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DOI: 10.1002/anie.200605205

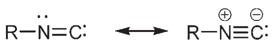
**VIP Nucleophilicity**

# Nucleophilicity Parameters for Alkyl and Aryl Isocyanides**

*Vasily V. Tumanov, Alexander A. Tishkov, and Herbert Mayr**

*Dedicated to Professor Lutz F. Tietze on the occasion of his 65th birthday*

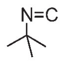
Alkyl and aryl isocyanides have a unique carbene-like structure with a formally divalent carbon atom. Their electronic structure can be represented by the resonance formula **1′** and **1″**. They are readily accessible by a variety of



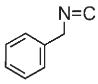
**1'** **1"**

methods and are important substrates for several useful synthetic transformations including the Passerini and Ugi reactions.[1] Many of these reactions proceed by the attack of a carbon electrophile at the isocyano group,[2] but there is only little information about the thermodynamics and kinetics of these reactions.[3–5]

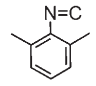
The most comprehensive nucleophilicity scale presently available is based on the benzhydrylium method, which uses reference electrophiles of comparable structure but widely differing reactivity (24 orders of magnitude).[6] We report now on the use of this method for determining the nucleophilic reactivities of the isocyanides **1a**–**e** (Ts = toluene-4-sulfonyl).



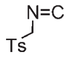
**1a**



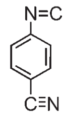
**1b**



**1c**



**1d**

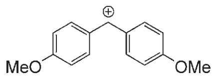
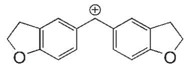
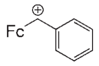
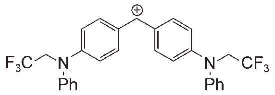
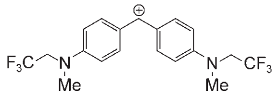
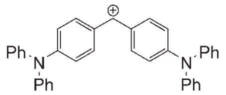
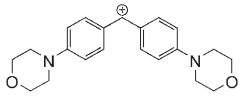
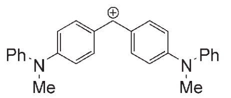


**1e**

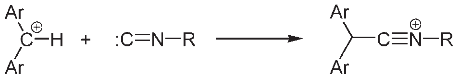
We observed that the rates of the reactions of isocyanides **1a**–**e** with benzhydrylium ions **2** having electrophilicity values $E$ between −6 and 0 were in a conveniently measurable range. For that reason, compounds **2a**–**h** (Table 1) were selected as reference electrophiles for this investigation.[7]

Treatment of the colored solutions of **2**-$BF_4$ and **2**-$ZnCl_3$ with isocyanides **1a**–**e** in $CH_2Cl_2$ resulted in decolorization, which we attributed to the formation of the colorless nitrilium ions **3** (Scheme 1). In accord with this interpretation, the iminoesters **5d** and **5e** were isolated when solutions of chlorobis(4-methoxyphenyl)methane **2a**-Cl and $ZnCl_2/Et_2O$ in $CH_2Cl_2$ were combined with **1d** and **1e** to give the nitrilium ions **3d** and **3e** (Scheme 1), respectively, and successively treated with the silyl ketene acetal **4** (Scheme 2). Treatment of the nitrilium salt **3a**-$ZnCl_3$ with **4** did not yield the iminoester

*Table 1:* Reference electrophiles used in this work for determining the nucleophilic reactivities of isocyanides **1a**–**e**.

| | $Ar_2CH^+$ | $E$[a] |
|---|---|---|
| **2a** |  | 0.00 |
| **2b** |  | −1.36 |
| **2c**[b] |  | −2.64 |
| **2d** |  | −3.14 |
| **2e** |  | −3.85 |
| **2f** |  | −4.72 |
| **2g** |  | −5.53 |
| **2h** |  | −5.89 |

[a] Electrophilicities $E$ of reference electrophiles from Ref. [7]. [b] Fc = ferrocenyl.



**2a–h** **1a–e** **3**

*Scheme 1.* Reaction of benzhydrylium ions **2a**–**h** with isocyanides **1a**–**e** in $CH_2Cl_2$ to give nitrilium ions **3**.

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[**] We thank the Deutsche Forschungsgemeinschaft (Ma673/19-2) for support of this work and Dr. A. R. Ofial for helpful discussions.

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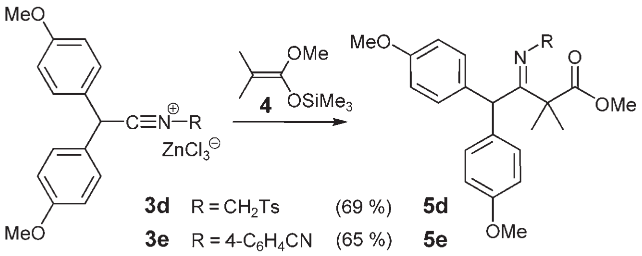
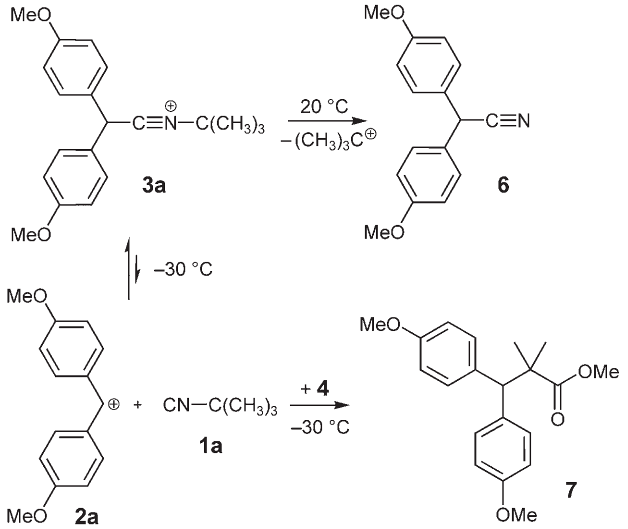


**Scheme 2.** Reactions of nitrilium ions **3d** and **3e** with the silyl ketene acetal **4** to give the imino esters **5d** and **5e**.

**5a** (R = *t*Bu), but resulted in the formation of nitrile **6** when the reaction was carried out at 20 °C (Scheme 3). Compound **7** was produced when this reaction was performed at −30 °C. Whereas the reaction of the silyl ketene acetal **4** with the nitrilium salt **3c**-$ZnCl_3$, arising from **1c** and **2a**-$ZnCl_3$, yielded a mixture of **7** and the iminoester **5c** (R = 2,6-dimethylphenyl), only polymeric material could be isolated from the reactions of benzhydrylium salts with benzyl isocyanide (**1b**).



**Scheme 3.** Reaction of nitrilium ion **3a** to give **6** (at 20 °C) and **7** (at −30 °C).

When solutions of benzhydrylium tetrafluoroborates or triflates **2**-X were treated with more than 10 equivalents of isocyanides **1a–e** in $CH_2Cl_2$, the formation of the colorless nitrilium ions **3** was accompanied by an exponential decay of the benzhydrylium absorbances as a result of the almost constant concentration of **1**. Plots of the resulting first-order rate constants $k_{obs}$ versus the concentrations of **1a–e** are linear, as shown for one example in Figure 1 and for all other kinetic runs in the Supporting Information. The slopes of these correlations gave the second-order rate constants $k_2$ listed in Table 2.

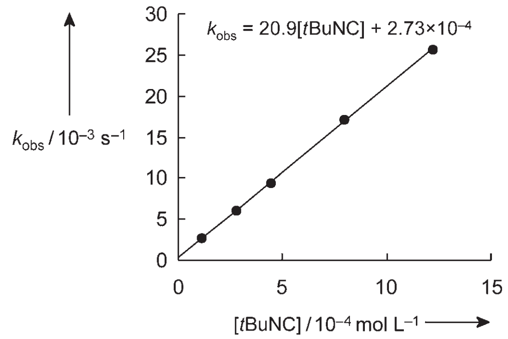


**Figure 1.** Kinetics of the reaction of **2e**-$BF_4$ with *t*BuNC (**1a**) in $CH_2Cl_2$ at 20 °C.

**Table 2:** Rate constants for the reactions of isocyanides **1a–e** with benzhydrylium ions **2a–h** ($CH_2Cl_2$, 20 °C).

| Isocyanide | $Ar_2CH^+$ | $k_2$ [$M^{-1}s^{-1}$] | $N/s$ for **1a–e** |
|---|---|---|---|
| **1a** | **2d** | 57.2 | 5.47/0.77 |
| | **2e** | 20.9 | |
| | **2f** | 3.67 | |
| | **2g** | 0.892 | |
| | **2h** | 0.460 | |
| **1b** | **2d** | 21.8 | 4.90/0.74 |
| | **2e** | 6.04 | |
| | **2f** | 1.09 | |
| | **2g** | 0.392 | |
| **1c** | **2c** | 52.4 | 4.59/0.87 |
| | **2d** | 17.9 | |
| | **2e** | 4.55 | |
| **1d** | **2a** | 421 | 3.50/0.76 |
| | **2b** | 46.5 | |
| | **2c** | 4.24 | |
| **1e** | **2a** | 380 | 3.57/0.72 |
| | **2b** | 39.6 | |

The benzhydrylium-based nucleophilicity scale[6,7] rests on the fact that the second-order rate constants for the reactions of nucleophiles with benzhydrylium ions can be described by Equation (1), where electrophiles are characterized by one

$$\lg k_{20^\circ C} = s(E + N) \qquad (1)$$

parameter (electrophilicity $E$) and nucleophiles are characterized by two parameters (slope $s$ and nucleophilicity $N$). Equation (1) also holds for the reactions of nucleophiles with other types of carbocations[8] including metal-coordinated C electrophiles[7] and Michael acceptors.[9] Recently, it has been demonstrated that the nucleophilicity parameters $s$ and $N$ derived by the benzhydrylium method[6,7] can also be used for describing $S_N2$ reactions, if Equation (1) is extended by an electrophile-specific slope parameter $s_E$.[10]

The linear correlations between $\lg k_2$ and the electrophilicity parameters $E$ of the benzhydrylium ions **2** in Figure 2 show that Equation (1) holds also for the reactions of isocyanides **1** with benzhydrylium ions **2**. In this way we can derive the $N$ and $s$ values for the isocyanides **1a–e** listed in the last column of Table 2.

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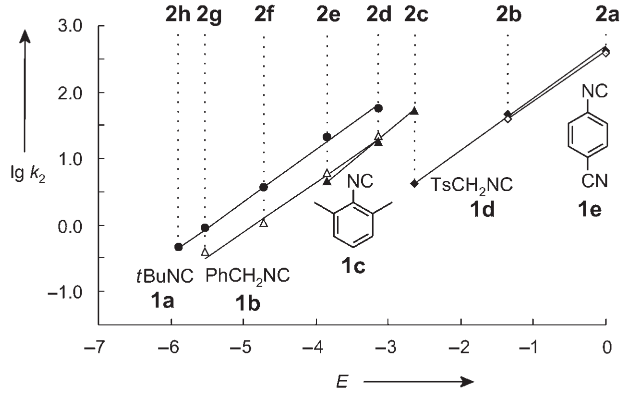
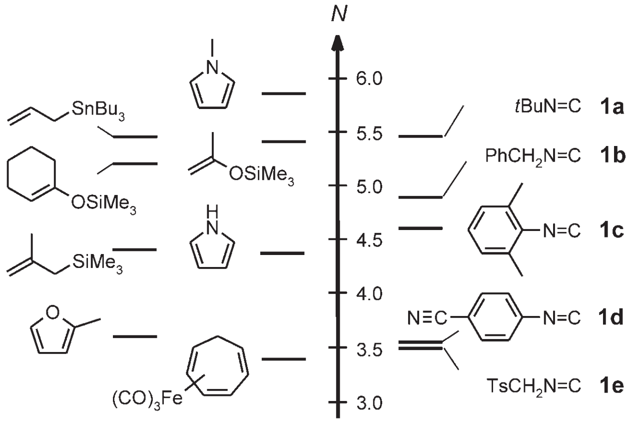


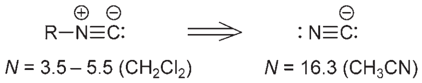
***Figure 2.*** Plots of lg$k_2$ ($CH_2Cl_2$, 20°C) for the reactions of the isocyanides **1a–e** with benzhydrylium ions **2a–h** versus their electrophilicity parameters *E*.

Table 2 and Figure 2 show that *tert*-butyl isocyanide (**1a**) is the most reactive nucleophile in this series, followed by benzyl isocyanide (**1b**) and 2,6-dimethylphenyl isocyanide (**1c**). Remarkably, the acceptor-substituted isocyanides **1d** and **1e** are only one to two orders of magnitude less nucleophilic than the isocyanides **1a–c**, which bear only hydrocarbon moieties. Therefore, it can be expected that the nucleophilicities of most isocyanides are in this range, comparable to the reactivities of furans, pyrroles, allylsilanes, and silyl enol ethers (Scheme 4). This ranking is in good agreement with the relative proton affinities of these compounds: Meot-Ner et al. determined proton affinities of 868 kJ mol$^{-1}$ for *tert*-butyl isocyanide (**1a**) and 867 kJ mol$^{-1}$ for PhNC,[3c] values similar to those reported for 2-methylfuran (866 kJ mol$^{-1}$) and pyrrole (875 kJ mol$^{-1}$).[11]



***Scheme 4.*** Comparison of the nucleophilicities of isocyanides **1a–e** and other C nucleophiles (*N* parameters of the other nucleophiles from Refs. [6,7]).

Analogous kinetic investigations have recently yielded a nucleophilicity parameter of $N = 16.3$ for free $CN^-$ in acetonitrile solution,[12] showing that attachment of an alkyl or aryl group to the N terminus of the cyanide ion reduces the nucleophilicity of the carbon atom by more than ten units on the logarithmic *N*-scale (Scheme 5).



***Scheme 5.*** Nucleophilicity parameters of $CN^-$ and alkly and aryl isocyanides.

Additional work is needed to elucidate whether the nucleophilicity parameters *s* and *N* of isocyanides can also be applied to $S_N2$ reactions as previously shown for the nucleophilicity parameters of alcohols, amines, phosphanes, and some carbanions.[10]

Received: December 22, 2006
Published online: March 30, 2007

**Keywords:** carbocations · isocyanides · kinetics · nitrilium ions · reactivity

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[1] Reviews: a) I. Ugi, S. Lohberger, R. Karl in *Comprehensive Organic Synthesis*, *Vol. 2* (Ed.: C. H. Heathcock), Pergamon, Oxford, **1991**, pp. 1083–1109; b) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89; c) L. Banfi, R. Riva, *Org. React.* **2005**, *65*, 1–140; d) M. Suginome, Y. Ito in *Science of Synthesis*, *Vol. 19*, Thieme, Stuttgart, **2004**, pp. 445–530; e) S.-I. Murahashi in *Science of Synthesis*, *Vol. 19*, Thieme, Stuttgart, **2004**, pp. 1–16; f) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen, L. Balagopal, *Acc. Chem. Res.* **2003**, *36*, 899–907; g) R. V. A. Orru, M. de Greef, *Synthesis* **2003**, 1471–1499; h) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133–1144; i) C. Rüchardt, M. Meier, K. Haaf, J. Pakusch, E. K. A. Wolber, B. Müller, *Angew. Chem.* **1991**, *103*, 907–915; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 893–901; j) I. Ugi, B. Werner, A. Dömling, *Molecules* **2003**, *8*, 53–66; k) G. Dyker in *Organic Synthesis Highlights IV* (Ed.: H.-G. Schmalz), Wiley-VCH, Weinheim, **2000**, pp. 53–57; l) I. Ugi, *Pure Appl. Chem.* **2001**, *73*, 187–191; m) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300–3344; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210.

[2] J. Campo, M. Garcia-Valverde, S. Marcaccini, M. J. Rojo, T. Torroba, *Org. Biomol. Chem.* **2006**, *4*, 757–765.

[3] Proton affinities: a) J. S. Knight, C. G. Freeman, M. J. McEwan, *J. Am. Chem. Soc.* **1986**, *108*, 1404–1408; b) J. E. Del Bene, *J. Am. Chem. Soc.* **1993**, *115*, 1610–1611; c) M. Meot-Ner, Z. Karpas, C. A. Deakyne, *J. Am. Chem. Soc.* **1986**, *108*, 3913–3919.

[4] Kinetics of acid-catalyzed hydrolysis: a) Y. Y. Lim, A. R. Stein, *Can. J. Chem.* **1971**, *49*, 2455–2459; b) K. Sung, C.-C. Chen, *Tetrahedron Lett.* **2001**, *42*, 4845–4848.

[5] Hydrogen-bond-donor abilities: a) A. C. Legon, *J. Chem. Soc. Perkin Trans. 2* **1992**, 329–330; b) M. Meot-Ner, L. W. Sieck, K. K. Koretke, C. A. Deakyne, *J. Am. Chem. Soc.* **1997**, *119*, 10430–10438.

[6] a) R. Lucius, R. Loos, H. Mayr, *Angew. Chem.* **2002**, *114*, 97–102; *Angew. Chem. Int. Ed.* **2002**, *41*, 91–95; b) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77; c) H. Mayr, A. R. Ofial in *Carbocation Chemistry* (Eds.: G. A. Olah, G. K. S. Prakash), Wiley, Hoboken, NJ, **2004**, Chap. 13, pp. 331–358; d) H. Mayr, A. R. Ofial, *Pure Appl. Chem.* **2005**, *77*, 1807–

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1821; e) for a collection of reactivity parameters *E*, *N*, and *s*, see: http://www.cup.uni-muenchen.de/oc/mayr/DBintro.html.

[7] H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel, *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512.

[8] a) H. Mayr, C. Fichtner, A. R. Ofial, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1435–1440; b) C. Fichtner, G. Remennikov, H. Mayr, *Eur. J. Org. Chem.* **2001**, 4451–4456.

[9] a) T. Lemek, H. Mayr, *J. Org. Chem.* **2003**, *68*, 6880–6886; b) G. Ya. Remennikov, B. Kempf, A. R. Ofial, K. Polborn, H. Mayr, *J. Phys. Org. Chem.* **2003**, *16*, 431–437; c) F. Terrier, S. Lakhdar, T. Boubaker, R. Goumont, *J. Org. Chem.* **2005**, *70*, 6242–6253.

[10] T. B. Phan, M. Breugst, H. Mayr, *Angew. Chem.* **2006**, *118*, 3954–3959; *Angew. Chem. Int. Ed.* **2006**, *45*, 3869–3874.

[11] E. P. Hunter, S. G. Lias, *J. Phys. Chem. Ref. Data* **1998**, *27*, 413–658.

[12] A. A. Tishkov, H. Mayr, *Angew. Chem.* **2005**, *117*, 145–148; *Angew. Chem. Int. Ed.* **2005**, *44*, 142–145.

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