem.* **1996**, *61(23)*, 7986-7987.

(12) Similar values were measured for reaction solutions diluted with chloroform.

(13) These values of ρ are smaller by a factor of ~2 than those calculated from Olah's data for benzylation *via* the standard Friedel-Crafts approach[4] [ρ (4-nitrobenzyl) = -2.3; ρ (benzyl) = -4.3; ρ (4-methylbenzyl) = -6.6; and ρ (4-methoxybenzyl) = -8.4]. This factor of ~2 is consistent with the evidence presented elsewhere[11] that essentially free and highly active carbocations are intermediates in the deaminative approach but that less reactive and more selective electrophiles (with higher ρ values), such as polarized alkyl halide-aluminum chloride complexes or ion-pairs,[7,8] are intermediates in the standard Friedel-Crafts alkylation.

(14) In order for ρ (4-nitrobenzyl) [-1.2] to equal ρ (4-methylbenzyl) [-3.4] through errors in measurement, an increase in the experimental quantities, k_T/k_B x %p/100, of ~500% would be required, far beyond the error present in the measurement (estimated at ~3-4%).[11]

(15) A graphical illustration of the "reactivity reversal" has been published; however, the plot of log k *vs* σ is based on the erroneous assumption (see text) that a linear free energy relationship is followed.[4] Plotting errors also are apparent. The line for 4-methoxybenzyl is shown passing through the X-axis at $\sigma+ = 0$ and it has apparently been taken directly from a Hammett plot in which log $k_{tol(p)}/k_{benzene/6}$ is plotted on the Y-axis (Fig 1, *e.g.*); the shift on the Y-axis equivalent to log $k_{benzene/6\ (OCH3)}$ has not been made.

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