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Nucleophilic Reactivities of Imide and Amide Anions

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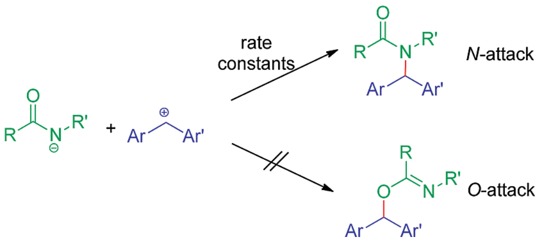
Received May 25, 2010



The kinetics of the reactions of amide and imide anions **2a−o** with benzhydrylium ions **1a−i** and structurally related quinone methides **1j−q** have been studied by UV−vis spectroscopy in DMSO and acetonitrile solution. The second-order rate constants (log k_2) correlated linearly with the electrophilicity parameters E of **1a−q** according to the correlation $\log k_2 = s(N + E)$ (*Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938−957), allowing us to determine the nucleophilicity parameters N and the nucleophile-specific parameters s for these nucleophiles. The reactivities of all sulfonamide and diacylimide anions are found in a relatively small range ($15 < N < 22$). Comparison with structurally related carbanions revealed that amide and imide anions are less reactive than carbanions of the same pK_{aH}. These effects can be attributed to the absence of resonance stabilization of one of the lone pairs in the amide or imide anions. As amide and imide anions are exclusively attacked at nitrogen by benzhydrylium ions, Kornblum's interpretation of the ambident reactivity of amide anions has to be revised.

Introduction

Gabriel's phthalimide method, which has been reported more than 120 years ago,[1] has repeatedly been optimized[2] and is still an important synthesis for primary amines. Hendrickson modified Gabriel's procedure by replacing the divalent protecting group in phthalimide by two monovalent ones which can subsequently be removed (Scheme 1).[3] Over the years, Hendrickson's procedure was further optimized for the synthesis of a wide range of primary and secondary amines,[4] alkylated hydrazines,[5] and amino acids.[6]

Amide anions, like lithium benzamide or phthalimide, have furthermore been reported to be effective Lewis base catalysts in Mannich-type reactions between silyl enol ethers and *N*-tosylaldimines.[7]

Despite the importance of amide anions in organic synthesis and materials, there is only little quantitative data on their nucleophilic reactivity.[8,9] In 1971, Bunnett and Beale studied the kinetics of the reactions of several imide and sulfonamide anions with methyl iodide[8a] and methyl methanesulfonate[8b] in methanol and reported that the nucleophilic reactivities of these anions correlate with their basicities. Bordwell and Hughes investigated the reactivities of several amide anions toward benzyl chloride in DMSO and concluded that the anion of 1,2,3,4-tetrahydrochinolin-2-one is

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(1) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2224–2236.

(2) Gibson, M. S.; Bradshaw, R. W. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 919–930.

(3) (a) Hendrickson, J. B.; Bergeron, R.; Sternbach, D. D. *Tetrahedron* **1975**, *31*, 2517–2521. (b) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1991**, *24*, 285–289.

(4) (a) Johnstone, R. A. W.; Payling, D. W.; Thomas, C. *J. Chem. Soc. C* **1969**, 2223–2224. (b) Harland, P. A.; Hodge, P.; Maughan, W.; Wildsmith, E. *Synthesis* **1984**, 941–943.

(5) Ragnarsson, U. *Chem. Soc. Rev.* **2001**, *30*, 205–213.

(6) (a) Kubo, A.; Kubota, H.; Takahashi, M.; Nunami, K.-i. *Tetrahedron Lett.* **1996**, *37*, 4957–4960. (b) Albanese, D.; Landini, D.; Lupi, V.; Penso, M. *Eur. J. Org. Chem.* **2000**, 1443–1449.

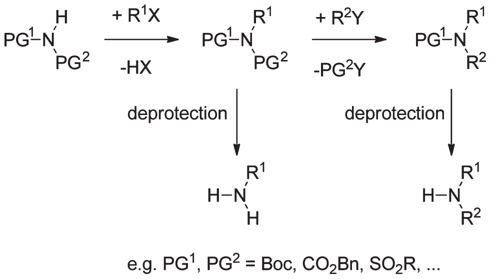
(7) Fujisawa, H.; Takahashi, E.; Mukaiyama, T. *Chem.—Eur. J.* **2006**, *12*, 5082–5093.

(8) (a) Bunnett, J. F.; Beale, J. H. *J. Org. Chem.* **1971**, *36*, 1659–1661. (b) Beale, J. H. *J. Org. Chem.* **1972**, *37*, 3871–3872. (c) Bordwell, F.; Hughes, D. L. *J. Am. Chem. Soc.* **1984**, *106*, 3234–3240.

(9) (a) Kondo, Y.; Kondo, K.; Kusabayashi, S. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1141–1145. (b) Kondo, Y.; Tsukamoto, T.; Moriguchi, C. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1699–1703. (c) Kondo, Y.; Tsukamoto, T.; Kimura, N. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1765–1769.

DOI: 10.1021/jo1009883

SCHEME 1. **Modified Gabriel Synthesis with Monovalent Protective Groups PG^1 and PG^2**



9 times more reactive than the anion of acetanilide and 280 times more reactive than the anion of benzanilide.[8c] Later, Kondo and co-workers examined the S_N2 reactions of several imide anions with ethyl iodide in acetonitrile and acetonitrile−methanol mixtures.[9] Although the pK_{aH} values of succinimide and phthalimide anions differ by more than 1 order of magnitude (9.66 vs 8.30 in water), the second-order rate constants in acetonitrile vary by less than a factor of 3 (1.65×10^{-1} vs 6.43×10^{-2} L mol^{-1} s^{-1}).[9a]

In earlier work we have reported that benzhydrylium ions (Table 1) can be used as reference electrophiles with tunable reactivity[10] for characterizing a large variety of π-nucleophiles (e.g., alkenes,[11] arenes,[11] enol ethers,[11] ketene acetals,[11] enamines,[11] delocalized carbanions[12]), n-nucleophiles (e.g., amines,[13] alcohols[14]), and σ-nucleophiles like hydrides.[10,15] The rate constants at 20 °C of the reactions of these nucleophiles with benzhydrylium ions have been described by eq 1,[16] where s and N are nucleophile-specific parameters and E is an electrophile-specific parameter.

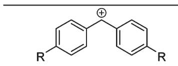
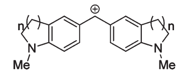
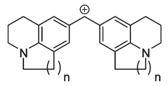
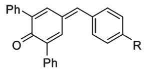
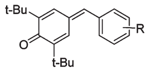
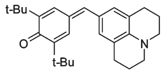
$$\log k_{20^\circ\mathrm{C}} = s(N + E) \qquad (1)$$

We now report on the kinetics of the reactions of imide and amide anions with the reference electrophiles listed in Table 1 in order to determine the nucleophile-specific parameters N and s of these N-centered nucleophiles (Scheme 2) and to include them into our comprehensive nucleophilicity scale.[17]

Results

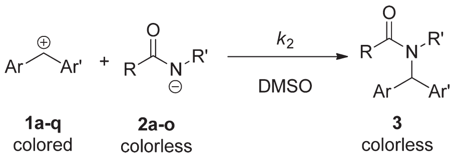
Reaction Products. As ambident nucleophiles, imide and amide anions may react with benzhydrylium ions at either the nitrogen or the oxygen atom (Scheme 3). NMR spectroscopy shows that in all cases examined in this work,

TABLE 1. **Reference Electrophiles Employed in this Work and Wavelengths Monitored in the Kinetic Experiments**

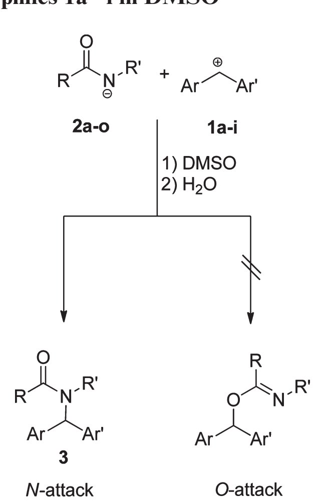
Electrophile			E^a	λ^b / nm
	R = NPh$_2$	**1a**	−4.72	672
	R = N(CH$_2$CH$_2$)$_2$O	**1b**	−5.53	620
	R = NMePh	**1c**	−5.89	622
	R = NMe$_2$	**1d**	−7.02	613
	R = N(CH$_2$)$_4$	**1e**	−7.69	620
	n = 2	**1f**	−8.22	618
	n = 1	**1g**	−8.76	627
	n = 2	**1h**	−9.45	635
	n = 1	**1i**	−10.04	630
	R = OMe	**1j**	−12.18	422
	R = NMe$_2$	**1k**	−13.39	533
	R = 4-NO$_2$	**1l**	−14.32	374
	R = 3-F	**1m**	−15.03	354
	R = 4-Me	**1n**	−15.83	371
	R = 4-OMe	**1o**	−16.11	393
	R = 4-NMe$_2$	**1p**	−17.29	486
		**1q**	−17.90	521

[a] Electrophilicity parameters from refs 10 and 18. [b] Wavelength λ used to follow the kinetics of the reactions.

SCHEME 2. **Reaction of Amide Anions with Benzhydrylium Ions**



SCHEME 3. **Reactions of the Imide and Amide Anions 2a−o with the Electrophiles 1a−i in DMSO**



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[10] 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*, 9500–9512.

[11] Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66–77.

[12] (a) Lucius, R.; Mayr, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1995–1997. (b) Bug, T.; Lemek, T.; Mayr, H. *J. Org. Chem.* **2004**, *69*, 7565–7576.

[13] (a) Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679–3688. (b) Kanzian, T.; Nigst, T. A.; Maier, A.; Pichl, S.; Mayr, H. *Eur. J. Org. Chem.* **2009**, 6379–6385.

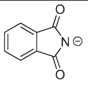
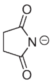
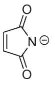
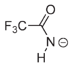
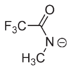
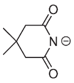
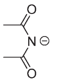
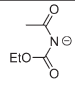
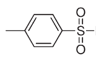
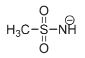
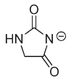
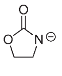
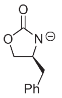
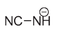
[14] (a) Minegishi, S.; Kobayashi, S.; Mayr, H. *J. Am. Chem. Soc.* **2004**, *126*, 5174–5181. (b) Phan, T. B.; Mayr, H. *Can. J. Chem.* **2005**, *83*, 1554–1560.

[15] (a) Würthwein, E.-U.; Lang, G.; Schappele, L. H.; Mayr, H. *J. Am. Chem. Soc.* **2002**, *124*, 4084–4092. (b) Mayr, H.; Lang, G.; Ofial, A. R. *J. Am. Chem. Soc.* **2002**, *124*, 4076–4083. (c) Richter, D.; Tan, Y.; Antipova, A.; Zhu, X.-Q.; Mayr, H. *Chem. Asian J.* **2009**, *4*, 1824–1829. (d) Richter, D.; Mayr, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 1958–1961.

[16] Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938–957.

[17] For a comprehensive database of nucleophilicity parameters N and electrophilicity parameters E, see http://www.cup.uni-muenchen.de/oc/mayr/.

TABLE 2. Second-Order Rate Constants for the Reaction of Reference Electrophiles 1e−o with Imide and Amide Potassium Salts 2a−n in DMSO at 20 °C

Nucleophile		N / s	pK_{aH} (DMSO)	pK_{aH} (H$_2$O)	Electrophile	Products	k_2 / L mol^{-1} s^{-1}
	**2a**	15.52/ 0.67	13.4[a]	8.30[b]	**1e**		2.51×10^5
					1e		$2.49 \times 10^{5,c}$
					1f	**3af**, 51%	6.42×10^4
					1g		2.85×10^4
					1h		8.86×10^3
					1i		4.05×10^3
					1i		$4.21 \times 10^{3,c}$
					1j		1.93×10^2
					1k		2.74×10^1
					1k		$2.60 \times 10^{1,a}$
	**2b**	16.03/ 0.66	14.7[d]	9.66[b]	**1g**	**3bg**, 85%	$5.25 \times 10^{4,e}$
					1h		$2.01 \times 10^{4,e}$
					1i		$1.01 \times 10^{4,e}$
					1j		$3.91 \times 10^{2,e}$
					1k		$4.66 \times 10^{1,e}$
	**2c**	14.87/ 0.76	10.8[f]	~ 10[g]	**1d**	**3cd**, NMR	-
					1e		3.79×10^5
					1g		3.29×10^4
					1h		1.20×10^4
					1i		6.32×10^3
	**2d**	15.81/ 0.64	17.2[d]	-	**1e**		2.52×10^5
					1f	**3df**, 85%	6.80×10^4
					1g		2.59×10^4
					1i		4.66×10^3
					1j		2.65×10^2
					1k		3.47×10^1
	**2e**	15.70/ 0.71	17.2[h]	13.2[i]	**1d**	**3ed**, NMR	-
					1f		2.29×10^5
					1g		6.22×10^4
					1h		2.67×10^4
					1i		1.06×10^4
	**2f**	17.52/ 0.63	17.3[j]	-	**1d**	**3fd**, 86%	-
					1f	**3ff**, 51%	-
					1g		2.86×10^5
					1h		1.05×10^5
					1i		5.15×10^4
					1j		2.95×10^3
					1k		3.09×10^2
	**2g**	16.05/ 0.70	17.9[j]	12.4[k]	**1d**	**3gd**, NMR	-
					1f		3.45×10^5
					1g		9.89×10^4
					1h		3.62×10^4
					1i		1.77×10^4
	**2h**	15.99/ 0.70	-	-	**1d**	**3hd**, 54%	-
					1f		2.97×10^5
					1g		1.03×10^5
					1h		3.45×10^4
					1i		1.57×10^4
	**2i**	17.14/ 0.60	16.3[l]	10.2[m]	**1d**	**3id**, 73%	-
					1f		2.72×10^5
					1g		7.33×10^4
					1h		4.40×10^4
					1i		1.86×10^4
	**2j**	18.61/ 0.53	17.5[d]	10.8[n]	**1d**	**3jd**, NMR	-
					1g		$1.76 \times 10^{5,o}$
					1h		$7.14 \times 10^{4,o}$
					1i		$2.81 \times 10^{4,o}$
					1i		2.74×10^4
					1j		2.67×10^3
	**2k**	17.52/ 0.55	15.1[p]	9.2[q]	**1d**	**3kd**, 84%	-
					1g		$6.90 \times 10^{4,o}$
					1h		$2.25 \times 10^{4,o}$
					1i		$1.38 \times 10^{4,o}$
	**2l**	22.40/ 0.59	20.9[r]	-	**1d**	**3ld**, 84%	-
					1k		7.67×10^4
					1l		9.21×10^4
					1m		3.32×10^4
					1n		9.30×10^3
					1o		5.94×10^3
					1p		7.12×10^2
					1q		3.28×10^2
	**2m**	22.67/ 0.54	20.6[r]	-	**1d**	**3md**, 94%	-
					1j		3.29×10^5
					1k		5.24×10^4
					1l		9.38×10^4
					1m		2.71×10^4
					1n		6.14×10^3
					1o		4.01×10^3
					1p		5.81×10^2
					1q		2.59×10^2
	**2n**	20.33/ 0.64	17.0[s]	-	**1d**	**3nd**, 95%	-
					1j		1.63×10^5
					1n		7.38×10^2
					1o		5.10×10^2

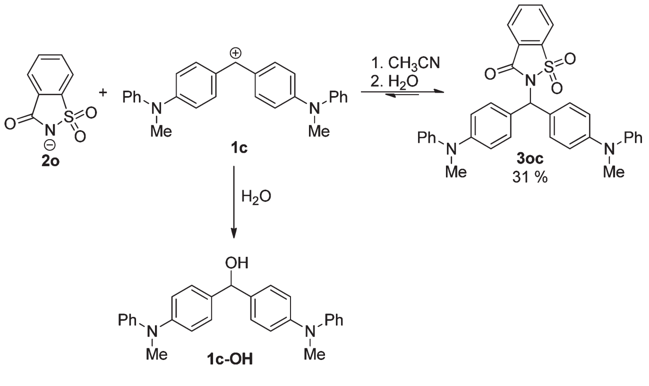
[a] Ref 19. [b] Ref 9a. [c] NMe_4^+ salt, not included in correlation. [d] Ref 20. [e] NBu_4^+ salt. [f] Ref 21. [g] Ref 22. [h] Ref 23. [i] Ref 24. [j] Ref 25. [k] Ref 26. [l] Ref 27. [m] Ref 28. [n] Ref 29. [o] In situ deprotonation with P$_2$-*t*Bu base (1-*tert*-butyl-2,2,4,4,4-pentakis(dimethylamino)-2Λ^5,4Λ^5-catenadi(phosphazene)), ref 34 [p] Ref 30. [q] Ref 31. [r] Ref 32. [s] Ref 33.

amides are formed exclusively (*N*-attack), but we cannot exclude a preceding reversible attack at oxygen. This result is in accordance with the findings of Bordwell and Hughes, who observed selective *N*-benzylation in the reactions of several amide anions with benzyl chloride in DMSO.[8c]

When equimolar amounts of the potassium or tetraalkylammonium salts of **2a−o** and representative benzhydrylium salts **(1a−i)-BF$_4^-$** were combined in dry DMSO (saccharin (**2o**) in dry CH$_3$CN), complete decolorization of the solutions was observed, indicating quantitative consumption of the electrophiles. The fact that some of the reaction products were obtained in only moderate yields (Table 2) is due to nonoptimized workup procedures. As shown by the low pK_{aH} values in water (Table 2), many of the investigated amide and imide anions are weak bases, with the consequence that their adducts with stabilized benzhydrylium ions undergo heterolytic cleavage during aqueous workup, as illustrated for **3oc** in Scheme 4. In such cases, the products could not be isolated and identified by mass spectrometry or elemental analysis and the product studies were performed by NMR spectroscopy in d_6-DMSO solution (see the Supporting Information for NMR spectra).

Kinetic Investigations. The reactions of the imide and amide anions **2a−n** with the benzhydrylium ions **1a−i** and structurally related quinone methides **1j−q** were studied in DMSO at 20 °C.

SCHEME 4. Reversible Reaction of the Saccharin Anion (2o) with 1c



The reactions were monitored by UV−vis spectroscopy at or close to the absorption maxima of the electrophiles (354 < λ < 635 nm) (Table 1). Due to the low reactivity of the saccharin anion (**2o**), more electrophilic carbocations (**1a−d**) had to be employed for determining its nucleophilicity. Since these benzhydrylium ions react with DMSO, the corresponding kinetic investigations were performed in acetonitrile.

To simplify the evaluation of the kinetic experiments, the nucleophiles were generally used in large excess over the electrophiles. Therefore, the concentrations of **2a−o** remained almost constant throughout the reactions, and pseudo-first-order kinetics were obtained in all runs. The first-order rate

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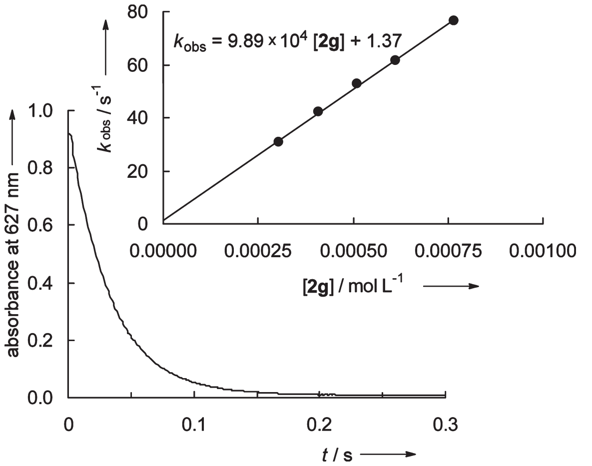
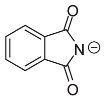
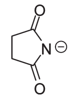
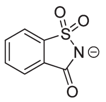


FIGURE 1. Plot of the absorbance (627 nm) vs time for the reaction of **1g** with the potassium salt of diacetamide (**2g-K**) in DMSO at 20 °C, and correlation of the first-order rate constants k_{obs} with the concentration of **2g** (insert).

constants k_{obs} were then derived by least-squares fitting of the time-dependent absorbances A_t of the electrophiles to the exponential function $A_t = A_0 \exp(-k_{obs}t) + C$. Second-order rate constants were obtained as the slopes of the plots of k_{obs} versus the concentrations of the nucleophiles (Figure 1).

In DMSO solution, where most investigations have been performed, the potassium salts (**2a**–**n**)-**K**$^+$ are dissociated into free ions in the concentration range under investigation ($c < 3.4 \times 10^{-3}$ mol L^{-1}).[12a,18a] Consequently, there is no significant change in k_2 when changing the counterion from potassium to tetraalkylammonium as demonstrated for the reactions of **2a** with **1e**,**i**,**k** and of **2j** with **1i** (Table 2). Furthermore, for several examples it has been shown that k_{obs} values, which were obtained for potassium salts **2-K**$^+$ in the presence and in the absence of crown ether, are on the same k_{obs} vs [**2**] plots (see the Supporting Information).

TABLE 3. Second-Order Rate Constants for the Reaction of Reference Electrophiles with Imide Anions 2a,b,o in Acetonitrile at 20 °C and Relative Reactivities *r* in Acetonitrile and DMSO

Nucleophile		Electrophile	k_2 / L mol^{-1} s^{-1}	r^a
	**2a**[b]	**1e**	1.50×10^6	6.00
		1i	2.42×10^4	5.86
	**2b**[c]	**1h**	7.77×10^4	3.87
		1i	4.76×10^4	4.71
		1j	3.54×10^2	0.91
		1k	5.22×10^1	1.12
	**2o**[b,d, e]	**1a**	2.33×10^5	-
		1b	2.91×10^4	-
		1c	2.04×10^{3}[f]	-

[a] $r = k_2$(in AN)/k_2(in DMSO). [b] Employed as NMe_4^+ salt. [c] Employed as NBu_4^+ salt. [d] pK_{aH}(**2o**, CH_3CN) = 14.6 (ref 35). [e] Nucleophile-specific parameters for **2o**: N = 10.78, s = 0.89. [f] Product **3oc** was isolated in 31% yield.

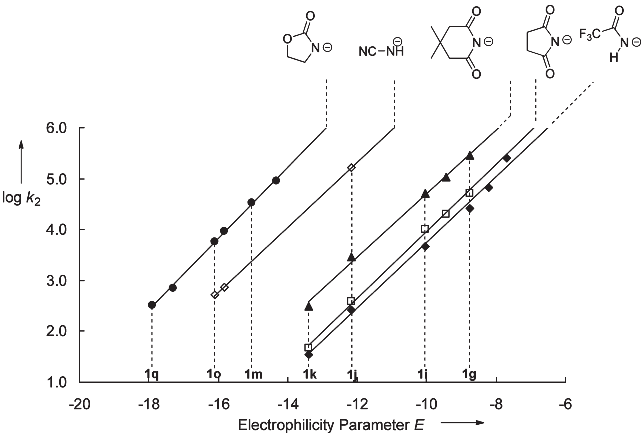


FIGURE 2. Plots of the rate constants log k_2 for the reactions of imide and amide anions with reference electrophiles in DMSO versus their electrophilicity parameters E.

Some kinetic measurements were also performed in acetonitrile. From the linear dependence of the pseudo-first-order rate constants k_{obs} on the concentrations of the potassium amides, it is concluded that ion-pairing also is not significant in acetonitrile under these conditions. Table 3 shows that the reactivities toward benzhydrylium ions and quinone methides are differently affected by the change of the solvent. Whereas the reactions with the positively charged reference electrophiles are 4–6 times faster in acetonitrile than in DMSO, the reactions with neutral electrophiles proceed with almost equal rates in both solvents.

Correlation Analysis. According to eq 1, linear correlations were obtained when log k_2 for the reactions of the imide and amide anions **2a**–**o** with the reference electrophiles **1a**–**q** were plotted against their electrophilicity parameters E, as shown for some representative examples in Figure 2. All reactions investigated in this work followed analogous linear correlations as depicted in the Supporting Information, indicating that eq 1 is applicable. The linearity over a wide range of reactivity furthermore supports the assumption that there is no change in the regioselectivity (N- vs O-attack) when varying the electrophile. The slopes of these correlations correspond to the nucleophile-specific parameter s,

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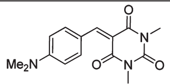
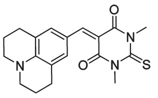
(36) Seeliger, F.; Berger, S. T. A.; Remennikov, G. Y.; Polborn, K.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 9170–9180.

TABLE 4. Rate Constants k_2 (L mol^{-1} s^{-1}) for the Reactions of 2*l*,n with the Michael Acceptors 5a,b in DMSO at 20 °C

Electrophile	E^a	Nucleophile	$k_{2,\mathrm{exp}}$	$k_{2,\mathrm{calc}}$
 **5a**	–12.76	**2l**	6.70×10^4	4.9×10^5
		2n	1.17×10^5	7.0×10^4
 **5b**	–11.89	**2l**	7.55×10^4	1.6×10^6
		2n	2.05×10^5	2.5×10^5

[a]Electrophilicity parameters E from ref 36.

whereas the negative intercepts on the abscissa ($\log k_2 = 0$) yield the nucleophilicity parameter N.

To examine the suitability of the nucleophilicity parameters N and s given in Table 2 for the prediction of rate constants of reactions with other types of electrophiles, we studied the kinetics of the reactions of the amide anions **2*l*** and **2n** with the Michael acceptors **5a** and **5b**. As shown in Table 4, the agreement between calculated and experimental data is better than a factor of 2 in the case of **2n** and better than a factor of 21 for the reactions of **2l**, i.e., the three-parameter eq 1, which presently covers a reactivity range of more than 40 orders of magnitude, can also be employed for the semiquantitative prediction of the rates of ordinary Michael additions of amide anions.

In previous work, we have shown that the relative reactivities of nucleophiles in S_N2 reactions also correlate with the N and s parameters which were derived from their reactions with benzhydrylium ions.[37] The linear correlation of $(\log k_2)/s$ for the reactions of the imide anions **2a**,**b**,**f** with ethyl iodide,[9c] shown in Figure 3, is in line with this observation, though the paucity of data inhibits a more detailed analysis.

As the nucleophilic reactivities of the amide anions **2** can be expected to be strongly reduced by hydrogen bond donor solvents, a comparison of our data with the S_N2 reactivities of these anions in alcoholic solvents[8a,b,9a] is not possible.

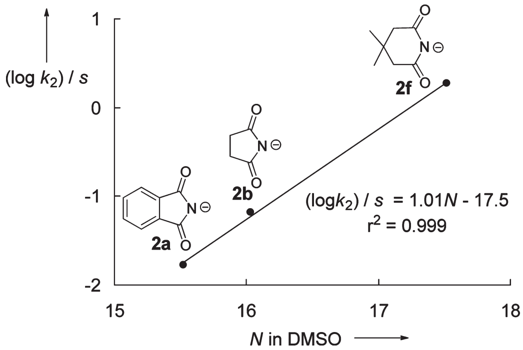


FIGURE 3. Correlation of the rate constants $(\log k_2)/s$ for the reactions of the imide anions **2a**, **2b**, and **2f** with ethyl iodide in acetonitrile (from ref 9c) with their nucleophilicity parameters N in DMSO.

Discussion

Ambident Reactivity of Amide and Imide Anions. Although all reactions discussed above proceed via nitrogen attack, amide and imide anions are ambident nucleophiles, and oxygen attack is also conceivable. While alkylation reactions of neutral amides often give product mixtures arising from *O*- and *N*-attack,[38] amide anions typically react at nitrogen.[39] However, oxygen-alkylation has only been observed when silver salts were employed,[40] and Kornblum rationalized this change of regioselectivity by the fact that silver ion enhances the carbocationic character of the electrophile and thus promotes the alkylation at the more electronegative oxygen atom.[41] Our observation that only *N*-substituted amides are isolated when amide anions are combined with benzhydrylium ions and that the linear correlations in Figure 2 do not give any clue that the more electrophilic benzhydrylium ions initially give *O*-alkylated products, which subsequently rearrange to the isolated *N*-alkylated products, disagrees with this interpretation. It appears more likely that the selective *O*-attack in the presence of silver salts is due to the coordination of the silver ion to the nitrogen atom of the imide anion, which is well documented by numerous X-ray studies.[42] In this way, attack at the nitrogen is blocked. The selective formation of isonitriles from alkylation agents and $[\mathrm{Ag(CN_2)}]^-$ has analogously been explained by the blocking of carbon attack by Ag^+.[43]

Structure Reactivity Relationships. The narrow range of s for all nucleophiles listed in Table 2 ($0.53 < s < 0.76$), which is illustrated by the almost parallel correlation lines in Figure 2 (exception: saccharin anion **2o**, $s = 0.89$ in CH_3CN) implies that the relative reactivities of these compounds depend only slightly on the electrophilicity of the reaction partner. The reactivities toward the benzhydrylium ion **1i**, for which most rate constants have directly been measured, can therefore be assumed to reflect general structure reactivity trends (Scheme 5).

The decreasing nucleophilicity of the amide anions RNH^- in the series R = CN > $SO_2CH_3 \approx SO_2Tol$ > $COCF_3$ (left column of Scheme 5) correlates neither with Hammett's σ_p nor σ_p^- constants of these substituents (see the Supporting Information for correlations) indicating that the mode of interaction of the substituents with N^- differs from the type of interaction with neutral or negatively charged C_{sp^2} centers.

From the comparison of **2d** and **2e** one can derive that replacement of N-H by N-CH_3 has little effect on nucleophilic reactivity, and the similar reactivities of the cyanamide anion **2n** and Evans' auxiliary **2m** reveal the comparable effects of cyano and ester groups.

A second acceptor group reduces the nucleophilic reactivity only slightly, and the comparison of **2i** (left column) and **2g** (middle column) shows that the effect of one sulfonyl group is comparable to that of two acetyl groups. The anion

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[38] (a) Challis, B. C.; Challis, J. In *The Chemistry of Amides*; Zabicky, J., Ed.; Interscience Publisher: London, UK, 1970; pp 731–858. (b) Stirling, C. J. M. *J. Chem. Soc.* **1960**, 255–262.

[39] Döpp, D.; Döpp, H. *Houben-Weyl Methods of Organic Chemistry, 1952–*, 4th ed.; Thieme: Stuttgart, Germany, 1985; Vol. E5, pp 934–1135.

[40] (a) Koch, T. H.; Sluski, R. J.; Moseley, R. H. *J. Am. Chem. Soc.* **1973**, *95*, 3957–3963. (b) Anderson, D. R.; Keute, J. S.; Koch, T. H.; Moseley, R. H. *J. Am. Chem. Soc.* **1977**, *99*, 6332–6340.

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[42] (a) Khayata, W.; Baylocq, D.; Pellerin, F.; Rodier, N. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1984**, *40*, 765–767. (b) Perron, J.; Beauchamp, A. L. *Inorg. Chem.* **1984**, *23*, 2853–2859. (c) Whitcomb, D. R.; Rajeswaran, M. *J. Chem. Crystallogr.* **2006**, *36*, 587–598. (d) Whitcomb, D. R.; Rajeswaran, M. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2007**, *63*, m2753. (e) Tao, X.; Li, Y.-Q.; Xu, H.-H.; Wang, N.; Du, F.-L.; Shen, Y.-Z. *Polyhedron* **2009**, *28*, 1191–1195.

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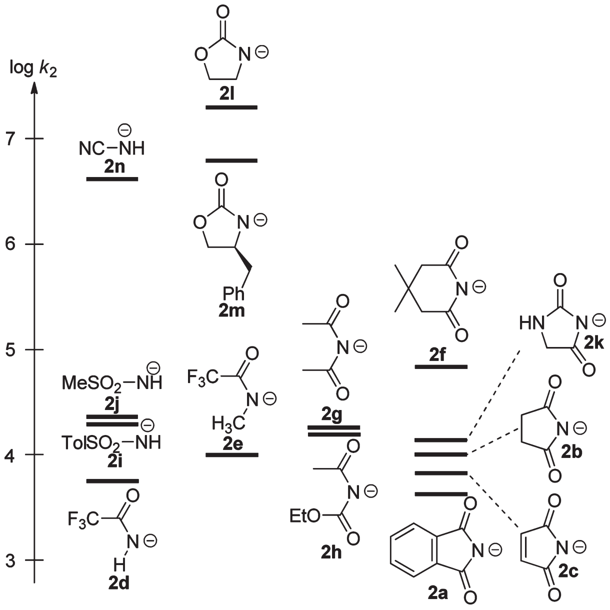
SCHEME 5. Comparison of the Reactivities of Imide and Amide Anions with the Benzhydrylium Ion 1i in DMSO (20 °C)[a]



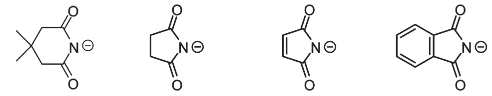
[a] Entries for **2*l*−n** were calculated by using eq 1, *N* and *s* parameters from Table 2, and *E*(**1i**) from Table 1.

of saccharin (**2o**), which is simultaneously stabilized by a sulfonyl and an acyl group, is approximately 10^4 times less nucleophilic than ordinary sulfonamide or diacylimide anions (Table 3, not included in Scheme 5).

Reduction of the ring size (**2f** → **2b**) is associated with a 5-fold reduction of nucleophilicity (possibly because of a reduced p-character of the nonconjugated lone pair at N in the smaller ring **2b**), and the replacement of the ethano-bridge in **2b** by a benzo- or etheno-bridge causes a further 2-fold reduction of nucleophilic reactivity (Scheme 6). The slight reduction of reactivity from succinimide **2b** to phthalimide **2a** and maleimide **2c** toward **1i** can be explained by the higher electronegativity of sp^2- compared to sp^3-hybridized carbon atoms. It shall be noted, that due to slightly different values of the slope parameter *s*, relative reactivities of compounds with similar reactivities may be inverted when the electrophile is changed, as indicated by the different order of k_2 and the *N* parameters in Scheme 6.

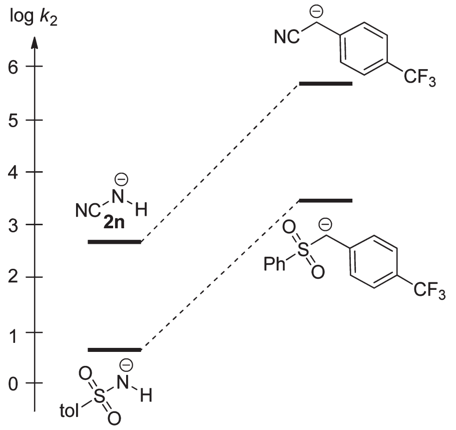
Comparison of Amide Anions and Carbanions. A direct comparison of the electrophilic reactivities of amide anions and carbanions, which carry only one acceptor group, is not possible, because the high reactivities of monoacceptor substituted carbanions have so far prevented the characterization of their nucleophilicities. On the other hand, the larger electronegativity of nitrogen enabled us to investigate amide anions carrying only one acceptor substituent. The observation that carbanions, which are stabilized by a trifluoromethyl substituted phenyl group in addition to a sulfonyl or cyano group,[44] are 10^3 times more nucleophilic than amide anions that carry a hydrogen atom instead of the acceptor-substituted phenyl group reflects the tremendous difference in reactivity of amide anions and carbanions with a single acceptor substituent (Scheme 7).

SCHEME 6. Reactivities toward Benzhydrylium Ion 1i and *N*-Values of Imide Anions (20 °C)



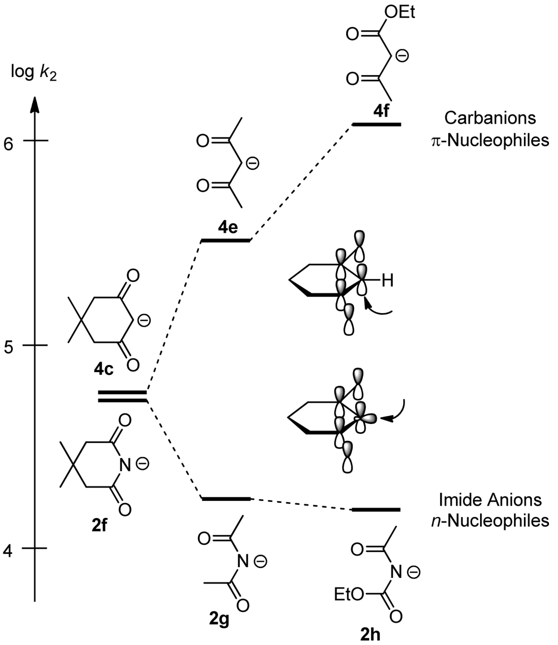
	2f	**2b**	**2c**	**2a**
k_2 [L mol^{-1} s^{-1}]	5.15×10^4	1.01×10^4	6.32×10^3	4.13×10^3
N	17.52	16.03	14.87	15.52

SCHEME 7. Comparison of the Reactivity of Amide Anions and Carbanions toward the Quinone Methide 1o in DMSO (20 °C)[a]



[a] Rate constants for **2i** and for the sulfonyl stabilized carbanion were calculated by eq 1, using *N* and *s* from Table 2 (this work) and ref 44.

SCHEME 8. Comparison of the Nucleophilic Reactivities of Structurally Related Imide Anions and Carbanions towards the Benzhydrylium Ion 1i (20 °C)



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(44) (a) Seeliger, F.; Mayr, H. *Org. Biomol. Chem.* **2008**, *6*, 3052–3058. (b) Kaumanns, O.; Appel, R.; Lemek, T.; Seeliger, F.; Mayr, H. *J. Org. Chem.* **2009**, *74*, 75–81.

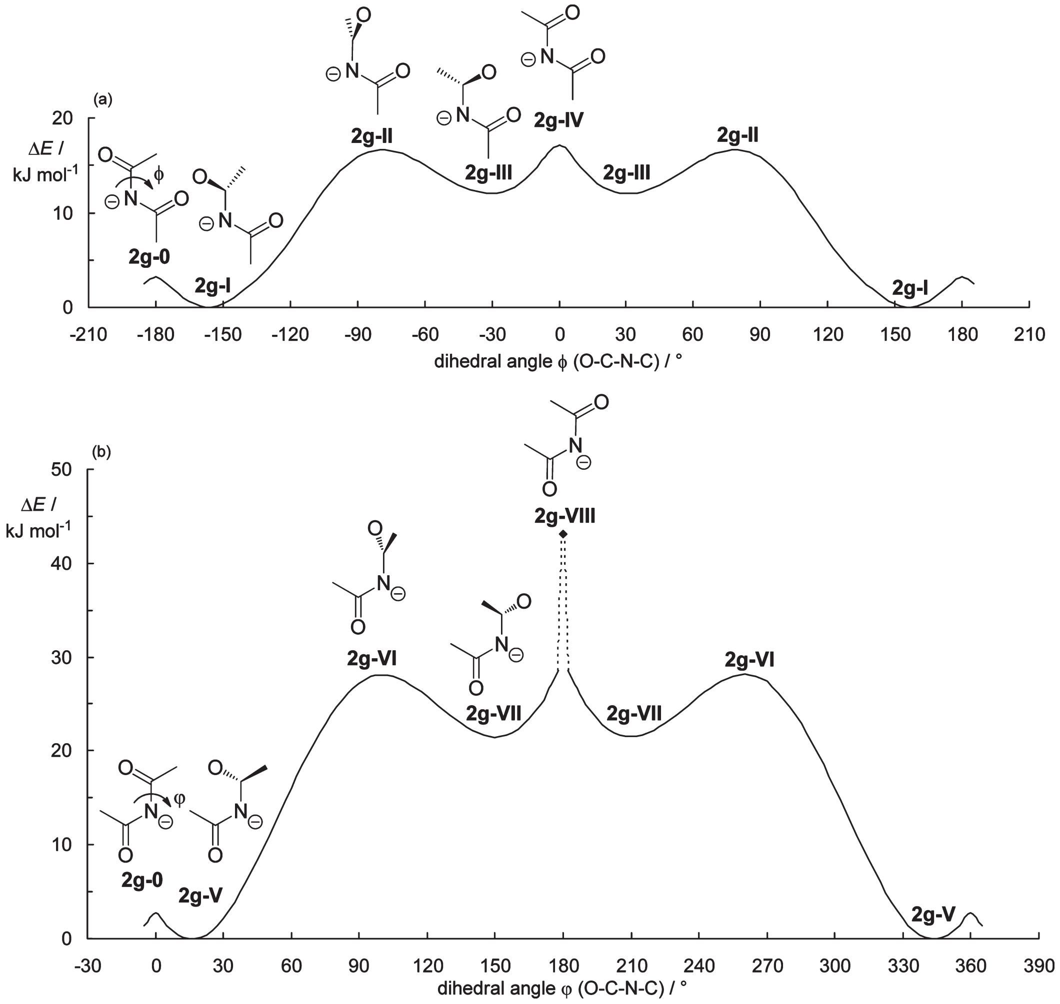

FIGURE 4. Relaxed potential energy surface scan (at B3LYP/6-31+G(d,p) level of theory) of the anion of diacetamide **2g**.

A completely different situation is found for imide anions and carbanions bearing two acceptor groups. Coincidently, the reactivities of the structurally analogous cyclic compounds, glutarimide anion **2f**, an *n*-nucleophile, and dimedone anion **4c**, a π-nucleophile, are almost identical (Scheme 8). Even when the ring is opened, dicarbonyl-substituted imide anions and analogously substituted carbanions differ by less than 10^2 in reactivity, as shown in Scheme 8. While ring-opening leads to a slight decrease of the reactivities of the imide anions (→ **2g**,**h**), the reactivities of the acyclic carbanions (→ **4e**,**f**) are somewhat higher than that of the cyclic analogue **4c**. Whereas acetyl groups stabilize carbanions better than ethoxycarbonyl groups, similar stabilizing effects on imide anions are found for acetyl and ethoxycarbonyl substituents (Scheme 8).

Calculated Structures of the Diacetamide Anion. To rationalize why a second carbonyl acceptor group causes only a weak reduction of nucleophilicity in the imide anion series (see Scheme 5), we have investigated the structures of the *N*,*N*-diacetylamide anion by quantum chemical calculations on the B3LYP/6-31+G(d,p) level of theory using Gaussian 03.[45] For that purpose, we have systematically varied the dihedral angles ϕ and φ in the anion **2g** by relaxed potential energy surface scans. When ϕ is varied (Figure 4a), φ remains at approximately 0°, and when φ is varied (Figure 4b), ϕ remains at about 180°. For the sake of clarity, the small deviations of the nonrotating groups from planarity are neglected in the drawings of Figure 4. Figure 4a shows that a slight change of ϕ from -180 to $-160°$ leads to the global minimum **2g-I**, an almost planar conformation, where both carbonyl groups are in conjugation with the same lone pair on nitrogen. When the acetyl group is further turned out of plane ($\phi \rightarrow -90°$), one observes only a small increase of energy, because now the rotating carbonyl group gets into conjugation with the second lone pair on nitrogen. The transition state **2g-II** with almost perpendicular arrangement of the two carbonyl groups is only 17 kJ mol^{-1} above the global minimum. Further rotation

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(45) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision E.01, Gaussian, Inc.: Wallingford, CT, 2004.

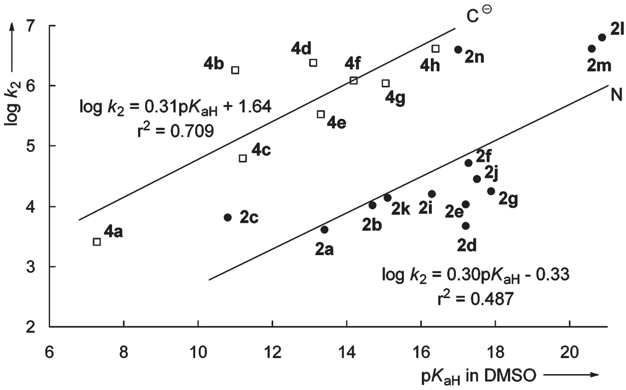


FIGURE 5. Relationship between Brønsted basicity and log k_2 for the reaction of **1i** with several amide and imide anions (●) as well as with some acceptor-stabilized carbanions (□) in DMSO. [pK_{aH} in DMSO (from ref 20): **4a**: Meldrum's acid 7.3; **4b**: malodinitrile 11.1; **4c**: dimedone 11.0; **4e**: acetylacetone 13.3; **4f**: ethyl acetylacetate 14.2; **4g**: 3-methylacetylacetone 15.05; **4h**: diethyl malonate 16.4; pK_{aH} in DMSO (from ref 48): **4d**: ethyl cyanoacetate 13.1].

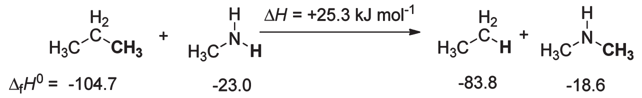
leads to a shallow minimum (**2g-III**), which corresponds to a slightly distorted conformation of the planar U-shaped conformer **2g-IV**, the energy maximum of this rotation.

Figure 4b describes the rotation of the second acetyl group around the C−N bond (variation of φ). When φ is increased from 0 to 15°, a decrease of energy is found and one arrives at the minimum structure **2g-V**. Though structures **2g-I** and **2g-V** look different in the drawings of Figure 4a,b, they are identical in reality because also the nonrotating amide bonds deviate slightly from planarity. A further increase of φ yields the transition state **2g-VI** with almost perpendicular arrangement of the two carbonyl groups. The 11 kJ mol^{-1} energy difference between **2g-II** and **2g-VI** can be explained by the more favorable orientation of the dipole moment of the in-plane carbonyl group with the nitrogen lone pair in **2g-II** than in **2g-VI**. A shallow minimum is reached for φ = 150°, but further increase of φ did not lead to **2g-VIII** as the transition state of the φ-rotation, because the structure converged to **2g-O**, when φ was fixed at 180°. The W-shaped arrangement **2g-VIII** was, therefore, calculated with fixed dihedral angles and found 43 kJ mol^{-1} above the global minimum **2g-V**. Steric hindrance of the two methyl groups in the W-conformer and unfavorable interactions of the dipole moments of the carbonyl groups with the lone pair on nitrogen account for its low stability.

In line with previous studies by Würthwein,[46] the C−N−C angle remains almost constant (122−124°) during both rotations, and not even the 90° transition states, where the two carbonyl groups interact with different lone pairs at nitrogen, adopt allenic structures with a quasi-linear C=N=C fragment. Since in the global minimum one of the two lone pairs at nitrogen is almost unaffected by the substituents, it is not surprising that the second electron acceptor substituent affects the nucleophilicity of imide anions only slightly, contrasting the situation in carbanions.

Correlation with Brønsted Basicities. Figure 5 shows that the correlation between nucleophilicity and Brønsted basicity is even worse for the amide and imide anions **2** than for the carbanions **4**. Thus, the cyanamide anion **2n** and the trifluoroacetamide anions **2d** and **2e**, anions of similar basicity, differ by 10^3 in nucleophilic reactivity. Despite the low quality of the correlations for both classes of compounds, it is evident from the two Brønsted plots in Figure 5 that nitrogen centered anions **2** are generally less nucleophilic than carbanions of similar pK_{aH}. Bordwell has analogously reported that the anions of substituted anilines ($ArNH^-$) react more slowly with *n*-butyl chloride in DMSO than carbanions ($ArCHCN^-$) of the same pK_{aH}.[47]

SCHEME 9. Reaction Enthalpy (Gas Phase, in kJ mol^{-1}) for the Methyl Hydrogen -Exchange between Carbon and Nitrogen[50]



$$H_3C{-}CH_2{-}CH_3 + H_3C{-}NH{-}H \xrightarrow{\Delta H = +25.3\ \mathrm{kJ\ mol^{-1}}} H_3C{-}CH_2{-}H + H_3C{-}NH{-}CH_3$$

Two effects have to be considered when explaining the separation of these Brønsted plots. While the Brønsted basicities refer to reactions with the proton (H^+), the nucleophilic reactivities refer to the formation of a bond to carbon. The isodesmic reaction in Scheme 9 shows that the transfer of a methyl group from carbon to nitrogen is endothermic by 25 kJ mol^{-1}, i.e., hydrogen prefers to sit at nitrogen and CH_3 prefers carbon. As a consequence, carbanions that have a similar affinity toward protons as amide anions (comparable pK_{aH}) have a higher affinity toward carbon, a trend that is also reflected by the kinetics, i.e., the higher k_2 values of carbanions toward carbon-centered electrophiles shown in Figure 5.

On the other hand, alkylations at nitrogen generally have lower intrinsic barriers than alkylations at carbon,[49] which should result in higher reactivities of the amide anions. Figure 5 shows that the intrinsic preference for reactions at nitrogen cannot compensate the thermodynamic term, which is responsible for the higher reactivities of carbanions.

Conclusion

The reactions of imide and amide anions with benzhydrylium ions and quinone methides follow the correlation (1) which allows us to include these compounds into our comprehensive nucleophilicity scales and compare their nucleophilicity with those of other nucleophiles (Figure 6). Despite the poor correlation between pK_{aH} and nucleophilic reactivity, carbanions are generally stronger nucleophiles than amide anions of similar basicity. Figure 6 furthermore shows that phthalimide and maleimide anions have similar nucleophilicities in DMSO as primary alkylamines and are weaker nucleophiles than secondary alkylamines though the amide anions are significantly stronger bases. The latter comparison again illustrates that Brønsted basicities are a poor guide for estimating nucleophilic reactivities, even when reagents with the same central atom are compared. The knowledge of carbon basicities[51] is needed to elucidate the reason for the breakdown of the Brønsted correlations.

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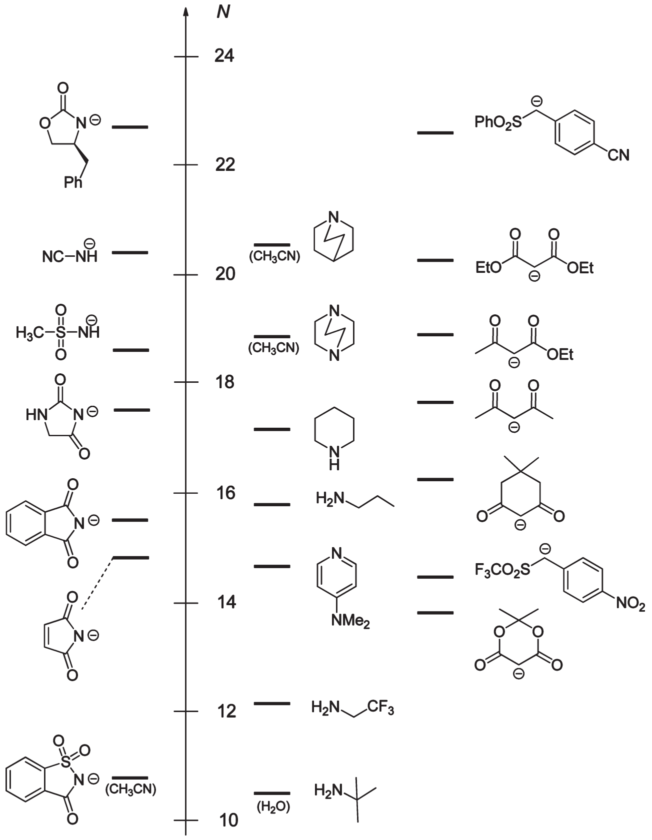

FIGURE 6. Comparison of the nucleophilicities *N* of imide and amide anions with other C- and N-nucleophiles in DMSO (data referring to other solvents are marked).

Experimental Section

Materials. Commercially available DMSO and acetonitrile (both: H_2O content < 50 ppm) were used without further purification. The reference electrophiles used in this work were synthesized according to literature procedures.[10] Ethyl acetylcarbamate was synthesized according to ref 52. Tetrabutylammonium succinimide and potassium phthalimide were purchased. Tetramethylammonium phthalimide and tetramethylammonium saccharin were synthesized according to ref 9a. Potassium salts of 2,2,2-trifluoroacetamide and of other amides were prepared by treatment of the corresponding amide with KO*t*Bu in dimethoxyethane.[53]

The synthetic procedures for **2c** and **3af** are described as representative examples for the product studies. A complete description for the preparation of all other products **2** and **3** is given in the Supporting Information.

Maleimide-potassium (2c-K$^+$). Maleimide (3.0 g, 31 mmol) was dissolved in dry dimethoxyethane (25 mL) under nitrogen atmosphere and KO*t*Bu (3.4 g, 30 mmol) was added at 0 °C. After 10 min of stirring, the solvent was evaporated under reduced pressure. The solid residue was washed several times with dry diethyl ether and filtrated under N_2. The salt **2c-K** (2.2 g, 27 mmol, 95%) could be isolated as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 6.28 ppm (s). ^{13}C NMR (100 MHz, d_6-DMSO) δ 126.6 (d), 180.1 ppm (s).

2-(Bis(1-methyl-1,2,3,4-tetrahydroquinolin-6-yl)methyl)isoindoline-1,3-dione (3af). In a carefully dried nitrogen-flushed Schlenk flask, a solution of **1a-K**$^+$ (223 mg, 1.20 mmol) in DMSO (5 mL) was added dropwise to a solution of the benzhydrylium tetrafluoroborate **1f** (393 mg, 1.00 mmol) in DMSO (5 mL). After stirring at ambient temperature for several minutes, cold water (ca. 50 mL) was added. Subsequently, the precipitated material was collected by filtration. After washing with water, the solid was dried under reduced pressure. **3af** (230 mg, 0.509 mmol, 51%) was isolated as a white solid; mp 151−152 °C (from dichloromethane−cyclohexane).

Kinetics. As the reactions of colored benzhydrylium ions or quinone methides with colorless imide or amide anions result in colorless products, the reactions were followed by UV−vis spectroscopy. Slow reactions ($\tau_{1/2} > 10$ s) were determined by using conventional UV−vis spectrophotometers. Stopped-flow techniques were used for the investigation of rapid reactions ($\tau_{1/2} < 10$ s). The temperature of solutions was kept constant at 20.0 ± 0.1 °C during all kinetic studies by using a circulating bath thermostat. The nucleophile concentration was always at least 10 times higher than the concentration of the electrophile, resulting in pseudo-first-order kinetics with an exponential decay of the electrophile concentration. First-order rate constants k_{obs} (s^{-1}) were obtained by least-squares fitting of the absorbance data to a single-exponential $A_t = A_0 \exp(-k_{obs}t) + C$. The second-order rate constants k_2 (L mol^{-1} s^{-1}) were obtained from the slopes of the linear plots of k_{obs} against the nucleophile concentration.

Acknowledgment. We thank the Fonds der Chemischen Industrie (scholarship to M.B.) and the Deutsche Akademische Austauschdienst (scholarship to T.T.). Financial support by the Deutsche Forschungsgemeinschaft (SFB 749) is gratefully acknowledged. We are grateful to Professor Ernst-Ulrich Würthwein, Professor Hendrik Zipse, and Dr. Armin R. Ofial for helpful discussions and to Nathalie Hampel for experimental support.

Supporting Information Available: Details of the computational data, kinetic experiments, synthetic procedures, and NMR spectra of all characterized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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