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Using Phenyl Cations as Probes for Establishing Electrophilicity−Nucleophilicity Relations

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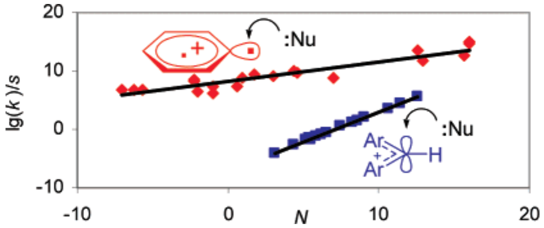

N,*N*-Dimethyl-4-aminophenyl cation is used as an electrophilic probe for determining the relative reactivity of nucleophiles. The singlet state (^{1}**1**) of this cation is completely unselective (reaction rates with benzene, MeCN, and trifluoroethanol within a factor of 5). The corresponding triplet (^{3}**1**) does not react with alcohols and MeCN. The rates of reaction of the latter intermediate with 23 π, σ, and n nucleophiles are measured by competition experiments and found to vary over only 2 orders of magnitude over a range of 22 units of the nucleophilicity parameter N introduced by Mayr. As far as one can judge with the considerable scatter of the data, fitting the data of both amines and π nucleophiles is possible only by using a modified Mayr's equation: $\log k = s(E + eN)$ with $e = 0.33$. The reduced dependence on N is explained by the fact that in the case of diradicalic triplet ^{3}**1** interaction with the nucleophile involves a half-filled (σ) orbital, which is empty in singlet ^{1}**1**. It is suggested that Mayr's equation can be extended to quite diverse reactions, but a scaling factor of $e < 1$ may have to be introduced in some cases, according to the electronic structure of the electrophilic probe used.

Introduction

Most organic reactions can be envisioned as the combination of an electrophile with a nucleophile. Therefore, it is useful to have available experimental scales of electrophilicity and nucleophilicity, in order to rationalize the reaction occurring and to predict whether a given reaction will take place.[1] The first attempt at a quantitative treatment of the reactivity of nucleophiles has been carried out by Swain and Scott for S_N2 reactions and resulted in eq 1,[1b] where s and n_x are empirical parameters of the electrophile and, respectively, of the nucleophile.

$$\log k_x/k_{H_2O} = sn_x \qquad (1)$$

This equation, as well as a more general one proposed by Edwards,[1f] has been used for a variety of reactions and has contributed to distinguishing S_N1 and S_N2 reactions when applied to solvolysis. Experimental attempts to develop a universal kinetic scale of nucleophilicity have been reported by several groups over the last 50 years. From this point of view, a convenient model is the reaction of a cation with an anion to form a covalent molecule, since this is an elementary step occurring in more complex reactions, e.g., S_N1 processes. In this case, the nucleophile attacks a positive center, without the necessity of displacing any leaving group, and one need not worry about a change in mechanism along a series of nucleophiles. Following this reasoning, Ritchie found the rate of reaction of various cations (trityl, aryldiazonium, and tropylium ions) with nucleophiles could be characterized by a single, electrophile-independent parameter and established a nucleophilicity scale.[1d] More recently, Mayr persuasively argued in favor of universal electrophilic/nucleophilic scales.[2] His work was based on the use of benzhydryl cations (diarylmethylium ions) as model electrophiles (see Scheme 1).[2a−d]

The second-order rate constants (k) for the reaction between such cations and a variety of nucleophiles of different nature,

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[1] (a) Phan, T. B.; Breugst, M.; Mayr, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3869. (b) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 141. (c) *Nucleophilicity*; Harris, M., McManus, S. P., Eds.; Adv. Chem. Ser. No. 215; American Chemical Society: Washington, DC, 1987. (d) Richtie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348. (e) Kane-Maguire, L. A. P.; Honig, E. D.; Sweigart, D. A. *Chem. Rev.* **1984**, *84*, 525. (f) Edwards, J. O. *J. Am. Chem. Soc.* **1956**, *78*, 1819. (g) Pearson, R. G. *J. Org. Chem.* **1987**, *52*, 2131. (h) Campodonico, P. R.; Aizman, A.; Contreras, R. *J. Phys. Org. Chem.* **2004**, *17*, 273.

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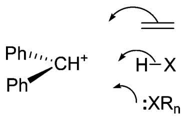
SCHEME 1. Reaction of Benzhydryl Cation with π-, σ-, and n-Nucleophiles



such as π- (alkenes, arenes, enolates), σ- (hydrides), and n- (*N*-, *O*-, *P*-centered) nucleophiles were measured and a logarithmic scale of the relative reactivity (parameter N) was established by taking 2-methyl-1-pentene as the reference, resulting in a range from $N = -4.47$ to 22.62. Likewise, comparing different cations the (nucleophile-independent) electrophilicity parameter E was determined, with a range from −10.04 of a 4,4′-diamino derivative to 6.02 of the 4,4′-dichloro derivative, with $E = 0$ for the 4,4′-dimethoxybenzhydryl cation.[2e] The rate constant for a given reaction was linearly related to such parameters, although the slope was somewhat nucleophile-dependent and a further parameter s (typically 0.6 to 1 for n-nucleophiles, 1 to 1.5 for π-nucleophiles) was introduced, see eq 2.

$$\log k(20\ ^\circ\mathrm{C}) = s(E + N) \qquad (2)$$

Benzhydryl cations were convenient probes because the strong absorption in the visible made their reaction easy to monitor and because they were practically generated under mild conditions. Furthermore, the electrophilicity could be conveniently tuned by introducing electron-donating or -accepting ring substituents.[2a−d] Having available the above set of parameters, the rate k could be predicted over a range of >40 orders of magnitude by means of eq 2. Most measurements were carried in MeCN, which is too weak a nucleophile for reacting with these delocalized carbocations.

Equation 2 has been successfully applied to nucleophiles of various nature (see Scheme 1), while maintaining a single set of parameters. The question is then, how general is this scale, e.g., when changing the electrophilic probe. Thus, further studies have shown that eq 2 applies to the reaction of the same nucleophiles with complexed allyl cations, iminium cations, and dithiocarbenium ions,[2f] as well as with some neutral electrophiles, including Michael acceptors such as benzylidenemalonitriles[2g] and metal-complexed and electron-withdrawing substituted aromatics (trinitrobenzene and heterocyclic analogues, see Chart 1).[2h] However, Mayr recently reported that the application of eq 2 to reactions of sulfonium salts or of alkyl halides proceeding via an S_N2 mechanism required some adjustment,[1a] as will be discussed below.

CHART 1. Charged and Neutral Electrophiles Tested Besides Benzhydryl Cations

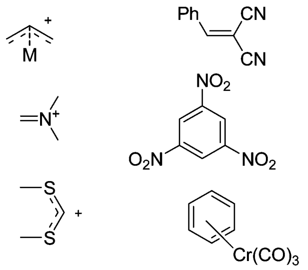
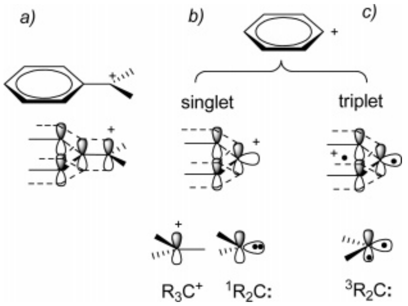


CHART 2



One may wonder whether the remarkably large span of reagents can be further extended. As an example, the simplest carbocations are alkyl carbocations. For the *tert*-butyl cation, the very high E 8.5−9 value has been estimated,[2i] although the high reactivity of these species have led some authors to doubt that these can be defined as intermediates.[3]

A significant step would be extension to divalent carbocations,[4a] such as phenyl cations. These high-energy intermediates have different characteristics with respect to previously considered intermediates. A look to Chart 1 shows in fact that both neutral and charged electrophiles tested in the work presented above shared a common characteristic, namely a delocalized π orbital as the LUMO. Differently from these (see as an example a benzyl cation in Chart 2, a), phenyl cations are not π cations. More precisely, phenyl cations exist in two spin states. The electronic configuration of the singlet is well described as $\pi^6\sigma^0$, and this is a localized carbocation, comparable to singlet carbenes or to a trivalent alkyl carbocation (see Chart 2, b), except for the sp^2 hybridization of the vacant orbital and the fact that C_1 is part of the aromatic system. On the contrary the triplet has a $\pi^5\sigma^1$ structure, similarly to triplet carbenes (see Chart 2, c).

Phenyl cations are virtually inaccessible by thermal reactions[4b] but are smoothly photochemically generated[5a] and have been demonstrated to be versatile electrophiles in synthesis.[5b] The fact that they do not enjoy the stabilization arising from delocalization characteristic of π cations suggests that these species may be a middle point between the poor selectivity of sp^3 alkyl carbocations and the high selectivity of benzhydryl cations. Similarly to carbenes, but differently from (necessarily singlet) benzhydryl cations, these have accessible singlet and triplet states of different structure and chemistry (in turn susceptible to tuning by substituents), further enriching the

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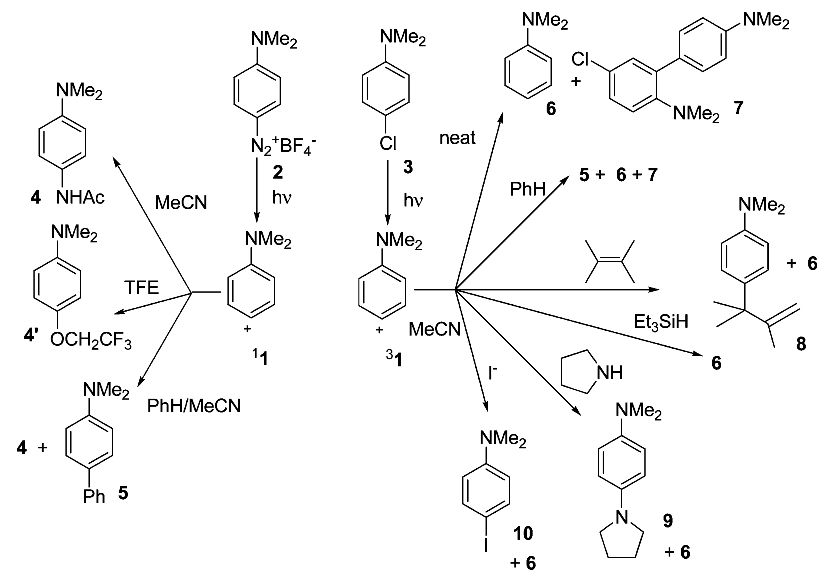
(2) (a) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed.* **1994**, *33*, 938. (b) Mayr, H.; Ofial, A. R. *Pure Appl. Chem.* **2005**, *77*, 1807. (c) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66. (d) Mayr, H.; Müller, K. H.; Ofial, A. R.; Bühl, M. H. *J. Am. Chem. Soc.* **1999**, *121*, 2418. (e) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500. (f) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem.* **1998**, *110*, 1096; *Angew. Chem., Int. Ed.* **1998**, *37*, 1045. (g) Lemek, T.; Mayr, H. *J. Org. Chem.* **2003**, *68*, 6880. (h) Terrier, F.; Lakhdar, S.; Boubacker, T.; Goumont, R. *J. Org. Chem.* **2005**, *70*, 6242. (i) Roth, M.; Mayr, H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2250.

(3) (a) Isaacs, N. *Physical Organic Chemistry*; Longman Scientific & Technical: Burnt Mill, NY, 1995. (b) Toteva, M. M.; Richard, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 11434. (c) Zheng, L. X.; Thibblin, A. *J. Chem. Soc., Perkin Trans. 2*, **2001**, 1600.

(4) (a) *Divalent Carbocations*; Stang, P. J., Rappoport, Z., Eds.; Wiley: Chichester, UK, 1997. (b) Stang, P. J. in ref 4a, p 451.

(5) (a) Freccero, M.; Fagnoni, M.; Albini, A. *J. Am. Chem. Soc.* **2003**, *125*, 13182. (b) Fagnoni, M.; Albini, A. *Acc. Chem. Res.* **2005**, *38*, 713.

SCHEME 2. Products from the Irradiation of *N*,*N*-Dimethyl-4-aminophenyldiazonium Tetrafluoroborate (2) and from *N*,*N*-Dimethyl-4-chloroaniline (3)



palette.[6] Importantly, at least some of these cations can be selectively generated either in the singlet or in the triplet state through the appropriate choice of the conditions. We reasoned that using phenyl cations as electrophilic probes may attain a twofold target. First, this should offer a test for the generality of eq 2. If these highly reactive electrophiles, in which the LUMO has a different character, were amenable to the same treatment and an *E* parameter could be assigned, the generality of the approach would be strengthened. Second, a kinetic study may improve the understanding of these as yet only partially characterized intermediates.[6d]

Results

In view of the above, we report here the reactivity with π-, σ-, and n-nucleophiles of a phenyl cation, 4-*N*,*N*-dimethylaminophenyl cation (**1**). As previously demonstrated through sensitization experiments, this intermediate could be generated either in the *singlet* state, by direct photolysis of the corresponding phenyldiazonium tetrafluoroborate (**2**) (see eq 3),[7] or in the *triplet* state, by photolysis of the corresponding phenyl chloride (**3**) (see eq 4).

$$\mathrm{Me_2NC_6H_4N_2^+}\,(\mathbf{2}) + h\nu \rightarrow {}^1\mathrm{Me_2NC_6H_4^+}\,({}^1\mathbf{1}) \qquad (3)$$

$$\mathrm{Me_2NC_6H_4Cl}\,(\mathbf{3}) + h\nu \rightarrow {}^3\mathrm{Me_2NC_6H_4^+}\,({}^3\mathbf{1}) \qquad (4)$$

To compare the reactivity, irradiations up to moderate (<25%) conversion were carried out.

Reactions of the Singlet Cation. Irradiation of diazonium salt (**2**) in MeCN gave 4-*N*,*N*-dimethylaminoacetanilide (**4**), the product from the Ritter addition of the cation to the solvent. Likewise, in trifluoroethanol (TFE) ether **4′** was obtained. The two solvents were compared by irradiating **2** in various mixtures of these solvents, showing that the ether was formed in a proportion somewhat lower than the solvents molar ratio. π-Nucleophiles were arylated too, provided that they were used at a sufficiently high concentration. Thus, with benzene (≥1 M) in MeCN 4-*N*,*N*-dimethylaminobiphenyl (**5**) was formed along with **4** in a higher proportion than the molar ratio between PhH and MeCN (see Scheme 2). The results in mixed solvents were plotted in Figure 1 as the ratio **4′**/**4** or **5**/**4** vs the NuH/MeCN ratio, where NuH is the other component. In the limits explored (up to 6 M benzene and to 4 M TFE) the data were roughly fitted by a straight line passing for the origin, as is expected for two traps (eqs 5 and 6) competing for the same intermediate $^1\mathbf{1}$, photochemically formed from **2**, see eq 7.

$${}^1\mathbf{1} + \mathrm{MeCN} \rightarrow \mathrm{Me_2NC_6H_4NHAc}\,({}^1k_{\mathrm{MeCN}}) \qquad (5)$$

$${}^1\mathbf{1} + \mathrm{NuH} \rightarrow \mathrm{Me_2NC_6H_4Nu}\,({}^1k_{\mathrm{NuH}}) \qquad (6)$$

$$[\mathbf{4'}]/[\mathbf{4}] \text{ or } [\mathbf{5}]/[\mathbf{4}] = {}^1k_{\mathrm{NuH}}[\mathrm{NuH}]/{}^1k_{\mathrm{MeCN}}[\mathrm{MeCN}] \qquad (7)$$

The slope from the plot gave the rate ratio $^1k_{\mathrm{NuH}}/^1k_{\mathrm{MeCN}}$, respectively 0.8 for TFE and 4.0 for benzene. Allyltrimethylsilane seemed to give practically the same trapping ratio as benzene, at least as far as was possible to measure, due to the lower miscibility of this alkene with MeCN. It appeared thus that cation $^1\mathrm{Me_2NC_6H_4^+}$ ($^1\mathbf{1}$) produced under these conditions reacted unselectively with solvent and trap even when large amounts of the latter were used and the study of this species was not further pursued.

Reactions via the Triplet Cation. On the other hand, anilide **4** was *not* formed in a detectable amount upon photolysis of *N*,*N*-dimethyl-4-chloroaniline (**3**) in MeCN, nor was ether **4′** in TFE. Under these conditions, the products were aniline **6** and diaminobiphenyl **7** resulting from the arylation of the starting material (Scheme 2).[6d] On the other hand, in the presence of 1

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[6] (a) Laali, K. K.; Rasul, G.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 2913. (b) Filippi, A.; Lilla, G.; Occhiucci, G.; Sparapani, C.; Ursini, O.; Speranza, M. *J. Org. Chem.* **1995**, *60*, 1250. (c) Aschi, M.; Harvey, J. N. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1059. (d) Guizzardi, B.; Mella, M.; Fagnoni, M.; Freccero, M.; Albini, A. *J. Org. Chem.* **2001**, *66*, 6353. (e) the chemical reactions of phenyl cation **1** have been exploited i.a. for characterizing ionic liquids: Dichiarante, V.; Betti, C.; Fagnoni, M.; Maia, A.; Landini, D.; Albini, A. *Chem. Eur. J.* **2007**, *13*, 1834. (f) Previous flash photolysis work had shown that in the case of **3** in MeCN only subsequent intermediates involved in the reduction of the triplet cation $^3\mathbf{1}$ had been detected, ref 6d.

[7] Milanesi, S.; Fagnoni, M.; Albini, A. *Chem. Commun.* **2003**, 216. Milanesi, S.; Fagnoni, M.; Albini, A. *J. Org. Chem.* **2005**, *70*, 603.

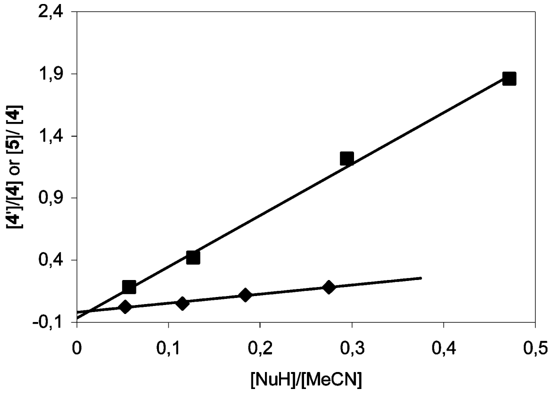

FIGURE 1. Plot of the photoproduct ratios (◆) [**4′**]/[**4**] and (■) [**5**]/[**4**] vs the molar ratio NuH (TFE or benzene)/MeCN in the mixed solvent.

TABLE 1. Product from the Photolysis of Compound 3 (0.05 M) in Acetonitrile[a]

additive	products (% yield)
none	**6** (57), **7** (36)
C_6H_6, 1 M	**5** (48), **6** (21), **7** (11)
$Me_2C{=}CMe_2$, 1 M	**6** (14), **8** (70)
Et_3SiH, 1 M	**6** (95)
pyrrolidine, 1 M	**6** (33), **9** (43)
NaI, 0.05 M	**6** (5), **10** (85)

[a] At 20−25% conversion.

M benzene in MeCN, biphenyl **5** became by far the main product (60%), competing only with the starting aniline that gave some **7**. The ratio **5**/**4** was ≥100 from **3** (based on the limit of detection of **4**) in contrast to 0.17 with the diazonium salt (similar results in TFE). Considering that MeCN and TFE were ca. 19 and 13.5 M, this indicated that benzene trapped triplet cation $^3Me_2NC_6H_4^+$ (^{3}**1**), produced under these conditions, at a rate >1 × 10^3 to 2 × 10^3 times larger than either of these solvents. This encouraged us to explore further traps (1 M), again in experiments at <25% conversion in MeCN. As it appears from Table 1, a further π-nucleophile such as 2,3-dimethylbutene gave the arylated alkene **8**, a σ-nucleophile such as triethylsilane caused a clean reduction to **6**, and a n-nucleophile such as pyrrolidine gave a mixture of reduced **6** and phenylendiamine **9**, in every case with no contamination by **4**. Likewise, in the presence of sodium iodide, iodoaniline **10** was obtained in a good yield (see Scheme 2 and Table 1).

The positive results with such different types of nucleophiles encouraged us to explore the reaction and to measure the competition between such traps. Indeed, it was found that similar reactions took place with further π nucleophiles, including alkenes, an alkyne, aromatics, and heterocycles (**11**−**28**), as well as with further amines (**30**−**33**, see below).

Competition Experiments. As hinted above, previous work supports that these reactions proceeded via the intermediacy of triplet phenyl cation ^{3}**1**.[5a] Trapping was effective at lower concentrations than in the case of singlet cation and the reactivity with the various nucleophiles could be explored under more uniform characteristics, in particular in MeCN. A direct measure of the rate $^3k_{NuH}$ by flash photolysis was precluded, however, because the cation had no convenient absorption.[6f] We thus determined the relative rates through competition experiments. Since iodide was a quite effective trap, the experiments were carried out on 1 or 0.5 M solutions of the above traps (NuH) in the presence of variable amounts of iodide (5 × 10^{-3} to 0.2 M). Reaction with the two traps, NuH and I^- (eqs 8 and 9), competed.

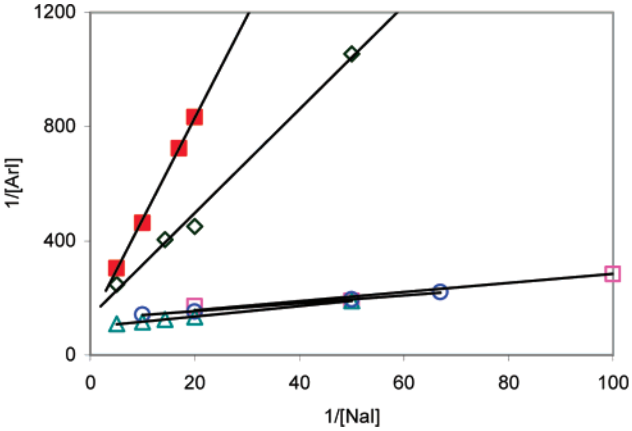

FIGURE 2. Double reciprocal plot (part of the experimental points shown) of iodoaniline formed vs iodide concentration in the presence of benzene (■), 2,3-dimethyl-2-butene (○), triethylsilane (△), pyrrolidine (◇), and pyrrole (□).

$$^3\mathbf{1} + \mathrm{NuH} \rightarrow \mathrm{Me_2NC_6H_4Nu}\ (^3k_{\mathrm{NuH}}) \qquad (8)$$

$$^3\mathbf{1} + \mathrm{I}^- \rightarrow \mathrm{Me_2NC_6H_4I}\ (^3k_{\mathrm{I^-}}) \qquad (9)$$

As mentioned, the solvent did not interfere and in the concentration range used, trapping according to eqs 8 and 9 predominated, minimizing other paths (such as reaction with ground state **3** to give **7**), and the iodide concentration was low enough as to disregard the salt effect. Therefore, the iodide and the nucleophile compete for the triplet cation, formed with efficiency η. The rate of formation of the iodoaniline **10** is given by the ratio between trapping by iodide ($^3k_{I^-}[I^-]$) and the overall reaction ($^3k_{NuH}[NuH] + {}^3k_{I^-}[I^-]$). This compound is formed at a rate expressed by eq 10 or, in the reverse form, eq 10′ predicting a linear dependence in the double reciprocal plot.

$$[\mathrm{ArI}] = \eta\ (^3k_{\mathrm{I^-}}[\mathrm{I^-}])/(^3k_{\mathrm{NuH}}[\mathrm{NuH}] + {}^3k_{\mathrm{I^-}}[\mathrm{I^-}]) \qquad (10)$$

$$[\mathrm{ArI}]^{-1} = \eta^{-1}(1 + {}^3k_{\mathrm{NuH}}[\mathrm{NuH}]/\,{}^3k_{\mathrm{I^-}}[\mathrm{I^-}]) \qquad (10')$$

Experiments with at least four I^- concentrations were carried out for each nucleophile. In accord with prediction, these gave linear fittings with constant intercept (±12%, representative examples are reported in Figure 2). The respective slope/intercept ratios are reported in Table 2 and, being [NuH] known, correspond to the rate constants ratios $^3k_{NuH}/^3k_{I^-}$. These values allow a comparison of the reactivity of cation ^{3}**1** with nucleophiles and a test of the application of eq 2 (see the Discussion).

Further parameters for evaluating the electrophilicity of cations were based upon calculated thermodynamic quantities. As an example, Houk and Mayr[8] compared the empirical *E* factor for benzhydryl cations with the calculated (B3LYP)

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[8] Schindele, C.; Houk, K. N.; Mayr, H. *J. Am. Chem. Soc.* **2002**, *124*, 11208.

TABLE 2. Rate of Reaction of Triplet 4-*N*,*N*-Dimethylaminophenyl Cation with Nucleophiles

nucleophiles	N	s	slope/intercept	$\log {}^3k_{\mathrm{NuH}}$	$\log {}^3k_{\mathrm{NuH}}/s$
		aromatics			
11, fluorobenzene	−5.60[a]	1.20[b]	0.007	7.96	6.64
12, chlorobenzene	−7.00[a]	1.20[b]	0.008	8.02	6.68
13, benzene	−6.29[c]	1.20[c]	0.013	8.23	6.86
14, 1,3-dimethoxybenzene	2.48[d]	1.09[d]	0.015	8.29	7.60[e]
15, mesitylene	−2.00[b]	1.30[b]	0.021	8.44	6.49
16, aniline	12.64[f]	0.68[f]	0.101	9.12	13.41
17, *N*,*N*-dimethylaniline	5.60[a]	1.10[b]	0.481	9.80	8.91
		heteroaromatics			
18, thiophene	−1.01[g]	1.10[g]	0.011	8.16	7.42
19, Furan	1.36[d]	1.31[d]	0.019	8.40	6.41[e]
20, pyrrole	4.63[h]	1.00[h]	0.303	9.60	9.60
		alkenes, alkynes			
21, 1-hexyne	−2.19[c]	0.70[c]	0.012	8.20	11.71
22, 1-hexene	−2.25[d]	0.99[d]	0.020	8.42	8.50
23, 2,3-dimethyl-2-butene	−1.00[g]	1.40[g]	0.022	8.46	6.04
24, 2-methyl-2-butene	0.65[d]	1.17[d]	0.035	8.66	7.40
25, 2-methyl-1-pentene	0.96[d]	1.00[d]	0.040	8.72	8.72
26, allyltrimethylsilane	1.79[d]	0.94[d]	0.052	8.83	9.40
27, 2,3-dihydrofuran	4.37[i]	0.90[i]	0.058	8.88	9.87
28, 2,5-dimethyl-2,4-hexadiene	3.00[b]	1.00[b]	0.107	9.15	9.15
		hydride			
29, triethylsilane	3.64[d]	0.65[d]	0.036	8.67	13.34[e]
		amines			
30, pyridine	12.90[j]	0.67[j]	0.006	7.90	11.78
31, *n*-propylamine	15.70[k]	0.64[k]	0.009	8.09	12.63
32, diethylamine	15.97[b]	0.60[b]	0.057	8.87	14.79
33, pyrrolidine	15.97[l]	0.62[l]	0.135	9.24	14.92

[a] From ref 9a. [b] Parameters estimated from literature values for related compounds. [c] From ref 2a. [d] From ref 2e. [e] Values not used for the plot in Figure 4. [f] From ref 9b. [g] From ref 2c. [h] From ref 9c. [i] From ref 9d. [j] From ref 9e, value in CH_2Cl_2. [k] From ref 9f. [l] From ref 1a.

affinities of the same ions with methyl anion (ΔE_{o}) and found a linear relation (eq 11).

$$E = -0.3496\Delta E_{\mathrm{o}} - 75.11 \tag{11}$$

Following this approach, the affinities of cations ${}^{1,3}\mathbf{1}$ with CH_3^- were calculated at the B3LYP-6-31g(d,p) level and the E factor evaluated by using eq 11. This gave $E = 27.7$ for the triplet and $E = 30.9$ for the singlet state of this ion.

Discussion

Singlet vs Triplet Phenyl Cation. The comparison between phenyl cations ${}^{1,3}\mathbf{1}$ and alkyl cations on one hand and benzhydryl cations on the other one is instructive under different aspects. The singlet phenyl cation shows the universal reactivity typical of alkyl cations. Paradigmatic is the trapping of both such ions by a weak nucleophile such as MeCN forming an iminium cation and, via water addition, an acetanilide (Ritter reaction). Triplet phenyl cation and benzhydryl cations, on the other hand, exhibit essentially the same chemistry, with formation of a C−C bond with π-nucleophiles, of a C−N bond with amines (accompanied by reduction with the phenyl cation) and hydride transfer from a σ-nucleophile such as triethylsilane. Neither of these cations react with MeCN; however, the two intermediates differ in the reaction with alcohols, since Ph_2CH^+ give ethers with both MeOH and TFE, while ${}^3\mathbf{1}$ does not (in TFE cation ${}^3\mathbf{1}$ is trapped by the π-nucleophile present, chloroaniline **3**, despite the relatively low concentration, 0.05 M, to give biphenylamine **7**; in MeOH an electron-transfer path leads to reduction).

The calculated affinity of both singlet and triplet **1** for the methyl anion is large. Although thermodynamic stabilities are not related to reactivities, less so because calculations in vacuo are considered, the qualitative indication is clearly for an electrophilicity parameter E around 30, much above the limit reached by benzhydryl cations ($E \approx 6$). On this basis, *both* states of cation **1** were expected to react at the diffusion-controlled rate (k reaching the diffusion limit, $k \cong 1.2 \times 10^{10}$ M^{-1} s^{-1} since $E + N \gg 10$) even with weak nucleophiles (e.g., benzene, $N = -6.29$, acetonitrile)[10a] with no selectivity.

The experiments showed that this is indeed the case for singlet ${}^1\mathbf{1}$ that was formed by photolysis of the diazonium salt **2**, eq 3, with benzene (and alkenes) reacting only 4−5 times as much as MeCN. It appears reasonable that the reaction rate with

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(9) (a) Gotta, M. F.; Mayr, H. *J. Org. Chem.* **1998**, *63*, 9769. (b) Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679. (c) Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem. Eur. J.* **2003**, *9*, 2209. (d) Dilman, A. D.; Mayr, H. *Eur. J. Org. Chem.* **2005**, 1760. (e) Brotzel, F.; Kempf, B.; Singer, T.; Zipse, H.; Mayr, H. *Chem. Eur. J.* **2007**, *13*, 336. (f) Minegishi, S. R.; Mayr, H. *J. Am. Chem. Soc.* **2003**, *125*, 286. (g) See also the following site: http://cicum92.cup.uni-muenchen.de/mayr/reaktionsdatenbank/.

(10) (a) The addition of benzhydryl cations to acetonitrile has been detected by flash photolysis [rate for the process $Ph_2CH^+ + MeCN \rightarrow Ph_2CHN{=}C^+Me$ is 1.1×10^5 M^{-1} s^{-1}] but is reversible and does not contribute to the products formed; see: Bartl, J.; Steenken, S.; Mayr, H.; McClelland, R. A. *J. Am. Chem Soc.* **1990**, *111*, 6918. Therefore, this has no effect on competitive trapping under steady state conditions and accordingly no N parameter has been assigned. If referred to the irreversible reaction, N must be largely negative and in the present discussion it has been assumed that it is at least two units below that of benzene, the reaction of which is not affected by MeCN. (b) The singlet phenyl cation is the intermediate also in the thermal decomposition of phenyldiazonium salts. However, just as in the case of alkyl cations it is doubtful whether the excessive reactivity of this species allows it to be considered an intermediate in thermal reactions; see: Glaser, R.; Horan, C. J.; Lewis, M.; Zollinger, H. *J. Org. Chem.* **1999**, *64*, 902.

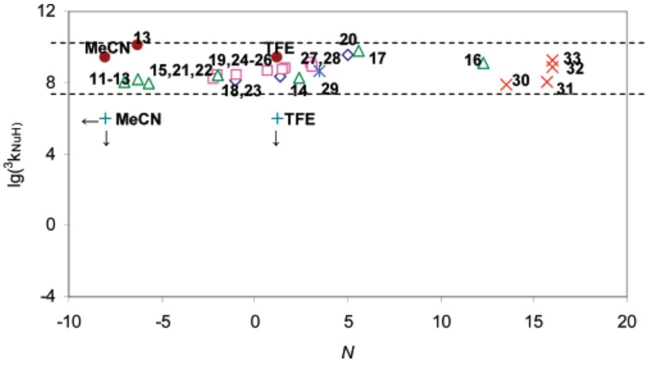

FIGURE 3. Rate of reaction of triplet 4-*N*,*N*-dimethylaminophenyl cation $^3\mathbf{1}$ with π-nucleophiles, viz. (△) aromatics, (◇) heterocycles, (□) alkenes, including 1-hexyne and 2,3-dihydrofuran, (∗) a σ-nucleophile (Et_3SiH), and (×) n-nucleophiles (amines) (numbering, see Table 2) vs Mayr's *N* parameters. Included are also the *maximal* rate values (+) for the case of MeCN (assumed $N \approx -8$,[10a] may be more negative) and TFE ($N = 1.23$), deduced from the nonreactivity in neat solvents ($^3k_{MeCN,TFE} \leq 1 \times 10^5$ M^{-1} s^{-1}) as well as (●) for the reaction of the singlet ion $^1\mathbf{1}$ with the two solvents and with benzene.

benzene is $\sim k_{diff}$. As shown above, all nucleophiles, including MeCN and TFE, react with this intermediate at a rate ($^1k_{NuH}$) within a factor of 5 from k_{diff}. Cation $^1\mathbf{1}^+$ is a completely unselective probe, and could be taken as a model (easier to monitor) of alkyl carbocations.[10b]

On the other hand, when exciting *N*,*N*-dimethyl-4-chloroaniline (**3**), ISC to the triplet precedes fragmentation that thus gives the triplet cation (this is the lowest lying spin state of **1**, $\Delta E_{ST} = 12.9$ kcal/mol).[6] Despite the predicted $E \gg 10$, in this case the reactivity is not uniform and intermolecular selectivity was observed. Thus, within the accessible window (a lower limit is given by the reaction with **3**) there is no significant (irreversible)[10a] reaction with alcohols or with acetonitrile. Rather, π-nucleophiles as well as better nitrogen-centered nucleophiles, such as amines, are selectively arylated with no interference by the solvent (thus, with such nucleophiles $^3k_{NuH} \geq 10^3 \times {}^3k_{MeCN}$); likewise, silane **29** transfers hydride as expected for a σ-nucleophile.

The relative rates of the nucleophiles tested span a factor of 10^2.[11a] When considering also nonreacting MeCN and TFE a 10^5 span results, as opposed to the change by only a factor of 5 for the same reagents with the singlet. We had previously shown[11] that the related triplet 4-methoxyphenyl cation reacted with benzene with a rate constant of about 1×10^8 M^{-1} s^{-1}. If we assume that the reaction of $^3\mathbf{1}^+$ with iodide occurs at the diffusion controlled rate, $^3k_{I^-} = 1.2 \times 10^{10}$ M^{-1} s^{-1}, one obtains $^3k_{NuH} = 1.7 \times 10^8$ M^{-1} s^{-1} for the reaction with benzene, which well fits with what is observed with the methoxy analogue. Thus, the above ratios were converted into rate constants, $^3k_{NuH}$, on this basis (see Table 2).

The constants $^3k_{NuH}$ are higher than those with benzhydryl cations and exhibit a limited dependence on the *N* parameter, varying by only 2 orders of magnitude in correspondence to a change of 22 *N* units. As an example, with the most reactive of benzhydryl cations, $(4\text{-}ClC_6H_4)_2CH^+$ ($E = 6.02$), k_{NuH} increases from 4×10^{-4} M^{-1} s^{-1} with benzene ($N = -6.29$) to 8.9×10^7 M^{-1} s^{-1} with 2,3-dimethyl-2-butene ($N = -0.96$)[2e] while the corresponding values for $^3\mathbf{1}$ are 1.7×10^8 and 2.9×10^8 M^{-1} s^{-1}.

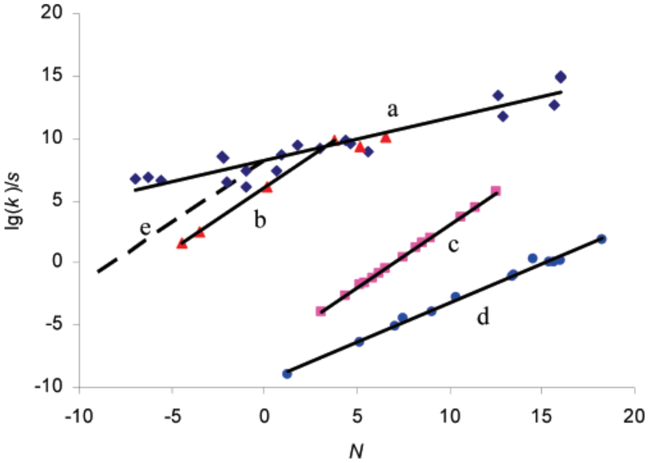

FIGURE 4. Dependence of (log $^3k_{NuH}$)/*s* vs *N* for the reactions (a, ◆) of $^3\mathbf{1}$ with the nucleophiles in Table 2 (except **21** and **29**). Also reported literature data for the reactions of two benzhydryl cations, viz. (b, ▲) $(4\text{-}ClC_6H_4)_2CH^+$ [2a,e] and (c, ■) $(4\text{-}Me_2NC_6H_4)_2CH^+$ [2e] as well as of (d, ●) *S*-methyldibenzothiophenium[1a] with various nucleophiles. The broken line (e) corresponds to the equation (log $^3k_{NuH}$)/$s = 8.11 + N$.

The compressed range precludes applying a treatment of the quality of that done by Mayr with benzhydryl cations, where the rate of trapping varied by >6 orders of magnitude. Still, the rates are *not uniform* with phenyl cations, e.g., pyrrole (**20**) reacts 50 times faster than pyridine (**30**), aniline (**16**) 11 times faster than *n*-propylamine (**31**), and a substituted diene (**28**) five times faster than a monosubstituted alkene (**22**) and ten times faster than a monosubstituted alkyne (**21**). This selectivity is sufficient for preparative purposes in both intra- and intermolecular competitions. As for the dependence on *N*, one can see from Figure 3 that π-nucleophiles and amines lie in two separated areas, within each of which there is a modest increase of log $^3k_{NuH}$ with *N*.

Correlation with Parameter *N*. A precise evaluation requires the use of the (nucleophile-dependent) slope parameters *s*, introduced by Mayr (see eq 2) for a better correlation. This often can be neglected, since *s* has roughly the same value within a chemical class and for benzhydryl cations the fast increase of log *k* with *N* limits the substrates for which measurable data are obtained to a single class. This is not the case here, where a single electrophile is tested with nucleophiles varying from aromatics to amines.[12] Thus, the (log $^3k_{NuH}$)/*s* values (see Table 2) were plotted vs *N* in Figure 4.[13] Since for amines this value is about a half of that of aromatics (*s* 0.65 vs 1.2−1.3), this has the effect of enhancing the amines values.

A consistent, if moderate, increase of the (log $^3k_{NuH}$)/*s* values for phenyl cation $^3\mathbf{1}$ over a very large range of 22 *N* units can be detected and a linear fitting including both the values of π-nucleophiles (omitting **14** and **19**) and those of amines (including pyridine) is possible (see line a in Figure 4, the σ donor **29** was also omitted). However, this involves a much

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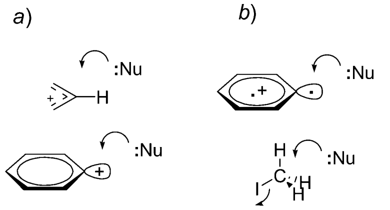
[11] (a) Computational work has shown that triplet cation $^3\mathbf{1}$ first forms a single bonded (triplet) adduct with alkenes that then undergoes ISC and evolves to the final products, see ref 5a; we assume that the rate-determining step is formation of the initial adduct. (b) Dichiarante, V.; Dondi, D.; Protti, S.; Fagnoni, M.; Albini, A. *J. Am. Chem. Soc.* **2007**, *129*, 5605.

[12] A (log *k*)/*s* vs *N* plot is used when a large span of *N* values is covered by several electrophiles, see ref 2e.

[13] Unfortunately the *s* values were not known for all of the compounds tested, and in some cases these were estimated from those of structurally analogous nucleophiles (see footnotes to Table 2).

SCHEME 3. More (a) and Less (b) Favored Nucleophile−Electrophile Interactions



lower than unitary dependence on N (0.33) and then an E value of 8.11 is evaluated

$$(\log {}^{3}k_{\mathrm{NuH}})/s = 8.11 + 0.33N \qquad (12)$$

For the sake of comparison, data by Mayr for two benzhydryl cations, viz. $(4\text{-ClC}_6\text{H}_4)_2\text{CH}^+$ (E = 6.02, line b in Figure 4) and the less strong electrophile $(4\text{-Me}_2\text{NC}_6\text{H}_4)_2\text{CH}^+$ (E −7.02, line c in Figure 4), are also reported in Figure 4 and exhibit the behavior expected from eq 2, unitary slope until k_{diff} is reached and then a plateau.

We are somewhat reluctant to draw an inference from this behavior, because of the limited range of the measured rates and their proximity to k_{diff},[14] as well as the considerable scatter of the data (expected in such a limited range). If the dependence is genuine, a hypothesis for low slope of line a in Figure 4 (compare with line e that would be expected for a unitary dependence on N, $(\log {}^{3}k_{\mathrm{NuH}})/s = 8.11 + N$, also reported in Figure 4) can be formulated. Indeed, the characteristics of triplet ${}^{3}\mathbf{1}$, viz., (i) that E is much smaller than for ${}^{1}\mathbf{1}$, so that, contrary to that case, reactions do not occur uniformly at the diffusion-controlled rate and (ii) the limited increase of the rate of reaction of ${}^{3}\mathbf{1}$ with N (weighting factor $e = 0.33$) in contrast to the unitary slope with benzhydryl cations, are both explained by the different *electronic structure* of these intermediates.

As indicated in Chart 2, singlet cation ${}^{1}\mathbf{1}$ ($\pi^6\sigma^0$ orbital population) has an empty (σ) orbital and stabilization in the interaction with nucleophiles is fully enjoyed (Scheme 3a). In this case, E is probably well represented by that calculated from methyl anion affinity (E = 30.9), although leveling to the diffusion limit only allows an estimate for $E > 18$ from the fact that the reactions with benzene ($N = -6.39$) and MeCN (N probably lower) are still diffusion controlled or close to it. In contrast, triplet cation ${}^{3}\mathbf{1}$ has a $\pi^5\sigma^1$ orbital population and the charge delocalized on the ring and the amino group.[6d] It thus resembles a triplet (diradicalic) carbene rather than a localized carbocation.[6d] The nucleophile thus interacts with a *half-filled*, rather than with an empty orbital (and forms a diradical rather than a closed-shell end product, see Scheme 3b and eq 13).[11a]

$$\mathrm{Ar}^{+(\uparrow\uparrow)} + \mathrm{Nu}{:} \rightarrow \mathrm{Ar}^{+(\uparrow)}\text{−}\mathrm{Nu}^{(\uparrow)} \qquad (13)$$

Accordingly, the stabilization when interacting with the nucleophile is reduced. The reaction does not occur when the nucleophile center is an alcohol oxygen, and when it does occur, as with amines as well as σ- and π-nucleophiles, the cation behaves as a less strong electrophile (E = 8.11) than would be expected from the affinity with the methyl anion (E = 27.7).[15]

Using eq 12 well reproduces a characteristic that has been noted in the study of phenyl cations,[5] viz., that the reaction rate with amines is slower than that with π-nucleophiles, whereas the contrary is true with benzhydryl cations. This is because amines have a small s and large N (the reverse applies to π-nucleophiles). Therefore, the advantage of having a high E, as is the case for ${}^{3}\mathbf{1}$, is in part lost since the contribution by the sE term increases less than that with π-nucleophiles and likewise the scaling factor $e < 1$ limits the increase of the seN term for strong nucleophiles (large N). As an example, the expected values of $\log {}^{3}k_{\mathrm{NuH}}$ for the reaction with ${}^{3}\mathbf{1}$ according to eq 12 are 8.60, 9.64, and 8.30 for 2,3-dihydrofuran, pyrrole, and pyrrolidine, whereas these are 3.93, 4.63, and 9.92 for the reaction of a 4,4′-dimethoxybenzhydryl cation (E = 0) with the same compounds according to eq 2.

Comparison with Other Reactions. The proposal that with phenyl cations eq 2 can be applied provided that a factor e limiting the contribution by N is introduced (eq 14) acquires

$$\log k = s(E + eN) \qquad (14)$$

significance in relation to the recent report by Mayr that application of eq 2 to the solvolysis of S-methyldibenzothiophenium ion, that is a $\mathrm{S_N2}$ reaction, required a reduction of the contribution by N (by a factor 0.6, these data are reported in Figure 4 for the sake of comparison, line d) and an even lower contribution (ca. 0.45) seemed to fit some $\mathrm{S_N2}$ reactions of methyl iodide (Scheme 3b).[1a] On the basis of these results, Mayr proposed generalized eq 15, including both an electrophile- and a nucleophile-dependent s factor (of which eq 2 was a particular

$$\log k = s_{\mathrm{E}}s_{\mathrm{N}}(E + N) \qquad (15)$$

case) for describing all of the nucleophile−electrophile combinations. As seen above, with the present aminophenyl cation (in the triplet state) the simplified form does not apply. We find more appropriate to use eq 14, with the weighting factor e, rather than eq 15, since it expresses more directly the rationalization based on the interaction of NuH with a semifilled orbital. The reduced dependence on N observed in $\mathrm{S_N2}$ reactions may likewise be explained by the less accessible (σ^*) orbital involved in the electrophile. Further cases are present in the literature, e.g., the selectivity in the addition of nucleophiles to a quinone methide has been found to be twice as much than that for the reaction with methyl iodide.[16]

Conclusion

In conclusion, a divalent cation, 4-dimethylaminophenyl cation, has been tested as a probe in the reaction with a series of nucleophiles. The observed behavior depends on multiplicity. The singlet ($E > 18$) reacts with any nucleophile at a rate equal or close to the diffusion constant, and its smooth photochemical generation from the diazonium salt may make it an experimentally convenient model of alkyl carbocations. The triplet, on the other hand, has been found to react with various π-, n-, and

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[14] As a matter of fact, the use of eq 2 is *not* recommended[2c] where $E + N > 8$, but for the reasons presented in the text we feel that the small dependence on N observed is meaningful in this case.

[15] Notice further that the approaching path of the nucleophile to the triplet cation is different. As an example, with alkenes, a single bond is first formed leading to a diradical cation, whereas with the singlet cation a closed shell phenonium ion is the first intermediate.[5a,11]

[16] Richard, J. P.; Poteva, M. M.; Crugeiras, J. *J. Am. Chem. Soc.* **2000**, *122*, 1664.

σ-nucleophiles, at rates that were high (10^8−10^{10} M^{-1} s^{-1}) but not flattened on k_{diff}. Importantly, this cation does not react with alcohols, but apart from this, the observed reactions are the same as in the case of benzhydryl ions, with C−C, C−H, and C−nitrogen bond formation. Application of Mayr's equation to amines and to (most of) π-nucleophiles is possible by introducing a scaling factor (0.33) for the nucleophilicity parameter, supporting that also in this case the electrophile−nucleophile interaction is the rate-determining step, with the value $E = 8.11$. The N contribution is reduced because a half-filled, rather than an empty, orbital is involved.[15]

The introduction of a scaling factor for the fast reactions of cations proposed here follows related observations,[2a,16] in particular Mayr's finding that $N < 1$ is required when using the N scale for the (much slower) S_N2 reactions, where again the electrophile interacts with a different (σ*) orbital. With this proviso, a single set of parameters E, N, and s can be used *independently on the mechanism* over an ever increasing range of rate constants, but changing the *nature of the electrophilic probe* may require the introduction of a characteristic parameter e tuning the N contribution. This has a unitary value when the structure of the electrophile strongly favors the interaction (π-type LUMO, as with benzhydryl cations and with the other planar, nonhindered electrophiles shown in Chart 1, as well as with the empty σ orbital in ^{1}**1**), but is otherwise expected to take a lower value, since the nucleophile−electrophile interaction is in some way hindered in other electrophiles (noncationic and nonplanar electrophiles, or a partially occupied MO), as indicated in Scheme 3a,b.

Experimental Section

General. The starting materials 4-*N*,*N*-dimethylaminophenyldiazonium tetrafluoborate (**2**)[7] and 4-chloro-*N*,*N*-dimethylaniline (**3**)[6d] were prepared according to published procedures. Solvents, reagents, and compound **6** were high-purity grade commercial samples and were used as received. The preparation and purification of photoproducts used for the calibration curves of the photoreactions has been reported in previous work (**4**−**10**),[6d,17] while compound **4′** was prepared and purified as reported below.

4-(2,2,2-Trifluoroethoxy)-*N*,*N*-dimethylaniline (4′). 4-(*N*,*N*-Dimethylamino)benzendiazonium tetrafluoroborate (587 mg, 2.5 mmol, 0.25 M) was dissolved in 10 mL of TFE. The solution was flushed with nitrogen and irradiated at 310 nm for 4.5 h. After removing the solvent, the residue was purified by column chromatography (cyclohexane/ethyl acetate 99:1 with 0.2% NEt_3 added), affording 285 mg of ether **4′** (colorless solid, 52% yield). **4′**: mp 67−69 °C. ^{1}H NMR ($CDCl_3$) δ 2.80 (s, 6H), 4.30 (q, 2H, $J = 8.3$ Hz), 6.75 (AA′BB′, 2H), 6.90 (AA′BB′, 2H). ^{13}C NMR ($CDCl_3$) δ 41.2 (CH_3), 67.1 (q, CH_2, $J = 35$ Hz), 114.1 (CH), 116.3 (CH), 123.4 (q, $J = 276$ Hz), 146.9, 149.5. IR (neat) ν/cm^{-1} 1082, 1156, 1247, 1518, 1637, 3440. Anal. Calcd for $C_{10}H_{12}F_3NO$: C 54.79, H 5.52. Found: C 54.9, H 5.1.

Photochemical Reactions of 2. Solutions of 4-(*N*,*N*-dimethylamino)benzendiazonium tetrafluoroborate (0.05 M) containing the nucleophile as well as an internal standard (dodecane 0.5 μL per mL) in 5 mL of MeCN in a quartz test tube were flushed with purified nitrogen and irradiated at 20 °C by means of 6×15W lamps (emission centered at 310 nm) for 10 min. The residual diazonium salt was trapped by addition of some drops of a basic aqueous solution of β-naphthol. Dilute aqueous $NaHCO_3$ was added. The mixture was extracted by diethyl ether, and the separated organic phases were brought to a fixed volume and analyzed by GC on the basis of calibration curves.

Photochemical Reactions of 3. Solutions of 4-chloro-*N*,*N*-dimethylaniline (0.05 M) containing the nucleophile (1 M), NaI (5×10^{-3} to 0.2 M), and triethylamine (5×10^{-3} M, in order to buffer the acidity liberated) were flushed, irradiated as above, and analyzed by GC on the basis of calibration curves.

Each determination is the average of 4 to 5 independent measurements. Double reciprocal plots of *N*,*N*-dimethyl-4-iodoaniline^{-1} vs NaI^{-1} drawn over four or five NaI concentrations for each nucleophile gave linear plots with constant intercept (±12%). The slope/intercept ratio corresponded to $^3k_{\mathrm{NuH}}/^3k_{\mathrm{I^-}}[\mathrm{I}^-]$. The relative rate values were converted into absolute rate constants by assuming $^3k_{\mathrm{I^-}} = 1.2 \times 10^{10}$ M^{-1} s^{-1}.

Calculations. The energy difference ΔE_o for the reaction between 4-*N*,*N*-dimethylaminophenyl cation (singlet and triplet, see coordinates in ref 6d) and methyl anion to give 4-methyl-*N*,*N*-dimethylaniline was calculated at the B3LYP-6-31g(d,p) level by using the Gaussian 03 package[18] and found to be −303.4 kcal/mol for the singlet and −294.7 kcal/mol for the triplet.

Acknowledgment. Dr. Daniele Dondi from this University is heartily thanked for carrying out the above calculations. Partial support of this work by Ministero dell'Università e della Ricerca, Rome, is gratefully acknowledged. Prof. H. Mayr from the Munich University is thanked for useful comments.

Supporting Information Available: NMR spectra of compound **4′** and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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