Electrophilicities of α -Chlorinating Agents Used in Organocatalysis

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Xin-Hua Duan and Herbert Mayr*

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstrasse 5-13 (Haus F), 81377 München, Germany

herbert.mayr@cup.uni-muenchen.de

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ABSTRACT



Kinetics of the reactions of the chlorinating agents 1a-c with π -nucleophiles have been studied to include these compounds in our comprehensive electrophilicity scale.

Nucleophilic substitutions of C–Cl bonds are an important method for the stereocontrolled generation of C–C, C–N, and C–O bonds.¹ For that reason, enantioselective constructions of stereogenic centers carrying a chlorine substituent are of eminent importance for organic synthesis. Among various methods developed for this purpose, organocatalytic α -halogenations of carbonyl compounds have been found to be particularly efficient, and the polychloroquinone derived reagents **1a**–**c** belong to the most frequently used chlorinating agents.²



During our efforts to rationalize scope and limitations of organocatalytic processes, we have previously characterized nucleophilicities and carbon basicities of frequently used organocatalysts such as amines and phosphanes.³ Using the linear free energy relationship (eq 1), where *E* is an electrophile-specific parameter, and *N* and *s* are nucleophile-specific parameters,⁴ we have furthermore characterized nucleophilicities of substrates for iminium-catalyzed reactions, e.g., pyrroles,^{5c} indoles,^{5b} and sulfur ylides,^{5e} as well as the nucleophilicities of enamines^{5a} and the electrophilicities of iminium ions,^{5d} key intermediates of organocatalytic reactions.

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

In previous reviews on scope and limitations of eq 1 we have stated that this correlation, which was initially derived for reactions of carbocations with olefins, 4a-c cannot be expected to hold for halogenation reactions, because bridging

^{(1) (}a) Smith, M. B.; March, J. March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 6th ed.; John Wiley & Sons: New York, 2007. (b) House, H. Modern Synthetic Reactions, 2nd ed.; W. A. Benjamin: New York, 1972. (c) De Kimpe, N.; Verhé, R. The Chemistry of α-Haloketones, α-Haloaldehydes, and α-Haloimines; John Wiley & Sons: New York, 1988.

⁽²⁾ Reviews: (a) France, S.; Weatherwax, A.; Lectka, T. *Eur. J. Org. Chem.* **2005**, 475–479. (b) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001–2011. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. (d) Czekelius, C.; Tzschucke, C. C. *Synthesis* **2010**, 543–566, and references cited therein.

^{(3) (}a) Kempf, B.; Mayr, H. *Chem.-Eur. J.* **2005**, *11*, 917–927. (b) Baidya, M.; Kobayashi, S.; Brotzel, F.; Schmidhammer, U.; Riedle, E.; Mayr, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6176–6179. (c) Baidya, M.; Mayr, H. *Chem. Commun.* **2008**, 1792–1794. (d) Baidya, M.; Horn, M.; Zipse, H.; Mayr, H. *J. Org. Chem.* **2009**, *74*, 7157–7164. (e) Kanzian, T.; Nigst, T. A.; Maier, A.; Pichl, S.; Mayr, H. *Eur. J. Org. Chem.* **2009**, 6379–6385.

electrophiles (Br_2 , Cl_2 , RS^+) are known to follow a different selectivity pattern as nonbridging electrophiles (Scheme 1). As shown in Scheme 1, the reactivities of CC double bonds

Scheme 1. Relative Reactivities of Alkenes toward Various Electrophiles (from ref 6) Reactivity order toward non-bridging electrophiles (R⁺, H₃O⁺).

/~ < / Reactivity order toward bridging electrophiles (Cl₂, Br₂).

~ < `` = L < `L

toward nonbridging electrophiles are hardly affected by alkyl groups at the position of electrophilic attack but are strongly increased by alkyl groups at the new carbenium center.⁶ In contrast, reactivities toward bridging electrophiles are increased almost equally by alkyl groups at both termini of the double bond.

Scheme 2. α-Chlorinations of Carbonyl Compounds Catalyzed by Secondary Amines



As illustrated in Scheme 2, enamines have been suggested to be the key intermediates in organocatalytic chlorinations of carbonyl compounds.² Because chloro-bridging does not occur in β -chloro-substituted iminium ions, we had speculated that the relative reactivities of enamines and other electron-rich π -systems toward "Cl⁺" may follow the same reactivity order as toward carbenium ions, with the consequence that the *N* and *s* parameters of the π -nucleophiles **2a**-**m** (Table 1) which have been derived from the rates of their reactions with benzhydrylium ions can also be used to describe the rates of their reactions with the electrophiles **1a**-**c**.

As shown in Scheme 3 for the reaction of 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dien-1-one (1a) with the indole 2a, the silyl enol ether 2c, and the enamine 2g, the chlorine transfer step is associated with the conversion of the cyclohexadienone chromophor of 1a ($\lambda_{max} = 378$ nm) into

			_				
Table 1.	N	and s	Parameters	of the	Employed	l Nucleo	philes

			-	-	-
nucleophile		N	S	solvent	ref
N Me	2a	5.75	1.23	CH_2Cl_2	5b
[2b	5.85	1.03	CH_2Cl_2	4b
Me ₃ SiO	2c	6.57	0.93	CH_2Cl_2	4b
Me ₃ SiO	2d	8.23	0.81	CH_2Cl_2	4b
Me Me	2e	8.69	1.07	CH ₃ CN	5c
Me ₃ SiO Me MeO Me	2f	9.00	0.98	CH_2Cl_2	4b
O_NPh	2g	9.96	0.79	CH_2Cl_2	5a
Me ₃ SiO	2h	10.61	0.86	CH_2Cl_2	4b
oNPh	2i	10.76	0.87	CH_2Cl_2	5a
0_N-{	2j	11.40	0.83	CH_2Cl_2	4b
Me ₃ SiO	2k	12.56	0.70	CH_2Cl_2	4b
	21	12.90	0.79	CH_2Cl_2	5a
o_N−√	2m	13.41	0.82	CH_2Cl_2	5a

that of the pentachlorophenolate ion, which absorbs at shorter wavelength ($\lambda_{max} = 351$ nm). For that reason, the kinetics of the reactions of **1a**, as well as of 5,7,7-trichloro-8(7*H*)-quinolinone (**1b**) and 2,2,4-trichloro-1(2*H*)-naphthalenone (**1c**), with the nucleophiles **2** could be determined photometrically by monitoring the disappearance of the absorbances of **1a**-**c** at 366–378 nm.

When equimolar amounts of the chlorinated quinones 1a and the *N*-methylindole (2a) were combined in CH₃CN at room temperature, the corresponding 3-chloro-*N*-methylindole was isolated in 81% yield after aqueous workup (Scheme 3). Silyl enol ethers usually gave moderate yields of α -chlorocarbonyl compounds. For instance, when 1a was slowly added to a solution of 1-(trimethylsiloxy)cyclopentene (2c) or 1-methoxy-2-methyl-1-(trimethylsiloxy)propene (2f) in CH₃CN at room temperature, 2-chlorocyclopentanone and methyl 2-chloroisobutyrate were obtained in low yields. The yields increased to 55% and 51%, respectively, when CH₂Cl₂ was used as the solvent. Treatment of 1a with 1 equiv of

⁽⁴⁾ Reviews: (a) Mayr, H.; Patz, M. Angew. Chem., Int. Ed. Engl. **1994**, 33, 938–957. (b) 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. (c) Mayr, H.; Kempf, B.; Ofial, A. R. Acc. Chem. Res. **2003**, 36, 66–77. (d) Mayr, H.; Ofial, A. R. J. Phys. Org. Chem. **2008**, 21, 584–595.

^{(5) (}a) Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem.—Eur. J.* **2003**, *9*, 2209–2218. (b) Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A. R.; Mayr, H. *J. Org. Chem.* **2006**, *71*, 9088– 9095. (c) Nigst, T. A.; Westermaier, M.; Ofial, A. R.; Mayr, H. *Eur. J. Org. Chem.* **2008**, 2369–2374. (d) Lakhdar, S.; Tokuyasu, T.; Mayr, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 8723–8726. (e) Lakhdar, S.; Appel, R.; Mayr, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 5034–5037.

⁽⁶⁾ Mayr, H. In *Cationic Polymerization: Mechanisms, Synthesis and Applications*; Matyjaszewski, K., Ed.; Marcel Dekker: New York, 1996; pp 51–136.

N-(1-phenylvinyl)morpholine (**2g**) in CH₂Cl₂ gave α -chloroacetophenone in 78% yield. Under the same conditions, the reactions of the polychlorinated quinones **1b** and **1c** also produced 60% and 65% yields of α -chloroacetophenone, respectively. Because analogous reaction products can be expected for the combination of **1a**–**c** with other substrates, product studies have not been performed for all reactions that have been studied kinetically.





As mentioned above, the kinetics of the reactions of 1a-cwith π -nucleophiles were determined photometrically by following the disappearance of the absorbances of the α -chlorinating agents at 366–378 nm, using conventional and stopped-flow UV/vis spectrometers. All kinetic experiments were performed at 20 °C in CH₃CN with a high excess of the nucleophiles 2a-m in order to achieve first-order conditions (eq 2).

$$-\mathrm{d}[\mathbf{1}]/\mathrm{d}t = k_{\mathrm{obs}}[\mathbf{1}] \tag{2}$$

As a consequence, exponential decays of the concentrations of the UV-active electrophiles were observed. The firstorder rate constants k_{obs} were obtained by least-squares fitting of the time-dependent absorbances of the electrophiles to A_t = $A_0 e^{-k_{obs}t} + C$. Plots of k_{obs} versus the concentrations of the nucleophiles [2] gave straight lines with the slopes k_2 as shown for one example in Figure 1. The slopes of these plots gave the second-order rate constants k_2 [M⁻¹ s⁻¹], which are summarized in Table 2.

If eq 1 were followed, plots of $(\log k)/s$ versus *N* should be linear with a slope of 1. Figure 2 shows that the reactivities of different classes of compounds, i.e., pyrroles, indoles, enol ethers, and ketene acetals, with the chlorinating agent **1a** are, indeed, linearly correlated with the nucleophilicity parameters *N*, but the slope (s = 1.25) is slightly larger than 1. Though the nonunity slope might be taken care of by introducing a second, electrophile-specific slope parameter, as previously suggested for the treatment of S_N2 reactions,⁷ we have abstained from introducing an electrophile-specific slope parameter and determined *E* by minimizing $\Delta^2 = \sum (\log k - s(N + E))^2$ with the nonlinear solver "What's Best!" by



Figure 1. Exponential decay of the absorbance at 378 nm during the reaction of **1a** (4.19 × 10⁻⁴ M) with **2g** (4.43 × 10⁻³ M) and correlation of k_{obs} with the concentrations of **2g** (in the insert).

Lindo systems. In this way a unity slope for the $(\log k_2)/s$ vs N plots was enforced. Table S1 in the Supporting Information shows that experimental and calculated rate constants determined in this way agree within a factor of 12. The correlations are of lower quality for the corresponding reactions of **1b** and **1c**, but also in these cases, the deviations between calculated and experimental rate constants are less than a factor of 22, which is quite satisfactory for a three-parameter equation covering a reactivity range of 40 orders of magnitude.

As an alternative to the direct chlorine attack at the π -bond of the enamine (Scheme 2 and upper reaction path in Scheme 4), initial *N*-chlorination and subsequent 1,3-sigmatropic shift of chlorine to the carbon atom (lower pathway in Scheme 4) has been suggested.⁸ Figure 2 shows that the relative

Table 2. Second-Order Rate Constants k_2 for the Reactions of the Polychlorinated Quinones **1a**-**c** with the π -Nucleophiles **2a**-**m** in CH₃CN at 20 °C

electrophile	λ_{\max} [nm]	nucleophile	$k_2 \; [\mathrm{M}^{-1} \; \mathrm{s}^{-1}]$
la	378	2a 2b 2c 2d 2e	$\begin{array}{c} 4.01\times10^{-2}\\ 1.89\times10^{-2}\\ 1.26\\ 6.52\\ 1.60\times10^{1} \end{array}$
1b	366	2f 2g 2i 2j 2f	$egin{array}{c} 1.36 imes 10^2 \ 1.36 imes 10^2 \ 3.24 imes 10^3 \ 1.04 imes 10^4 \ 8.76 imes 10^4 \ 4.59 imes 10^{-2} \end{array}$
		2g 2h 2j 2k 2/	1.38×10^{-1} 1.93×10^{-1} 6.97×10^{1} 2.91 2.82×10^{2}
1c	375	2m 2g 2h 2j 2k 2 <i>l</i>	$\begin{array}{c} 2.32 \times 10 \\ 6.21 \times 10^2 \\ 4.84 \times 10^{-1} \\ 2.40 \times 10^{-2} \\ 1.20 \times 10^1 \\ 3.81 \times 10^{-1} \\ 4.85 \times 10^1 \end{array}$
		2m	$1.18 imes 10^2$

⁽⁷⁾ Phan, T. B.; Breugst, M.; Mayr, H. Angew. Chem., Int. Ed. 2006, 45, 3869–3874.



Figure 2. Correlation of $(\log k_2)/s$ with the nucleophilicity parameter *N* for the reactions of the chlorinated quinones **1a** and **1b** with the nucleophiles **2** (CH₃CN, 20 °C).

reactivities of enamines, silylated enols, and ketene acetals, as well as of pyrroles and indoles toward the chlorinating agents **1a** and **1b**, are the same as toward donor-substituted diarylcarbenium ions, from which the *N*-scale has been derived. Though highly reversible *N*-attack by diarylcarbenium ions at enamines could not be excluded, it has been demonstrated that the observed second-order rate constants for these reactions reflect the rates of the CC bond-forming step.^{5a} As a consequence, the *N* and *s* parameters in Table 1, including those of enamines, reflect π -nucleophilicities, and the correlations shown in Figure 2 indicate analogous



transition states for electrophilic chlorinations and alkylations of the nucleophiles **2**. In view of these findings, the generality of the suggested *N*-attack⁸ of electrophilic chlorinating agents at enamines in amine-catalyzed α -chlorinations of aldehydes should be examined.

The kinetic data now allow us to include the chlorinating agents into our comprehensive electrophilicity scale (Figure

(10) (a) Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J.; Lectka, T. J. Am. Chem. Soc. 2001, 123, 1531–1532. (b) France, S.; Wack, H.; Taggi, A. E.; Hafez, A. M.; Wagerle, T. R.; Shah, M. H.; Dusich, C. L.; Lectka, T. J. Am. Chem. Soc. 2004, 126, 4245–4255.



Figure 3. Comparison of the electrophilicities of chlorinated quinones 1a-c with those of carbon electrophiles.

3), which shows that **1a** is a 10^{4} - to 10^{5} -fold stronger electrophile than **1b** and **1c**, comparable to amino-substituted benzhydrylium ions and α,β -unsaturated iminium ions. This reactivity order is in line with the observation that **1a** is a particularly suitable reagent for the imidazolidinone catalyzed α -chlorination reactions of aldehydes,⁹ or α -chlorinations of acyl chlorides via intermediate ketenes.¹⁰ On the other hand, the more reactive carbanions derived from 1,3-dicarbonyl compounds have been found to react with much better enantioselectivities with the mild chlorinating agent **1b** than with the more reactive electrophile **1a**.¹¹

The linear free-energy relationship log $k(20^{\circ}\text{C}) = s(N + E)$ (eq 1) has thus been found to be suitable for predicting the rate constants for the reactions of the chlorinated quinones **1a**-**c** with π -nucleophiles from the *E* parameters of **1a**-**c** determined in this work and the nucleophile specific parameters *N* and *s* for **2a**-**m** reported earlier.^{4,5} With these parameters at hand, one can compare the electrophilicities of chlorinated quinones with those of carbon electrophiles, and even more important, use them as a guide for selecting suitable electrophiles for organocatalytic halogenations.

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Supporting Information Available: Details of the product characterization and the kinetic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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^{(8) (}a) Halland, N.; Alstrup Lie, M.; Kjærsgaard, A.; Marigo, M.; Schiøtt,
B.; Jørgensen, K. A. *Chem.-Eur. J.* 2005, *11*, 7083–7090. (b) Marquez,
C. A.; Fabbretti, F.; Metzger, J. O. *Angew. Chem., Int. Ed.* 2007, *46*, 6915–6917.

⁽⁹⁾ Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. J. Am. Chem. Soc. 2004, 126, 4108–4109.

⁽¹¹⁾ Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. Angew. Chem., Int. Ed. 2005, 44, 6219-6222.