A New Look at the Friedel−Crafts Alkylation Reaction[1]

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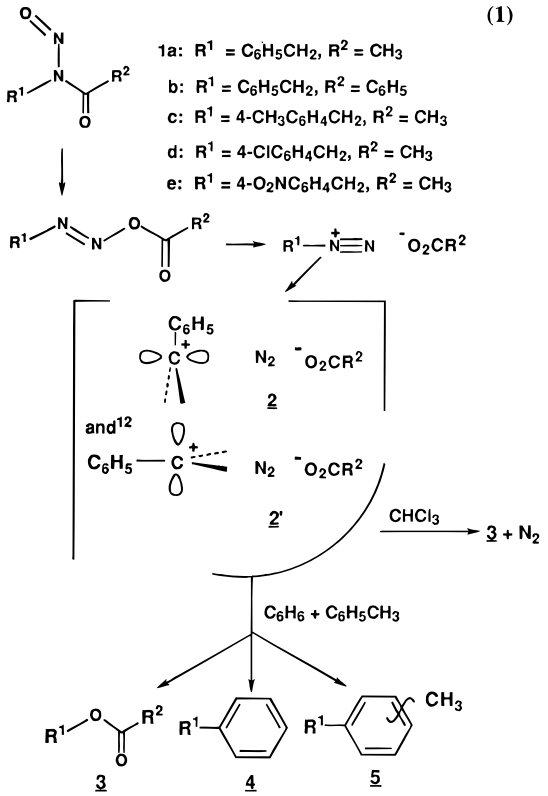
The bond-forming step in the Friedel−Crafts (F-C) alkylation reaction was investigated through use of a method for introducing essentially free carbocations into an aromatic solvent in the absence of catalysts. This direct approach led to elucidation of the reaction mechanism of the alkylation step.

Standard Friedel−Crafts alkylations involve aromatic substitution by an electrophile generally derived from some combination of an alkyl group and the conjugate base of a strong acid (RX).[2−4] In the alkylation of mixed solvents (benzene and toluene, e.g.) the intermolecular selectivity (k_T/k_B) is in proportion to the intramolecular selectivity for a wide variety of reactions (the Brown selectivity relationship, BSR).[2] Benzylation is a particularly important alkylation since substituent effects can be readily examined, but most previous studies of benzylation[3,4] have led to the conclusion that benzylation does not follow the BSR. This conclusion is of concern because of general problems with the standard F-C approach including product isomerization,[3e] disproportionation,[3e] overalkylation,[3b] extreme sensitivity to traces of water,[4c] rate of mixing,[3d] etc. The nitrosoamide approach (RX, X=N_2^+) (eq 1) circumvents those difficulties.



(1) Preceding publication: White E. H. *et al. J. Am. Chem. Soc.* **1992**, *114*, 8023−8031.

The Electrophile. The nitrosoamide decomposition introduces into the medium (eq 1) nitrogen-separated carbocation ion-pairs[1,5,8,9] by a unimolecular process. The counterion and the aromatic substrate compete for the carbocation in irreversible reactions,[10] and the high speed of the counterion reaction to yield ester, limited by the rate of diffusion of N_2 into the medium, results in the carbocation having an exceedingly short time to react with the aromatic compounds before being scavenged by the counterion.[1] The product distributions do not change during the course of the reaction or on standing, and product formation is under strict kinetic control. The alkylation yields are a function of the reactivities of the counterion, the cation, and the substrate;[11] excellent product balances can be achieved (Table 1). The carbocations formed by this approach are extraordinarily reactive,[9] and they probably represent as free a carbocation as can be generated in liquid media. The high *meta* yields obtained in benzylation (14−26%) relative to values found in the standard F-C studies (1.1−9.6%)[3,4] indicate that the alkylating agent in the standard F-C approach is less reactive than that acting in the deaminative approach; some type of carbocation−ligand complexing must be involved in the former case, therefore.[2,3a,4]

The Transition State(s). Most standard Friedel−Crafts alkylations, *e.g.*, methylation, ethylation, and isopropylation, follow the Brown selectivity relationship,[2] which correlates intermolecular selectivity among different substrates with intramolecular selectivity (*ortho*, *meta*, *para* distribution). A plot of our data *via* the equation of Brown, *et al.*, log $p_f = bS_f$,[13] is linear (R^2 = 0.985; slope = 1.52). This linearity of the BSR plot and also that of log % yield of alkylated aromatics *vs* log % *meta* isomer (data of Table 1), another type of selectivity plot (R^2 = 0.935), indicate that the mechanism of alkyl-

(2) Stock, L. M.; Brown, H. C. *Adv. Phys. Org. Chem.* **1963**, *1*, 35−154, and cited references therein to *J. Am. Chem. Soc.* **1953**, **1956**, **1959**.

(3) (a) Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1962**, *84*, 1688−1695. (b) Olah, G.; Olah, J. A. *J. Org. Chem.* **1967**, *32*, 1612−1614. (c) Olah, G. A.; Tashiro, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1970**, *92*, 6369−6371. (d) Olah, G. A. *Acc. Chem. Res.* **1971**, *4*, 240−248. (e) Olah, G.; Kobayashi, S.; Tashiro, M. *J. Am. Chem. Soc.* **1972**, *94*, 7448−7461. (f) Olah, G. A.; Olah J. A.; Ohyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 5284−5290. (g) Olah, G. A. *et al. J. Am. Chem. Soc.* **1987**, *109*, 3708−3713. (h) Olah, A.; Farooq, O.; Farnia, S. M. F.; Olah, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 2560−2565.

(4) (a) DeHaan, F. P. *et al. J. Am. Chem. Soc.* **1984**, *106*, 7038−7046. (b) DeHaan, F. P. *et al. J. Org. Chem.* **1984**, *49*, 3954−3958. (c) DeHaan, F. P. *et al. J. Am. Chem. Soc.* **1990**, *112*, 356−363.

(5) The predominant *retention* of configuration observed in homologous reactions under similar conditions[1] and ^{18}O studies of "intramolecular inversion"[6] require the existence of the carbocation for a finite period of time. The decomposition in toluene of *N*-methyl-*N*-nitroso-4-toluenesulfonamide (Diazald), expected to react *via* the diazonium ion,[7] does not yield the xylene isomers; only methyl tosylate is formed.

(6) White, E. H.; Aufdermarsh, C. A., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 1179.

(7) Brosch, D.; Kirmse, W. J. *J. Org. Chem.* **1991**, *56*, 907−908.

(8) White, E. H.; DePinto, J. T.; Polito, A. J.; Bauer, I.; Roswell, D. F. *J. Am. Chem. Soc.* **1988**, *110*, 3708.

(9) White, E. H.; McGirk, R. H.; Aufdermarsh, C. A., Jr.; Tiwari, H. P.; Todd, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 8107.

(10) White, E. H.; Woodcock, D. J. in *The Chemistry of the Amino Group*; Patai, S., Ed.; Wiley-Interscience: New York, 1968; pp 440−483.

(11) Reactive aromatics lead to high yields of products; e.g., pyrrole is benzylated in yields of ~80%. (Pyrrole cannot be alkylated directly by the standard F-C approach).

(12) For evidence related to rotation of the cation, see refs 1, 6, 8.

(13) $p_f = 6(kT/kB)(\%p/100)$; $S_f = \log p_f/[3(kT/kB)(\%m/100)]$ (ref 2).

(14) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row Publishers: New York, 1987; Chapter 7.

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Table 1. Yields and Relative Rates in Nitrosoamide-Mediated Benzylations (4-R-$C_6H_4CH_2^+$) of Benzene and Toluene[a-c]

alkylating agent	R	temp (°C)	yields (%) 3	yields (%) **4 + 5**	k_T/k_B[d]	isomer distribution (%) (4-R-benzyltoluenes) ortho	meta	para	inter/intra selectivities[e]
1a	H	80	91.5	8.5	2.51	43.8	17.8	38.4	1.0
1b		40	89.4	10.6	2.55	46.0	19.4	34.6	1.1
1b		25	87.2	12.8	2.66	46.6	18.6	34.8	1.1
1c	CH_3	80	98.0	2.0	4.39	44.1	14.1	41.8	1.3
1d	Cl	80	90.7	9.3	2.41	44.0	18.3	37.7	0.9
1e	NO_2	80	73.4	26.6	1.33	45.1	26.4	28.5	0.9

[a] Solvent = equimolar benzene and toluene. Product distributions by NMR and GLC (30 m SE-30, 0.25 mm i.d.; col temp = 145 °C); total yields of products ~97%. [b] [**1a**,**e**] = ~0.05 M; pyridine present in all runs (~0.1 M). [c] Standard deviations for $k_T/k_B \leq 0.12$, for relative yields ≤ 0.90. [d] Values are independent of total incubation times and initial solvent ratios. [e] See text.

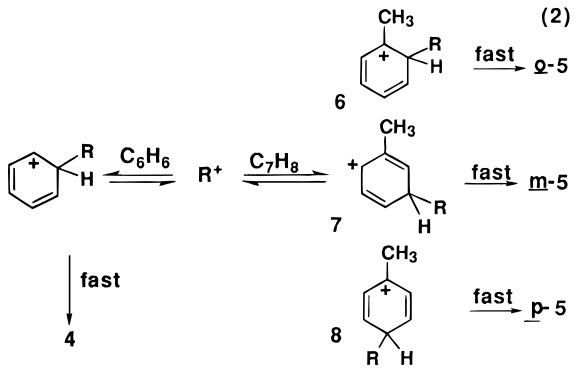
ation does not change over the range of *para*-substituents used (**1a**−**e**).[14] A single type of transition state, presumably of the σ type, is thus adequate to account for our data.

Benzylation *via* the standard F-C approach utilizing substituted benzyl chlorides has been reported not to follow the BSR,[3c−e,4a,15] and to account for that observation two types of transition states were proposed for the alkylations: a π-type for the more reactive benzyl electrophiles (including the parent "benzyl cation") "which determines substrate selectivity", "followed by σ-complex formation determining positional selectivity"[3d] and a σ-type for the less reactive ones.[3c−e] These conclusions have been criticized on the basis of theory[16] and experiment;[4b] further, if the published data[3c] for only the *para*-substituted benzyl chlorides are considered (to minimize steric effects and complications due to overalkylation), the BSR plot obtained is linear ($R^2 = 0.918$), consistent with the single transition state model.

The Arenium Ion Intermediate and the Source of the *Meta* Isomer. The decomposition of nitrosoamide **1e** in 2,4,6-trideuteriotoluene was carried out and the (nitrobenzyl)toluenes formed (**5**, R′ = 4-nitrobenzyl) (Table 1) were analyzed by GC-MS[17] for their deuterium content. The local electron ionization of the nitrophenyl ring permits an MS analysis of the deuterium content of the other ring. The data: *ortho*, 2.0; *meta*, 2.93; *para*, 2.0 D/molecule indicate that the *ortho* and *para* isomers and 90% of the *meta* isomer are formed with the loss of only the hydrogen isotope originally present at the substitution site; in the *meta* case, ~10% of the molecules have lost a deuterium atom, possibly *via* hydrogen exchange along a path leading to the most stable arenium ion (**7** → **9** (and 2-H isomer) → *meta* **5**). The deuterium labeling results indicating that the *ortho*, *meta*, and *para* isomers are formed by similar mechanistic pathways, the linear log % hydrocarbon yield *vs* log % *meta* yield relationship for our data, and the yield data (Table 1) provide evidence that the yield of the *meta* isomer in benzylation is in proportion to the reactivity of the electrophile.

Our benzylation results, thus, are not in agreement with a proposal that the *meta* isomer in alkylations stems, to an indeterminate degree, from *para* (and *ortho*) arenium ion intermediates that have undergone coupled hydrogen, alkyl rearrangements (eq 3).[18−20]

A General Reaction Mechanism. Proton loss in the deaminative benzylations is not a significant part of the rate-determining step since no hydrogen isotope effect was detected ($k_T/k_B = 2.34 \pm 0.08$ in fully deuterated solvents, in $C_6H_6 + C_7D_8$, and in $C_6D_6 + C_7H_8$). In view of the similarity in the effects of the methyl group of toluene on inter- and intramolecular selectivity in benzylation [$6/5(k_T/k_B)/2/3(o + p)/m = \sim 1$] (Table 1), it would appear that the same transition states that determine the intramolecular selectivity (those leading to **6** and **8** relative to the transition state leading to **7**, benzene-like with respect to the methyl substituent) also largely determine (relative to the transition state for the alkylation of benzene) the intermolecular selectivity; differences in four activation energies would thus determine both types of selectivity (eq 2). This interpretation



provides a conceptual basis for the empirical BSR and it may be applicable to other electrophilic substitutions that follow that relationship, although the identity and type of electrophile will differ from case to case.

Supporting Information Available: Experimental details (10 pages).

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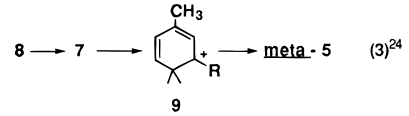

(15) In a few cases, however, *b* values calculated from the BSR equation have been reported near the theoretical value of 1.3.[3e,4b,c]

(16) Johnson, C. D.; Schofield, K. *J. Am. Chem. Soc.* **1973**, *95*, 270−272.

(17) (a) University of Illinois Mass Spectrometry Laboratory (Field Ionization used). (b) No detectible M − 1 peaks were observed for model compounds.

(18) Putative supporting evidence was obtained for the mechanism[19,20] in the methylation of 2,4,6-trideuteriotoluene; no data or details were given for the analysis of the xylene *mixture* produced, and the large M − 1 MS peak for toluene renders the analysis arguable.[21] Further, the observed order of arenium ion rearrangements[22] is nearly the opposite of the order cited[3g] in support of the rearrangement hypothesis.

(20) The coupled hydrogen-alkyl rearrangements were addressed in refs 3a,b,d−h.

(21) Biemann, K. *Mass Spectrometry: Organic Chemical Applications*; McGraw-Hill Book Company, Inc.: New York, 1962; p 209.

(22) Koptyug, V. A. *Contemporary Problems in Carbonium Ion Chemistry III: Arenium Ions−Structure and Reactivity*; Springer-Verlag: New York, 1984. (a) p 164. (b) p 159.

(23) Hedaya, A. E.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 1661−1672.

(24) Adapted from ref 3f.