

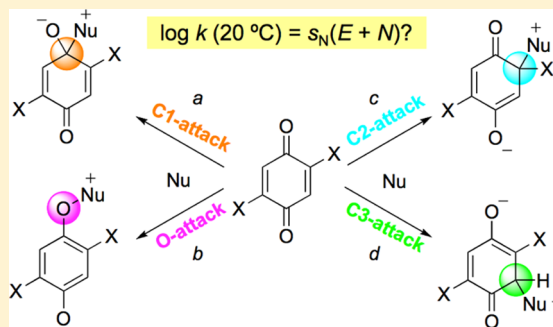
# Quantification of the Ambident Electrophilicities of Halogen-Substituted Quinones

Xingwei Guo and Herbert Mayr\*

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

**S** Supporting Information

**ABSTRACT:** Kinetics and mechanisms of the reactions of *p*-quinone, 2,5-dichloro-*p*-quinone, 2,3,4,5-tetrachloro-*p*-quinone (chloranil), 2,3,4,5-tetrafluoro-*p*-quinone (fluoranil), and 3,4,5,6-tetrachloro-*o*-quinone with  $\pi$ -nucleophiles (siloxyalkenes, enamines) and amines have been investigated. Products arising from nucleophilic attack at all conceivable sites, that is, at C and O of the carbonyl groups (pathways *a*, *b*) as well as at halogenated and nonhalogenated conjugate positions (pathways *c*, *d*), were observed. The partial rate constants for the C-attack pathways (*a*, *c*, *d*), which are derived from the photometrically determined second-order rate constants and the product ratios followed the linear free energy relationship  $\log k(20\text{ }^\circ\text{C}) = s_N(E + N)$  (Mayr, H.; et al. *J. Am. Chem. Soc.* 2001, 123, 9500–9512). It was, therefore, possible to calculate the electrophilicity parameters *E* of the different positions of the quinones from  $\log k(20\text{ }^\circ\text{C})$  and the *N* and  $s_N$  parameters of the nucleophilic reaction partners, which have previously been derived from their reactions with benzhydrylium ions. Almost all rate constants for the C-attack pathways (*a*, *c*, *d*) were considerably larger than those calculated for the corresponding SET processes, indicating the operation of polar mechanisms. SET mechanisms may only account for the formation of the products formed via O-attack. With the *E* parameters determined in this work, it is now possible to predict rate constants for the reactions of these quinones with a large variety of nucleophiles and, thus, envisage unprecedented reactions of quinones.



## INTRODUCTION

Since Wöhler carried out the first 1,4-addition of HCl to *p*-benzoquinone in 1844,<sup>1</sup> the chemistry of quinones has continuously been attracting the attention of chemists.<sup>2</sup> The realization of the oxidizing properties of quinones in the early 20th century<sup>3</sup> also paved the way to understanding the important role of quinones in biological processes.<sup>4</sup> In spite of this long history, quantitative mechanistic studies concerning the reactivities and selectivities of quinones in organic synthesis are still missing, especially in the border area between electron transfer and polar reaction pathways.

We have previously reported that the reactions of DDQ with  $\pi$ -nucleophiles usually proceed by polar pathways,<sup>5</sup> the rates of which can be described by eq 1, which had been developed to predict rates and selectivities of polar reactions.<sup>6</sup>

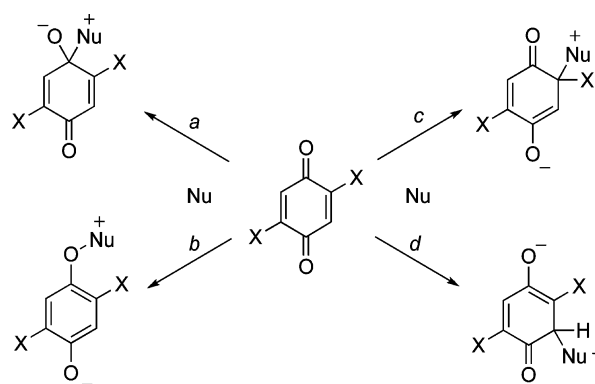
$$\log k(20^\circ\text{C}) = s_N(E + N) \quad (1)$$

In eq 1, the second-order rate constant ( $\log k$ ) is calculated by two solvent-dependent nucleophile-specific parameters ( $s_N$ , *N*) and one electrophile-specific parameter (*E*). A comprehensive nucleophilicity scale covering more than 30 orders of magnitude<sup>7</sup> has been created by using a series of benzhydrylium ions and structurally related quinone methides as reference electrophiles.<sup>8</sup> In this work, we will derive electrophilicity parameters *E* for five synthetically important quinones and show that they can be used as an organizing principle of

quinone reactivity with the potential to predict unprecedented reactions.

Nucleophilic attack at quinones may either occur at the carbonyl group (paths *a*, *b*, Scheme 1) or at conjugate positions (paths *c*, *d*). Depending on the substitution pattern of the quinone, one or more types of conjugate attack are conceivable.

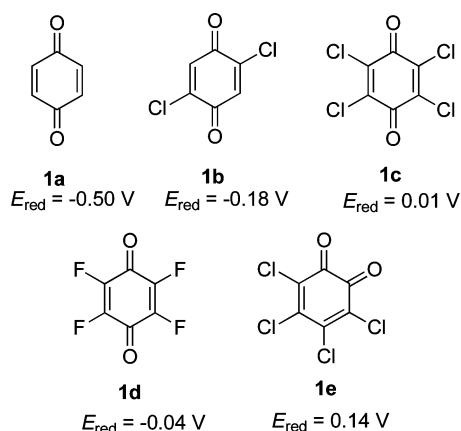
### Scheme 1. Ambident Reactivities of 2,5-Disubstituted Quinones



Received: June 11, 2014

Published: July 23, 2014

We have now used the linear free energy relationship (1) to elucidate the mechanisms of the reactions of different halogen-substituted quinones (Figure 1) with  $\pi$ -systems and amines (Table 1) and quantified their ambident electrophilicities and selectivities.



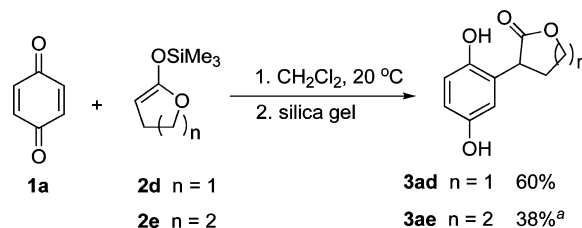
**Figure 1.** Quinones **1a–e** studied in this work and their reduction potentials  $E_{\text{red}}$  (vs SCE)<sup>9</sup> in acetonitrile.

## RESULTS

**Product Studies: Reactions with  $\pi$ -Nucleophiles.** 1,4-Benzoquinone **1a** reacted with the silyl ketene acetals **2d** and **2e** to give products of conjugate attack selectively. Chromatography of the crude mixture on silica gel led to hydrolysis with formation of the substituted hydroquinones **3ad** and **3ae**

(Scheme 2), which were fully characterized. Due to the low electrophilicity of **1a**, the reactions with less reactive silyl ketene acetals are rather slow and were not studied in this work.

### Scheme 2. Reactions of Benzoquinone (**1a**) with Silyl Ketene Acetals



<sup>a</sup>Yield includes traces of impurities which could not be removed by chromatography.

2,5-Dichlorobenzoquinone (**1b**) reacted analogously with the silyl ketene acetals **2(a,d,e)** and gave **3ba**, **3bd**, and **3be**, respectively (Scheme 3). As significant amounts of other products were not detected in the NMR spectra of the crude products, the moderate yields are due to nonoptimized workup procedures. In the reaction of **1b** with **2c**, the [3 + 2] cyclization products **4bc** (18%) and **5bc** (40%) were formed along with 19% of **6bc**, a product of O attack.

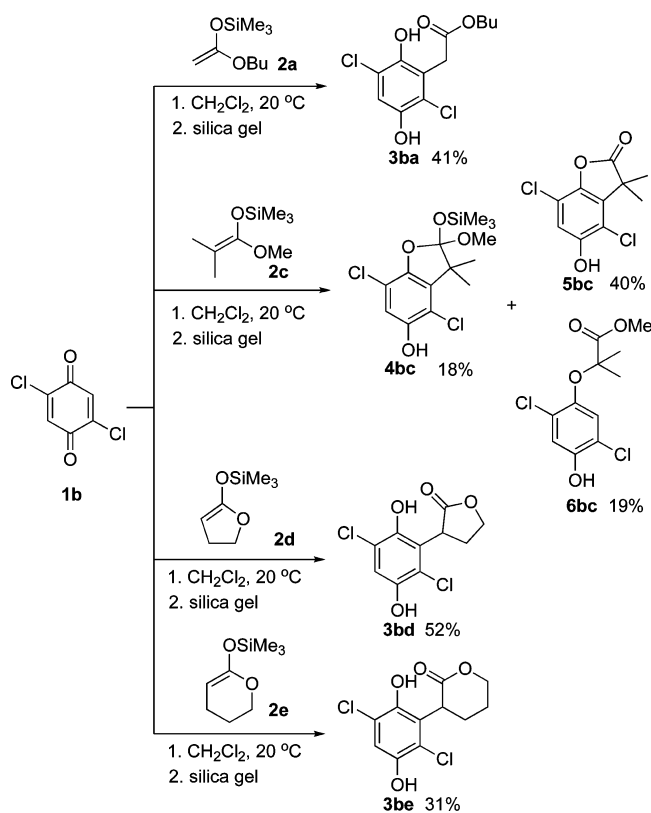
In line with Fukuzumi's and Otera's report,<sup>9</sup> the tetrachloro- and tetrafluoro-substituted para-quinones **1c** and **1d** were found to give 1,2-addition products (**7**) with the terminal silyl ketene acetal **2a**, and products of O attack (**6**) with **2c** (Scheme 4).

**Table 1.** Nucleophiles **2a–o** and Their Reactivity Parameters  $N$  and  $s_N$  in  $\text{CH}_2\text{Cl}_2$  (**2a–h**) or  $\text{CH}_3\text{CN}$  (**2i–o**) and Their Oxidation Potentials in  $\text{CH}_3\text{CN}$  (vs SCE)

Nucleophile	$N$ ( $s_N$ )	$E_{\text{ox}}$	Nucleophile	$N$ ( $s_N$ )	$E_{\text{ox}}$
<b>2a</b>	10.21 (0.82)	1.12 <sup>a</sup>	<b>2g</b>	13.41 (0.82)	0.60 <sup>c</sup>
<b>2a'</b>	10.32 (0.78)		<b>2h</b>	11.40 (0.83)	0.60 <sup>c</sup>
<b>2b</b>	8.23 (0.81)	1.24 <sup>a</sup>	<b>2i</b>	18.64 (0.60)	0.86 <sup>d</sup>
<b>2c</b>	9.00 (0.98)	0.90 <sup>b</sup>	<b>2j</b>	17.35 (0.68)	1.04 <sup>d</sup>
<b>2d</b>	12.56 (0.70)		<b>2k</b>	15.65 (0.74)	1.13 <sup>d</sup>
<b>2e</b>	10.61 (0.86)		<b>2l</b>	15.27 (0.63)	1.51 <sup>e</sup>
<b>2f</b>	6.22 (0.96)	1.32 <sup>b</sup>	<b>2m</b>	12.35 (0.72)	1.53 <sup>e</sup>
			<b>2n</b>	14.29 (0.67)	
			<b>2o</b>	15.51 (0.62)	

<sup>a</sup>Calculated values from ref 5. <sup>b</sup>From ref 10. <sup>c</sup>Peak potentials from ref 11. <sup>d</sup>From ref 12. <sup>e</sup>From ref 13.

Scheme 3. Reactions of 2,5-Dichlorobenzoquinone (1b) with Silyl Ketene Acetals



Mixtures of products were formed with cyclic silyl ketene acetals. When **2d** was combined with *p*-chloranil **1c**, products from C-1 addition (**7cd**) and C-2 monosubstitution (**8cd**), and traces of a disubstitution product (**9cd**) were formed. The C-1 addition product **7dd** was the major product of the reaction of **2d** with tetrafluoro-benzoquinone **1d**. Although only a trace of the monosubstitution product (**8dd**) was observed, the disubstitution product **9dd** was isolated in 27% yield as a 1:2 mixture of diastereomers.

Concomitant C- and O-attack were observed in the reaction of the six-membered ring silyl ketene acetal **2e** with *p*-chloranil **1c**, to give the quinone **8ce** and the hydroquinone **6ce**. In the reaction of **2e** with tetrafluoro-*p*-benzoquinone (**1d**), only the substitution product **8de** was obtained.

Though **1c** reacted with enamine **2h** in the same way as with **2c** to give **6ch** by O-attack, the corresponding reaction of **1d** with **2h** gave a complex mixture of products, which was not analyzed.

*o*-Chloranil (**1e**) reacted with the terminal silyl ketene acetals **2a** and **2b** to give the C-1 addition products **7ea** and **7eb**, respectively, whereas its reaction with **2c** yielded the [4 + 2] cycloaddition product **10ec** exclusively (Scheme 5).

The reaction of **1e** with **2d** gave a mixture, from which the C-1 addition product **7ed**, the product of O-attack **6ed** (for the X-ray structure, see Supporting Information, page S20), and the tricyclic compound **11ed** were isolated in 13%, and 31%, and 11% yield, respectively. Only a single diastereomer of **11ed** was observed and characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and high-resolution mass spectroscopy. The analogous tricyclic compound **11ee**, which was the only product obtained in the reaction of **1e** with **2e**, was characterized by X-ray crystallography (page S21, in Supporting Information).

The reaction of **1e** with silyl enol ether **2f** proceeded with attack at the carbonyl oxygen and gave hydroxyacetophenone (**12ef**) after chromatography on silica gel. NMR-spectroscopic investigation of the reaction of **1e** with enamine **2h** showed the exclusive formation of the [4 + 2] cycloaddition product **10eh-1**; its chromatography on silica gel led to hydrolysis, and **10eh-2** was isolated in 61% yield as a 1:1 mixture of diastereomers.

**Reactions with Amines.** In agreement with earlier reports,<sup>2b,14</sup> pyrrolidine was found to react with 1,4-benzoquinone with formation of the monosubstituted benzoquinone **13ai** in 85% yield, when 4 equiv of quinone was used (Scheme 6).

Products arising from C-2 and C-3 attack were formed by the reaction of 2,5-dichloroquinone (**1b**) with pyrrolidine.<sup>2b,15</sup> Scheme 7 shows that the ratio **13bi/8bi** depends strongly on the concentration of the reactants. The ratio **13bi/8bi** decreases from 58/26 to 3/82 when reducing the concentration of quinone **1b** from 0.25 to 0.001 mol L<sup>-1</sup> in CH<sub>3</sub>CN while keeping the ratio [**1b**]/[**2i**] = 5 constant.

As chloranil **1c** has previously been reported to react with more than one molecule of amine,<sup>2g</sup> the reactions of **1c–e** with **2i** and **2j** have been performed with 4 equiv of quinones (Schemes 8 and 9).

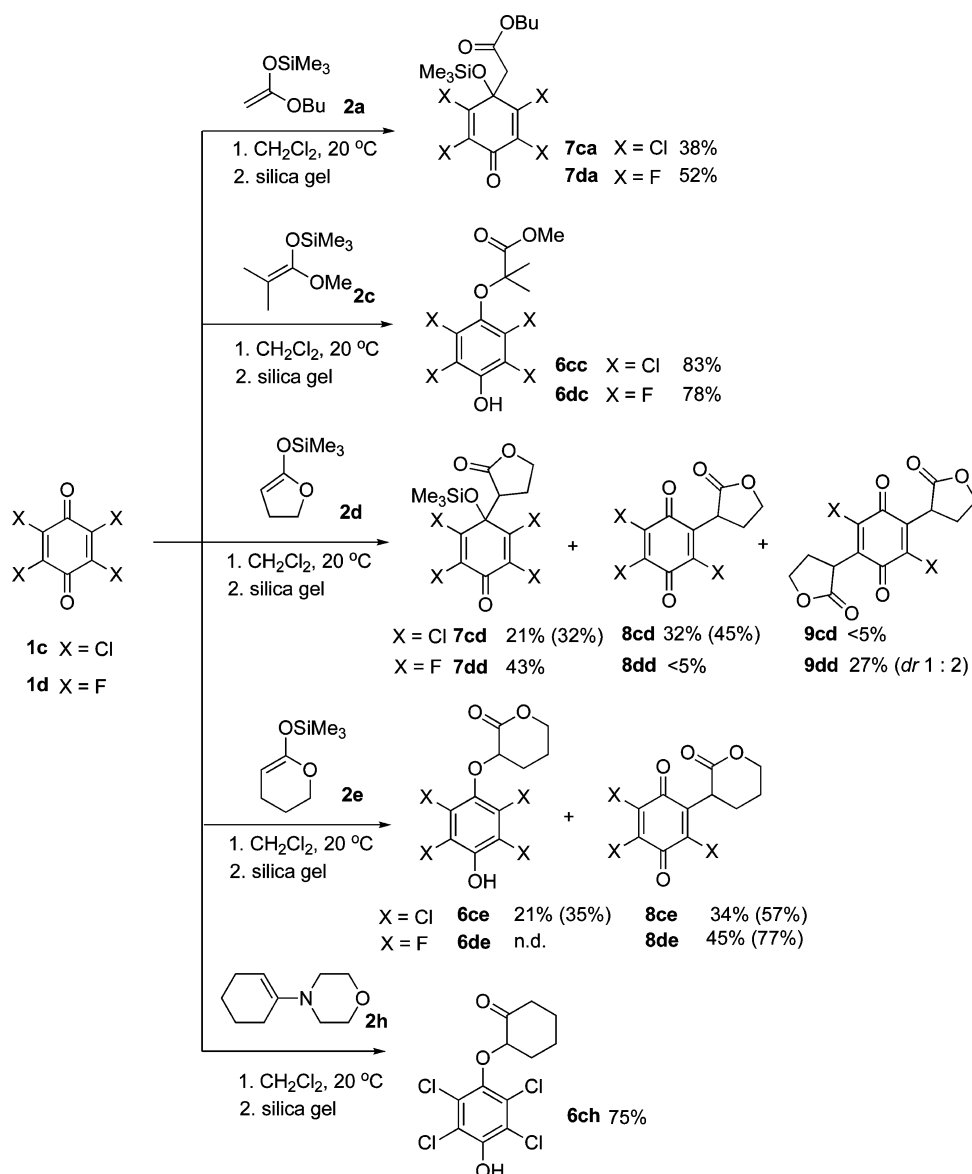
The <sup>13</sup>C NMR spectrum of pyrrolidine-substituted ortho-quinone **8ei** shows a similar pattern as that of **8ci**, that is, only one carbon signal (C-3) is significantly shifted to high field because of the mesomeric electron donation of the lone pair of the nitrogen atom, in line with structure **8ei**, where the pyrrolidino group is located at the C-4 position. The corresponding C-3 substitution by pyrrolidine would result in an NMR spectrum in which two carbon signals (conjugate C-4 and C-6 positions) are shifted to higher field. This assignment is in line with Koch's report<sup>16</sup> that the reaction of *o*-chloranil with 2,2'-bipyridine proceeds via C-4,5 substitution (Scheme 10).

**Reaction Mechanism.** From the fact that *p*-benzoquinone **1a** as well as 2,5-dichloro-benzoquinone **1b** do not give products of C-1 attack with any of the investigated nucleophiles, we can conclude that conjugate attack at these quinones is generally preferred over attack at the carbonyl carbon C-1. For that reason, the nucleophilic attack at the carbonyl carbon of **1b** is not considered in Scheme 11.

As summarized in Scheme 11, ketene acetals attack exclusively at O or C-6 (C–H) of **1b** with formation of the zwitterions **15** or **14**, respectively, which undergo subsequent desilylation to give the isolated products **6** and **3**; nucleophilic attack at the chlorinated carbon is not observed. Analogously, amines also attack faster at C–H than at the chlorinated carbon to give the zwitterion **16**. However, the intermediate **16** may undergo retroaddition, and the subsequent slower attack at C-2 leads to nucleophilic substitution of the chloride with formation of **8**. Only in the presence of high concentrations of quinone, oxidation of **16** can take place to give the amino-substituted quinones **13**. This situation—fast reversible nucleophilic attack at a C–H position followed by slow irreversible attack at the chlorinated position—reminds of the mechanisms of nucleophilic aromatic substitution of Cl<sup>-</sup> in acceptor substituted chlorobenzenes, where the initial nucleophilic attack also occurs at a C–H group.<sup>17</sup>

If a highly electrophilic C–H position is not available, as in the tetrahalo-substituted quinones **1c–e**, attack of  $\pi$ -nucleophiles at the carbonyl carbon, which was not observed in the reactions with **1a** and **1b**, becomes competitive. As shown in

Scheme 4. Isolated and (in Parentheses) NMR Yields for the Reactions of Chloranil (1c) and Fluoranil (1d) with Silyl Ketene Acetals and an Enamine



Scheme 12, nucleophiles may either attack at a halogen-substituted position (Scheme 12, path *c*) or at the carbonyl group, where C or O attack may occur (paths *a* and *b*).

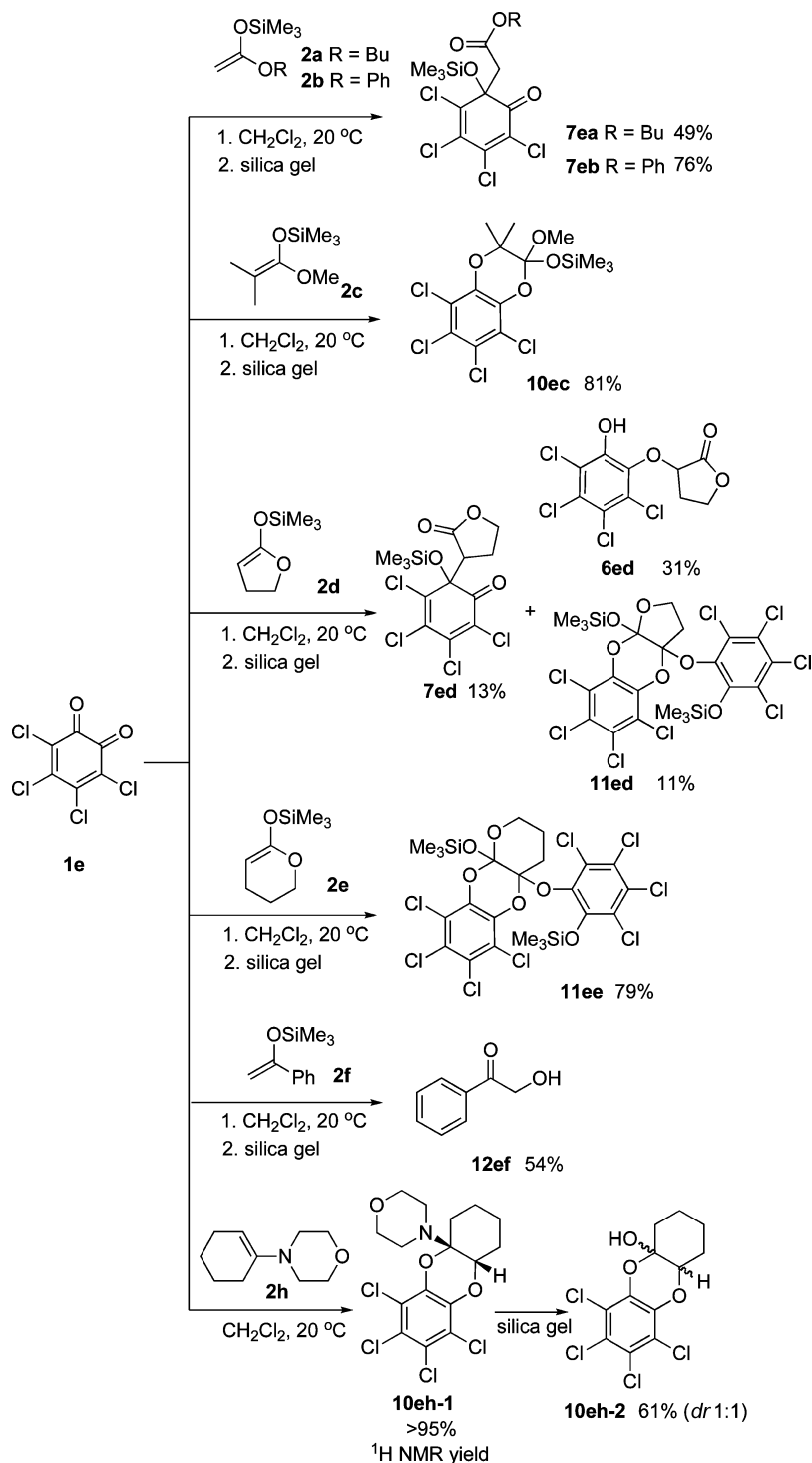
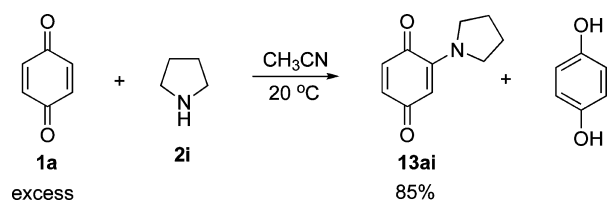
Pathway *a* (C-1 attack) is only followed by the terminal ketene acetal **2a**, and it is the only pathway followed by this nucleophile. Pathway *b* (O attack) is partially followed by the cyclic ketene acetal **2e**, and it is the only pathway followed by the enamine **2h** and the sterically demanding ketene acetal **2c**. Pathway *c* (C-2 attack), which leads to substitution via initial conjugate addition, is the exclusive process for all amines and is partially followed by the ketene acetals **2d** and **2e**, which concomitantly react via pathways *a* or *b*.

The presence of an *s-cis* configured heterodiene system in the ortho-quinone **1e** provides additional reaction pathways. Although amines selectively substitute 4-Cl of chloranil (**1c**) according to reaction pathway *c* in Scheme 12, and the terminal ketene acetal **2a** attacks the carbonyl carbon C-1 according to pathway *a* in Scheme 12. All other investigated  $\pi$ -nucleophiles **2c-e,h** behave partially or exclusively as dienophiles in Diels–

Alder reactions with inverse electron demand. The formation of the tricyclic compounds can be rationalized by the mechanism shown in Scheme 13. Initial [4 + 2] cycloaddition gives intermediate **17**, which undergoes ring-opening and proton transfer to form the silyl ketene acetal **18**. Its Diels–Alder reaction with **1e** and subsequent silylation of the hydroxyl group gives the isolated product **11ee**. Alternatively, silylation of the hydroxyl group may occur at an earlier stage of the reaction cascade.

**Kinetic Studies: Reactions with  $\pi$ -Nucleophiles.** Kinetic investigations of the reactions of the quinones **1a–e** with the  $\pi$ -nucleophiles **2a–h** were performed in dichloromethane solution at 20 °C. Most of these reactions were monitored by UV–vis spectroscopy at or close to the absorption maxima of the quinones (2,5-dichloro-*p*-benzoquinone (**1b**), 275 nm; *p*-chloranil (**1c**), 290 nm; tetrafluoro-benzoquinone (**1d**), 256 nm; *o*-chloranil (**1e**), 457 nm). Only the reaction of **1a** with **2d** as well as the reaction of **1d** with **2b** were monitored by UV–vis spectroscopy at or close to the absorption maxima of the

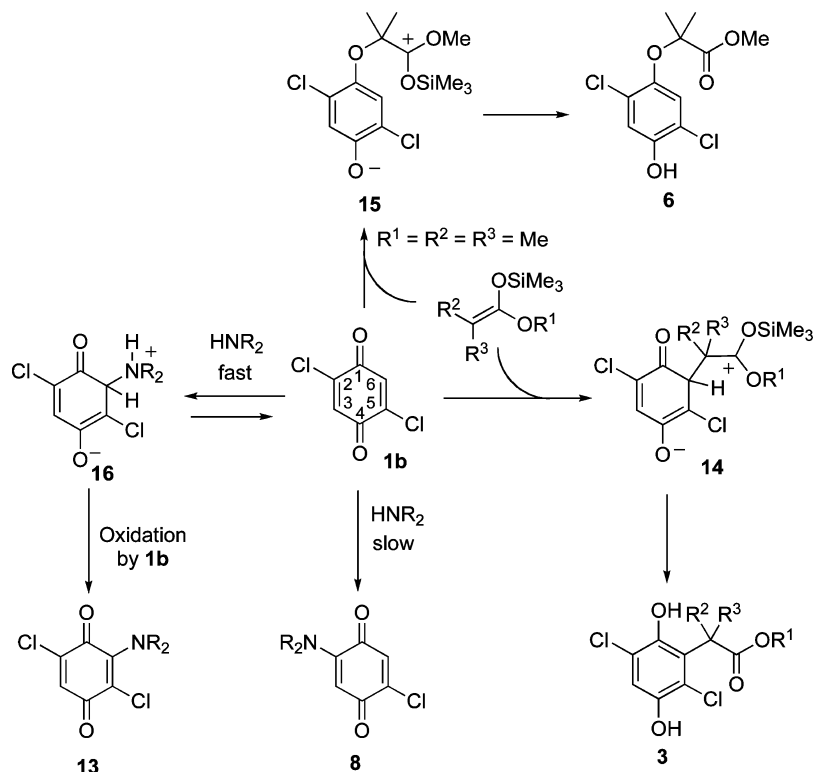
Scheme 5. Reactions of Ortho-Chloranil (1e) with Silyl Ketene Acetals and an Enamine

Scheme 6. Reaction of Pyrrolidine with *p*-Benzoquinone (1a)

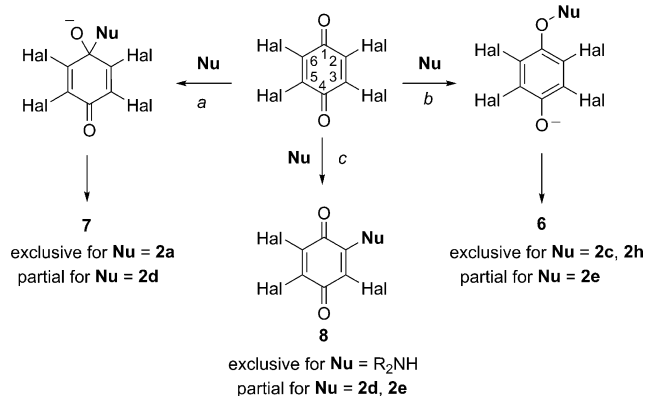
products (at  $\sim 290$  nm), and the reaction of **1a** with **2e** was followed by  $^1\text{H}$  NMR spectroscopy. In all runs, an excess of the nucleophiles (at least 10-fold) over the quinones was used to achieve pseudo-first-order kinetics. The pseudo-first-order rate constants  $k_{\text{obs}}$  were obtained by least-squares fitting of the monoexponential function  $A_t = A_0 e^{-k_{\text{obs}}t} + C$  (for decrease) or  $A_t = A_0 (1 - e^{-k_{\text{obs}}t}) + C$  (for increase) to the absorbances. The second-order rate constants  $k_2$  (summarized in Table 2) were derived from the linear correlations of  $k_{\text{obs}}$  ( $\text{s}^{-1}$ ) with the concentrations of the nucleophiles as illustrated in Figure 2.



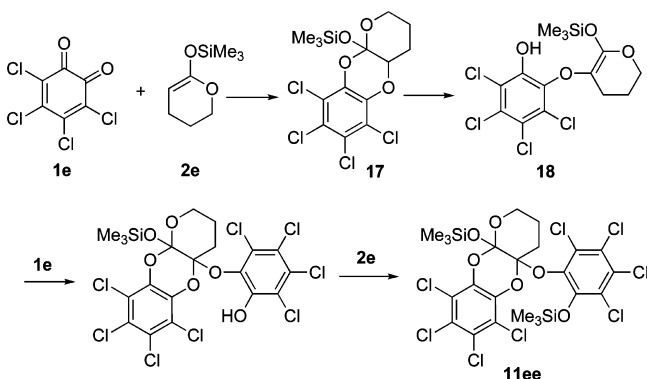
Scheme 11. Reaction Pathways of 2,5-Dichlorobenzoquinone (1b)



Scheme 12. Reaction Pathways of Tetrahalogen-Substituted Quinones



Scheme 13. Possible Mechanism for the Reaction of 1e with 2e



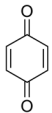
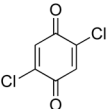
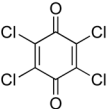
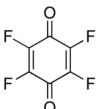
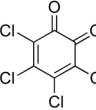
most stable product. Like the para-quinones 1c,d, the ortho-quinone 1e also reacts exclusively at C-1 with the terminal ketene acetal 2a, but increasing steric shielding now leads to Diels–Alder reactions.

The linear plot of  $(\log k)/s_N$  vs the benzhydrylium-derived nucleophilicity parameters  $N$  of the ketene acetals 2 in Figure 6 shows that the conjugate attack of the ketene acetals at a C–H position of 1a and 1b follows eq 1. Please note that also the two-point correlation for the parent quinone 1a has significance because a slope of 1.0, as required by eq 1, was enforced for the least-squares minimizations. The similar reactivities of the trimethylsilyl (2a) and *tert*-butyldimethylsilyl (2a') ketene acetals indicate that the silyl transfer must occur after the rate-determining step. Comparison of the reactivities of 1a and 1b shows that the dichloro-substitution in 1b increases the electrophilicities of the C–H positions by approximately 3 orders of magnitude. It should be noted, however, that the high electrophilicities of these positions can only become effective when the initially formed zwitterions undergo fast subsequent reactions, for example, silyl transfer in the reactions with silylated ketene acetals or oxidation by a second molecule of quinone in the reactions with amines.

When studying the kinetics of the reactions of 1b with amines, the concentrations of the quinone 1b were rather small, with the consequence that the measured rate constants referred to the attack at the chlorinated position and formation of 8. From the fact that second-order kinetics were observed from low to high degree of conversion, we conclude that the concentration of the rapidly formed zwitterion 16 (Scheme 11) remains so small under the conditions of the kinetic experiments that its intermediacy is not relevant for the kinetics.

The linear correlations for the attack at the C–Cl or C–F positions of 1b–e show (Figure 7) that also for these reactions,

Table 2. Rate Constants for the Reactions of the Quinones 1a–e with the Nucleophiles 2a–o<sup>d</sup>

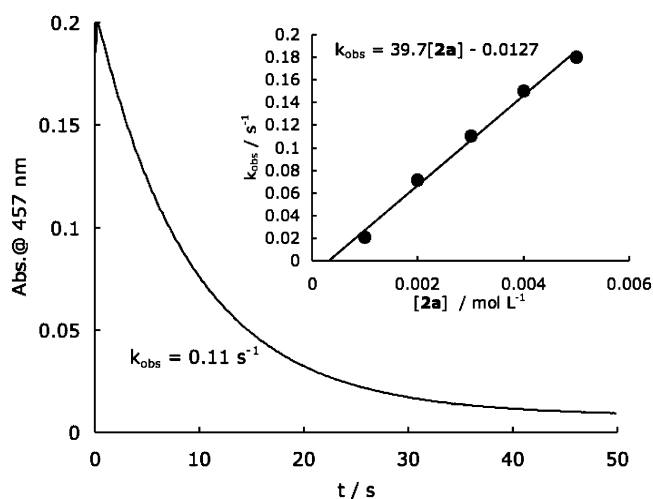
Quinone	attacked position	<i>E</i> parameter	Nucleophile	<i>k</i> <sub>2</sub> <sup>exp</sup>	<i>k</i> <sub>2</sub> <sup>calcd, a</sup>	log( <i>k</i> <sub>2</sub> <sup>exp</sup> / <i>k</i> <sub>2</sub> <sup>calcd</sup> )	<i>k</i> <sub>et</sub> <sup>max, b</sup>	log( <i>k</i> <sub>2</sub> <sup>exp</sup> / <i>k</i> <sub>et</sub> <sup>max</sup> )
	C(-H)	-16.19	<b>2d</b>	2.2 × 10 <sup>-3</sup>	2.9 × 10 <sup>-3</sup>	-0.12		
			<b>2e</b>	2.0 × 10 <sup>-5</sup>	1.6 × 10 <sup>-5</sup>	0.10		
	O		<b>2c</b>	2.8 × 10 <sup>-4 c</sup>			8.5 × 10 <sup>-5</sup>	0.52
	C(-H)	-12.28	<b>2a</b>	3.3 × 10 <sup>-2</sup>	2.0 × 10 <sup>-2</sup>	0.22	1.4 × 10 <sup>-8</sup>	6.37
			<b>2a'</b>	1.0 × 10 <sup>-2</sup>	3.0 × 10 <sup>-2</sup>	-0.47		
			<b>2c</b>	8.3 × 10 <sup>-4 c</sup>	6.1 × 10 <sup>-4</sup>	0.13	8.5 × 10 <sup>-5</sup>	0.99
	C(-Cl)	-16.11	<b>2d</b>	3.1	1.6	0.30		
			<b>2e</b>	2.5 × 10 <sup>-2</sup>	3.7 × 10 <sup>-2</sup>	-0.17		
			<b>2i</b>	5.4 × 10 <sup>1</sup>	3.3 × 10 <sup>1</sup>	0.21	4.2 × 10 <sup>-4</sup>	5.11
	O		<b>2j</b>	8.0	7.0	0.06	3.3 × 10 <sup>-7</sup>	7.38
			<b>2k</b>	2.6 × 10 <sup>-1</sup>	4.6 × 10 <sup>-1</sup>	-0.24	9.4 × 10 <sup>-9</sup>	7.44
			<b>2l</b>	2.7 × 10 <sup>-1</sup>	3.0 × 10 <sup>-1</sup>	-0.04	2.7 × 10 <sup>-15</sup>	13.99
			<b>2o</b>	4.7 × 10 <sup>-1</sup>	4.2 × 10 <sup>-1</sup>	0.04		
	C(=O)	-12.13	<b>2c</b>	2.1 × 10 <sup>-2</sup>			1.6 × 10 <sup>-1</sup>	-0.88
			<b>2e</b>	1.3 × 10 <sup>-2 c</sup>			2.3 × 10 <sup>4</sup>	-0.52
			<b>2g</b>	6.9 × 10 <sup>3</sup>			2.3 × 10 <sup>4</sup>	-2.38
	C(-Cl)	-13.84	<b>2a</b>	1.0 × 10 <sup>-1</sup>	2.7 × 10 <sup>-2</sup>	0.57	2.6 × 10 <sup>-5</sup>	3.59
			<b>2a'</b>	3.4 × 10 <sup>-2</sup>	3.9 × 10 <sup>-2</sup>	-0.05		
			<b>2d</b>	4.8 × 10 <sup>-1 c</sup>	2.0	-0.62		
	O		<b>2d</b>	7.2 × 10 <sup>-1 c</sup>	1.3 × 10 <sup>-1</sup>	0.75		
			<b>2e</b>	2.1 × 10 <sup>-2 c</sup>	1.7 × 10 <sup>-3</sup>	1.10		
			<b>2i</b>	5.6 × 10 <sup>2</sup>	7.6 × 10 <sup>2</sup>	-0.13	7.7 × 10 <sup>-1</sup>	2.86
			<b>2j</b>	8.8 × 10 <sup>1</sup>	2.4 × 10 <sup>2</sup>	-0.44	6.2 × 10 <sup>-4</sup>	5.15
<b>2k</b>			1.9	2.2 × 10 <sup>1</sup>	-1.06	1.7 × 10 <sup>-5</sup>	5.04	
<b>2l</b>			4.7	8.0	-0.23	5.1 × 10 <sup>-12</sup>	11.97	
<b>2n</b>			6.8 × 10 <sup>-1</sup>	2.0	-0.47			
<b>2o</b>	1.8 × 10 <sup>1</sup>	1.1 × 10 <sup>1</sup>	0.22					
	C(=O)	-9.37	<b>2c</b>	3.1 × 10 <sup>-1</sup>			2.2 × 10 <sup>-2</sup>	1.15
			<b>2g</b>	6.1 × 10 <sup>4</sup>			3.1 × 10 <sup>3</sup>	1.29
			<b>2h</b>	9.2 × 10 <sup>2</sup>			3.1 × 10 <sup>3</sup>	-0.53
	C(-F)	-11.12	<b>2a</b>	2.0 × 10 <sup>1</sup>	4.9	0.61	3.6 × 10 <sup>-6</sup>	6.75
			<b>2a'</b>	1.2 × 10 <sup>1</sup>	5.5	0.34		
			<b>2b</b>	3.3 × 10 <sup>-2</sup>	1.2 × 10 <sup>-1</sup>	-0.56	3.1 × 10 <sup>-8</sup>	6.09
	O		<b>2d</b>	5.9 × 10 <sup>1 c</sup>	1.7 × 10 <sup>2</sup>	-0.46		
			<b>2d</b>	3.8 × 10 <sup>1 c</sup>	1.0 × 10 <sup>1</sup>	0.57		
			<b>2e</b>	1.8	3.6 × 10 <sup>-1</sup>	0.69		
			<b>2i</b>	3.5 × 10 <sup>4</sup>	3.3 × 10 <sup>4</sup>	0.04	1.1 × 10 <sup>-1</sup>	5.52
<b>2j</b>			1.6 × 10 <sup>4</sup>	1.7 × 10 <sup>4</sup>	-0.03	8.5 × 10 <sup>-5</sup>	8.27	
<b>2k</b>			3.0 × 10 <sup>2</sup>	2.3 × 10 <sup>3</sup>	-0.88	2.4 × 10 <sup>-6</sup>	8.09	
<b>2l</b>			5.0 × 10 <sup>2</sup>	4.1 × 10 <sup>2</sup>	0.08	7.0 × 10 <sup>-13</sup>	14.85	
<b>2m</b>	2.5	7.7	-0.49	3.2 × 10 <sup>-13</sup>	12.90			
	C(=O)	-8.77	<b>2c</b>	4.6 × 10 <sup>2</sup>			2.7 × 10 <sup>1</sup>	1.23
			<b>2d</b>	1.2 × 10 <sup>3 c</sup>				
			<b>2e</b>	1.0 × 10 <sup>2</sup>			3.9 × 10 <sup>6</sup>	-0.45
	C(-Cl)	-12.02	<b>2g</b>	1.4 × 10 <sup>6</sup>				
			<b>2h</b>	>10 <sup>6</sup>				
			<b>2f</b>	3.2 × 10 <sup>-3</sup>			1.6 × 10 <sup>-6</sup>	3.29
	O		<b>2a</b>	4.0 × 10 <sup>1</sup>	1.5 × 10 <sup>1</sup>	0.42	4.5 × 10 <sup>-3</sup>	3.95
			<b>2b</b>	1.6 × 10 <sup>-1</sup>	3.7 × 10 <sup>-1</sup>	-0.36	3.9 × 10 <sup>-5</sup>	3.62
			<b>2d</b>	3.8 × 10 <sup>2 c</sup>	4.5 × 10 <sup>2</sup>	-0.07		
			<b>2i</b>	2.5 × 10 <sup>4</sup>	9.4 × 10 <sup>3</sup>	0.43	1.3 × 10 <sup>2</sup>	2.28
<b>2j</b>			5.5 × 10 <sup>3</sup>	4.2 × 10 <sup>3</sup>	0.12	1.1 × 10 <sup>-1</sup>	4.71	
C(-Cl)	-12.02	<b>2k</b>	1.3 × 10 <sup>2</sup>	4.9 × 10 <sup>2</sup>	-0.57	3.0 × 10 <sup>-3</sup>	4.64	
		<b>2l</b>	2.0 × 10 <sup>2</sup>	1.1 × 10 <sup>2</sup>	0.25	8.8 × 10 <sup>-10</sup>	11.36	
		<b>2n</b>	2.7 × 10 <sup>1</sup>	3.3 × 10 <sup>1</sup>	-0.09			

<sup>a</sup>*k*<sub>2</sub><sup>calcd</sup> are rate constants calculated by eq 1 from the *E* parameters in this table and *N*/*s*<sub>N</sub> from Table 1. <sup>b</sup>*k*<sub>et</sub><sup>max</sup> are the maximal rate constants calculated by eq 4 for single electron transfer. <sup>c</sup>Calculated from overall rate constant and the ratio of products. <sup>d</sup>20 °C, L mol<sup>-1</sup> s<sup>-1</sup>.

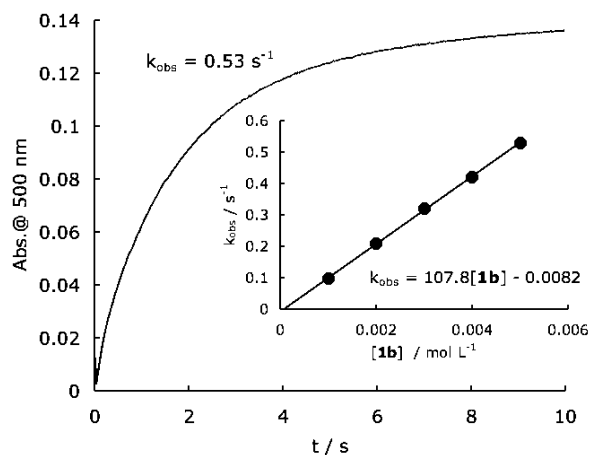
eq 1 and the benzhydrylium-derived nucleophile-specific reactivity parameters *N* and *s*<sub>N</sub> are applicable; as mentioned above, a slope of 1.0 is enforced in this type of plot. Since the

partial rate constants<sup>18</sup> for the attack of the ketene acetals **2d** and **2e** at the C-Halogen positions of **1c** and **1d** are on the same correlation line (deviation less than a factor of 20, see





**Figure 2.** UV-vis spectroscopic monitoring of the reaction of *o*-chloranil (**1e**,  $1.0 \times 10^{-4}$  mol L $^{-1}$ ) with **2a** ( $3.0 \times 10^{-3}$  mol L $^{-1}$ ) at 457 nm in CH $_3$ CN at 20 °C. Determination of the second-order rate constant  $k_2 = 40$  L mol $^{-1}$  s $^{-1}$  from the dependence of the first-order rate constants  $k_{\text{obs}}$  on the concentrations of **2a**.



**Figure 3.** UV-vis spectroscopic monitoring of the reaction of 2,5-dichloro-benzoquinone (**1b**,  $5.0 \times 10^{-3}$  mol L $^{-1}$ ) with **2i** ( $1.0 \times 10^{-4}$  mol L $^{-1}$ ) at 500 nm in CH $_3$ CN at 20 °C. Determination of the second-order rate constant  $k_2 = 54$  L mol $^{-1}$  s $^{-1}$  from the dependence of the first-order rate constants  $k_{\text{obs}}$  on the concentrations of **1b**.

Table 2) as the rate constants for the reactions with amines, it is demonstrated that the electrophilic reactivities ( $E$ ) of the halogen-substituted positions of the quinones are again almost independent of the nature of the nucleophilic reaction partner.

The absence of a kinetic isotope effect ( $k_{\text{H}}/k_{\text{D}} = 1.0$ , Scheme 14) in the reaction of 2,5-dichloro-benzoquinone (**1b**) with *N*-deuterated-morpholine (90% D) indicates that proton transfer is not involved in the rate-determining-step.

Analogous correlations in Figure 8 show that the carbonyl carbons of tetrachloro-*o*-quinone (**1e**) and fluoranil (**1d**) have similar electrophilicities, 2–3 orders of magnitude greater than that of the carbonyl carbon of chloranil (**1c**).

According to eq 1, the electrophilicity parameters of the C-1, C-2, and C-3 positions of the quinones listed in Table 2 were determined by least-squares minimization of  $\Delta^2 = \sum (\log k_2 - s_{\text{N}}(N + E))^2$  using the second-order rate constants  $k_2$  given in Table 2 and the  $N$  and  $s_{\text{N}}$  parameters of the nucleophiles **2a–o**

from Table 1, which have been derived from reactions with benzhydrylium ions.<sup>6–8</sup>

**SET vs Polar Reaction.** In previous work we have shown that DDQ reacts much more slowly with  $\pi$ -nucleophiles than expected from the correlation between electrophilicity and redox potential of benzhydrylium ions and quinone methides,<sup>19</sup> that is, DDQ was found to be far below the correlation line for benzhydrylium ions and quinone methides. By adding data for the quinones studied in this work to the plot (Figure 9), one can see that the electrophilic reactivities of the most reactive positions of quinones also correlate linearly with their redox potentials. The correlation line for quinones is  $\sim 10$  orders of magnitude below the line for benzhydrylium ions and quinone methides.

As the rate constant for electron transfer can be calculated by the Eyring equation (eq 2), and  $\Delta G_{\text{et}}^\ddagger$  must be greater than  $\Delta G_{\text{et}}^\circ$  (eq 3) according to Figure 10, the maximal accessible rate constants for electron transfer from nucleophiles to quinones are given by eq 4, where  $c$  is the Coulomb term, that is, the energy needed to separate the radical ion pair to infinite distance in CH $_2$ Cl $_2$  solution; a value of  $c = 9.6$  kJ/mol as suggested by Fukuzumi and Otera was used for the Coulomb term in the following analyses:<sup>9</sup>

$$k_{\text{et}} = (k_{\text{b}}T/h)\exp(-\Delta G_{\text{et}}^\ddagger/RT) \quad (2)$$

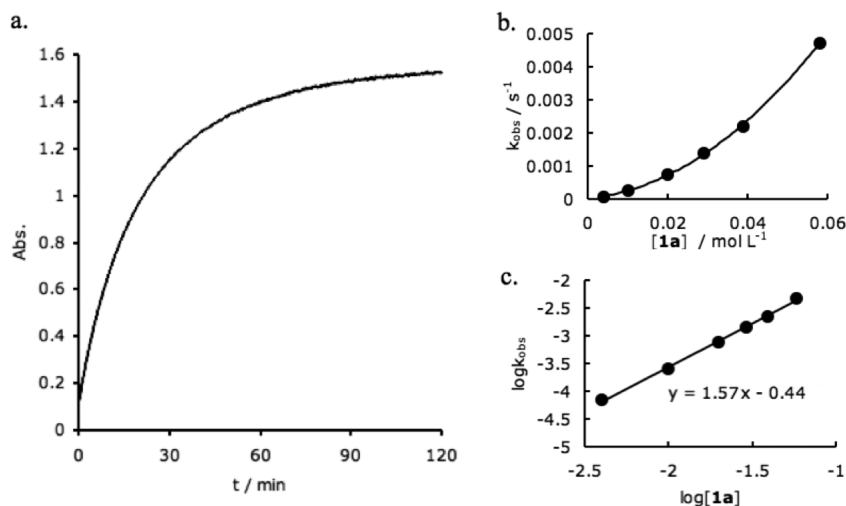
$$\Delta G_{\text{et}}^\ddagger > \Delta G_{\text{et}}^\circ = F(E_{\text{ox}} - E_{\text{red}}) - c \quad (3)$$

$$k_{\text{et}}^{\text{max}} = (k_{\text{b}}T/h)\exp\{-[F(E_{\text{ox}} - E_{\text{red}}) + c]/RT\} \quad (4)$$

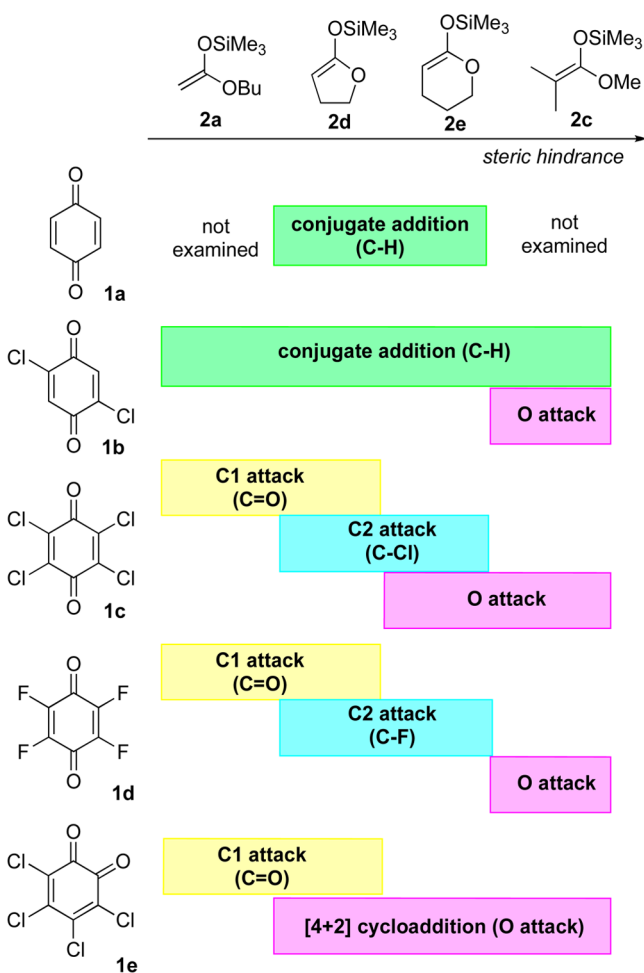
The comparison of the experimental rate constants with the maximal rate constants for electron transfer (i.e., for  $\Delta G_{\text{et}}^\ddagger = \Delta G_{\text{et}}^\circ$ ), which is given in the last column of Table 2, is illustrated in Figure 11. Because the drawn diagonal characterizes reactions of quinones with nucleophiles, which proceed with the same rate as the fastest conceivable SET processes, one can derive that the operation of SET processes can certainly be excluded for the reactions of quinones with amines ( $\blacktriangle$ ). As all amines react several orders of magnitude faster than the SETs can proceed, they must react via polar processes. Most of the reactions of  $\pi$ -nucleophiles with a carbon center of the quinones are also 4–7 orders of magnitude faster than the fastest conceivable SET processes ( $\bullet$ , exception **1b** + **2c** which gives both C- and O-attack products), and only the reactions that involve O attack at the quinones ( $\circ$ ) proceed with rate constants which are compatible with SET processes.

**Computational Studies: Stepwise or Concerted Substitution?** The question whether conjugate addition or elimination of chloride is rate-determining in the reaction of 2,5-dichloro-benzoquinone (**1b**) with pyrrolidine (**2i**) was studied by quantum chemical calculations using Gaussian 09<sup>20</sup> at B97D/6-31+G(d,p)//B97D/6-31+G(d,p)//PCM/UFF level of theory in CH $_3$ CN. The potential energy surface for the substitution process was calculated by a relaxed PES scan (with geometry optimization at each point) on the bond length of C–N and C–Cl.

Interestingly, the potential energy surface for the substitution reaction of **1b** with **2i** shows that there is no intermediate between the reactants and products (Figure 12). The substitution proceeds via an asymmetric concerted process, in which breaking of the C–Cl bond starts before the formation of C–N bond is complete.<sup>21</sup>



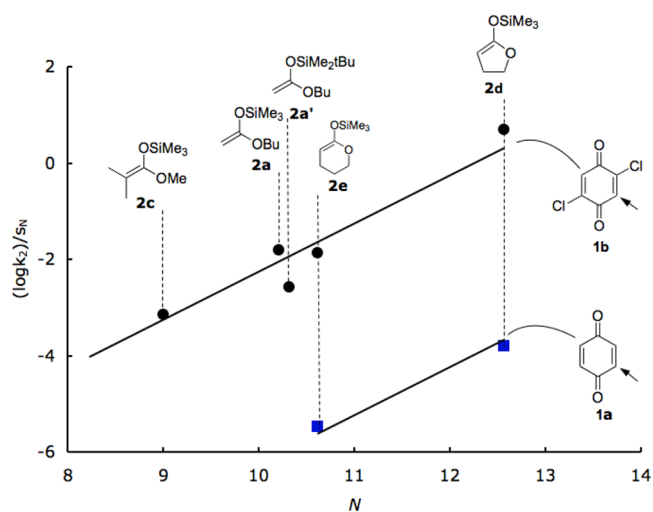
**Figure 4.** (a) UV-vis spectroscopic monitoring of the reaction of **2i** ( $1.0 \times 10^{-3}$  mol L $^{-1}$ ) with **1a** ( $2.0 \times 10^{-2}$  mol L $^{-1}$ ) at 500 nm in CH $_3$ CN at 20 °C. (b) Correlation of the observed pseudo-first-order rate constant  $k_{\text{obs}}$  with the concentration of **1a**. (c) Correlation of  $\log k_{\text{obs}}$  vs  $\log [1a]$ .



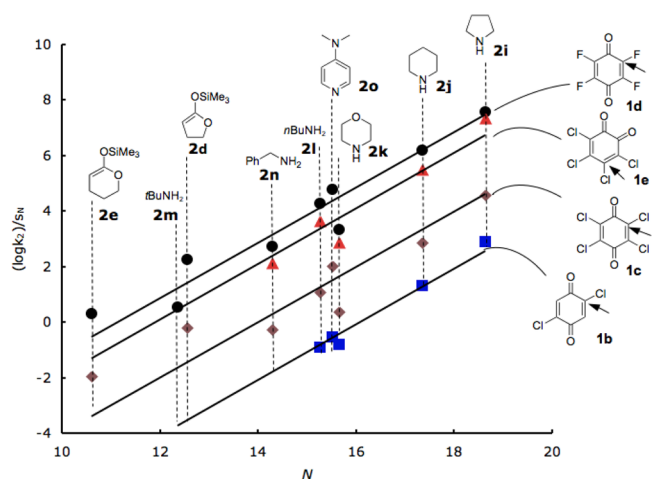
**Figure 5.** Steric effect on the product selectivities of quinones with silyl ketene acetals.

## CONCLUSION

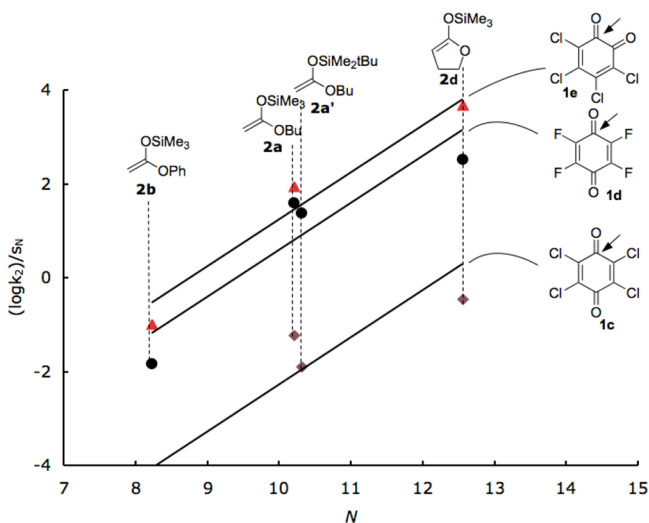
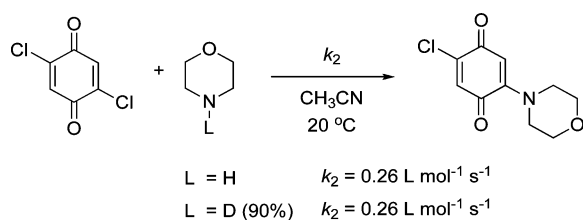
Figure 13 summarizes the behavior of the quinones **1(a–e)** toward nucleophiles. In the right part, quinones are ordered according to their electrophilicity at the different C-centers. O-Reactivity is not included because eq 1 is only applicable for



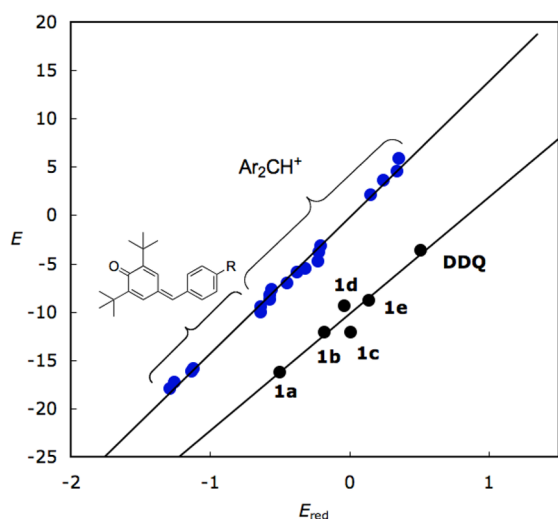
**Figure 6.** Plot of  $(\log k_2)/s_N$  vs  $N$  for the addition reactions (at C(-H)) of **1a,b** with  $\pi$ -nucleophiles in CH $_2$ Cl $_2$  at 20 °C (the slope is enforced to 1).



**Figure 7.** Plot of  $(\log k_2)/s_N$  vs  $N$  for the substitution or addition reactions of **1b–e** (at C-Halogen) with amines **2i–o** in CH $_3$ CN and silyl ketene acetals **2d** and **2e** in CH $_2$ Cl $_2$  at 20 °C (the slope is enforced to 1).

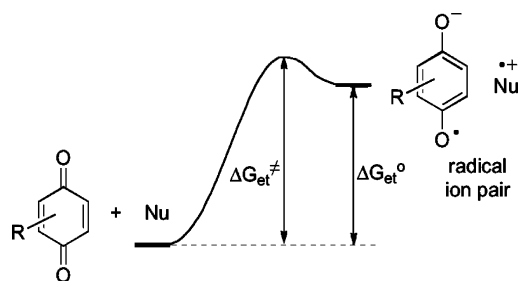
Scheme 14. Kinetic Isotope Effect for the Reaction of **1b** with Morpholine

**Figure 8.** Plot of  $(\log k_2)/s_N$  vs  $N$  for the attack of  $\pi$ -nucleophiles at the carbonyl carbon of **1c–e** in  $\text{CH}_2\text{Cl}_2$  at  $20^\circ\text{C}$  (the slope is enforced to 1).

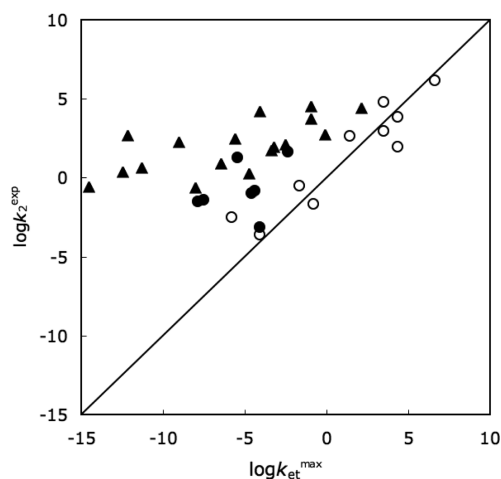


**Figure 9.** Correlation between the electrophilicity parameters  $E$  and the reduction potentials  $E_{\text{red}}$  of benzhydrylium ions and quinone methides (reference electrophiles)<sup>19</sup> and quinones.

predicting electrophile–nucleophile combinations, when at least one of the reaction centers is carbon. Figure 13 shows that the most electrophilic position of the parent compound **1a** is the C–H-group. Attack at this position can only lead to products, however, when the initially formed adduct can be stabilized, for example, by silyl migration, as in the reactions with silyl ketene acetals, or by subsequent proton transfer or oxidative hydride abstraction, as in the reactions with amines.



**Figure 10.** Energy profile for electron transfer processes.



**Figure 11.** Correlation of measured rate constants ( $\log k_{\text{exp}}$ ) with calculated maximal rate constants of SET ( $\log k_{\text{et,max}}$ ) for the reactions of quinones with amines ( $\blacktriangle$ ) and  $\pi$ -nucleophiles via C attack ( $\bullet$ ) and  $\pi$ -nucleophiles via O attack ( $\circ$ ).

Introduction of two chlorine atoms, as in **1b**, increases the electrophilicities of the C–H-positions by 3–4 units, whereas the electrophilicities of the chlorine substituted positions remain the same as in the parent **1a**. As a consequence, products arising from attack at a C–H-position of **1b** are formed, when the initially formed adduct can undergo subsequent reactions. Otherwise, the C–H attack is reversible, and the final product is formed by the slower attack at the chloro-substituted position.

The additional chlorine substituents in **1c** increase the electrophilicities of the C–Cl positions in **1c** relative to those of **1b** by more than two units of  $E$ . Four halogen substituents in chloranil **1c** or fluoranil **1d** activate the carbonyl groups so strongly, however, that now the carbonyl carbons adopt similar electrophilicities as the halogen-substituted positions, and it depends on the nature of the nucleophile and the rate of the subsequent reactions, where products will eventually be formed. It is interesting to note that the C–Cl positions in chloranil **1c** are still less reactive than the C–H positions of dichloroquinone **1b**.

The higher electrophilicities of both positions of fluoranil **1d** compared to those of chloranil **1c** are analogous to the relative reactivities of nitrated fluoro- and chlorobenzenes in nucleophilic aromatic substitutions.<sup>17</sup>

Both, C-1 and C-4 of ortho-chloranil **1e** are more electrophilic than the corresponding positions in para-chloranil **1c**, and the regioselectivity of nucleophilic attack at **1e** is again controlled by the feasibility of subsequent reactions.

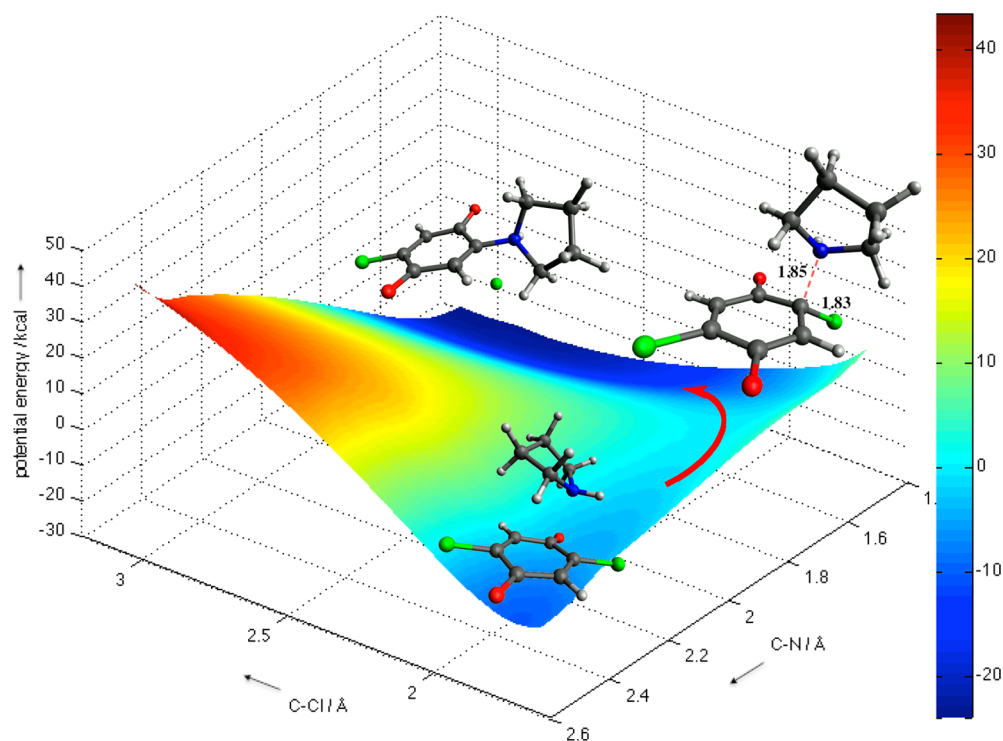


Figure 12. Potential energy surface of the reaction of **1b** with **2i**.

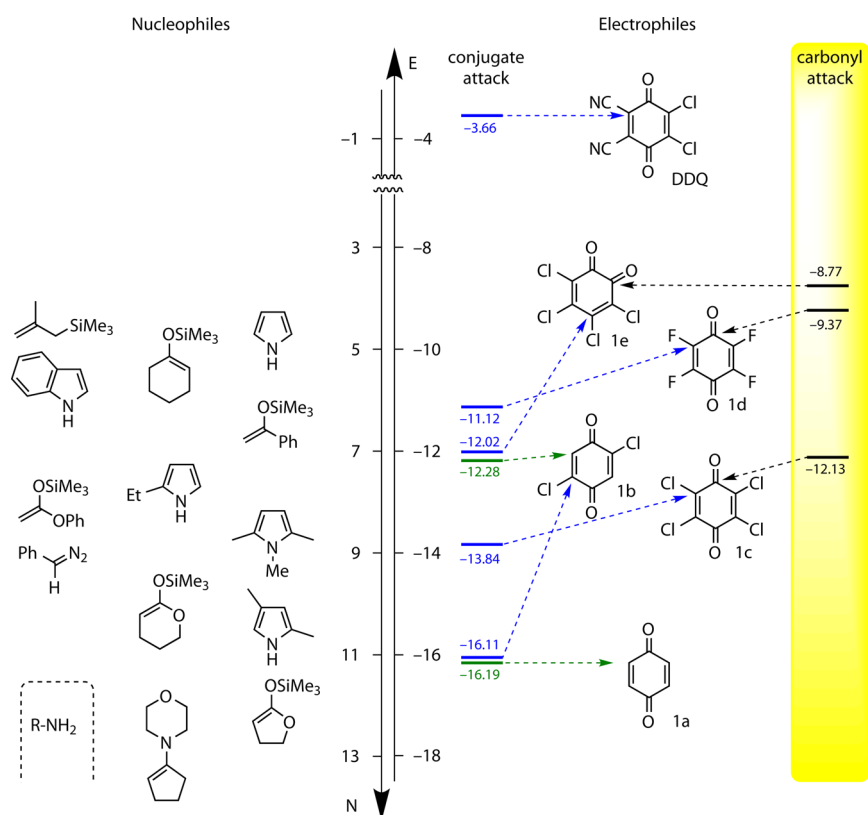


Figure 13. Synthetic potential of halogen-substituted quinones.

Comparison with the previously reported electrophilicity of DDQ<sup>5</sup> reveals the enormous activating effect of the cyano groups—ten units in *E* compared with chloranil **1c**.

In summary, most reactions of quinones with amines and  $\pi$ -nucleophiles investigated in this work proceed via polar

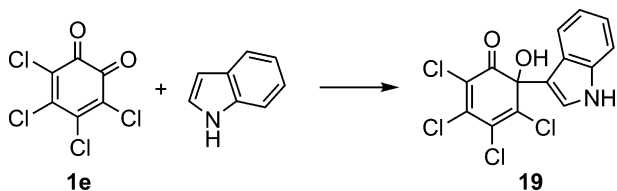
reactions—much faster than calculated for SET processes from the corresponding redox potentials. Only for the reactions that involve O-attack at the quinones, the measured rate constants do not allow to differentiate between the two mechanisms because the measured rate constants were close to

those expected for SET processes. However, because in all cases, the measured rate constants agreed with those calculated by eq 1, our rule of thumb applies, which states that reactions of electrophiles with nucleophiles can be expected to take place at 20 °C if  $E + N > -5$ .<sup>6</sup> The electrophilicity parameters  $E$  derived in this work, thus, provide a semiquantitative basis for characterizing the synthetic potential of additions of nucleophiles to 1,4-benzoquinone **1a** and its halogen-substituted derivatives **1b–e**.

In Figure 13, the  $E$ -scale for quinones is complemented by an inversely ordered  $N$ -scale, and the two scales are arranged in a way that quinones and nucleophiles, which are positioned at the same level ( $E + N = -5$ ), are calculated by eq 1 to combine with rate constants of  $\log(k/M^{-1} s^{-1}) = -5s_N$ . For typical values of  $s_N$  (0.6 to 1.0), this term translates into second-order rate constants in the range of  $10^{-5} < k(M^{-1} s^{-1}) < 10^{-3}$  at 20 °C, corresponding to slow reactions at typical concentrations for synthetic transformations. One can, therefore, expect the quinones **1a–e** to react at room temperature with the nucleophiles located below them in Figure 13, whereas reactions with nucleophiles positioned above the corresponding quinones should not occur readily.

This qualitative rule summarizes not only the reactions described in this work but also various results reported in the literature. Thus, Figure 13 explains, why 2,4-dimethylpyrrole, but not 2-ethylpyrrole and 1,2,5-trimethylpyrrole, react with 1,4-benzoquinone (**1a**) at room temperature.<sup>22</sup> From the calculated rate constant of  $6 \times 10^{-10} M^{-1} s^{-1}$  for the reaction of pyrrole ( $N = 4.61$ ,  $s_N = 1.0$ ) with a conjugate position of chloranil (**1c**), one would derive that 20% conversion of the reaction in neat pyrrole would take about 7000 h [ $c(\text{pyrrole}) = 14 M$  in neat pyrrole], if the solvent effect on  $N$  is neglected; this number is in reasonable agreement with the experimental value of 150 h.<sup>23</sup> Horner's observation of the formation of adduct **19** in the uncatalyzed reaction of indole with tetrachloro-*o*-quinone (**1e**) at ambient temperature (Scheme 15) is also in line with the relative position of these substrates in Figure 13.<sup>24</sup>

**Scheme 15.** Reaction of Indole with Tetrachloro-*o*-quinone **1e**<sup>24</sup>



Although we had previously reported the noncatalyzed reaction of DDQ with trimethyl-2-methylallylsilane,<sup>5</sup> 1,4-benzoquinone (**1a**), and other nonactivated quinones require Lewis acid catalysis to react with allylsilanes.<sup>25</sup> A similar situation is encountered for the reactions with silylated enol ethers. Though they undergo noncatalyzed reactions with DDQ,<sup>5</sup> their reactions with nonactivated quinones, as **1a**, have been achieved under catalysis of trityl perchlorate<sup>26</sup> or lithium perchlorate.<sup>27</sup> The more nucleophilic enamines, on the other hand, undergo noncatalyzed reactions also with unactivated quinones.<sup>28</sup> As most primary and secondary amines have  $N$  values greater than 10, they undergo Michael additions to the parent quinone **1a** to give substituted hydroquinones by

tautomerization; alternatively, the initial adducts are oxidized to give amino-substituted quinones.

From the nucleophilicity parameters for isocyanides ( $N \approx 5$ ),<sup>7</sup> one can derive that they will not react at room temperature with **1a**. Reactions of **1a** with phenylisocyanide in boiling toluene or xylene have been reported, however.<sup>29</sup>

A three-parameter equation cannot be expected to give an accurate description of the whole field of organic reactivity, and we have repeatedly emphasized the semiquantitative character of eq 1.<sup>6</sup> However, with a typical confidence limit of a factor of 10–100, eq 1 allows the prediction of the rates of polar organic reactions in a range of 40 orders of magnitude.<sup>30</sup> We were delighted to find that the reactions of quinones with  $n$ - and  $\pi$ -nucleophiles also follow eq 1, which could not a priori be expected because of the known tendency of quinones to act as one-electron oxidants. As a consequence, it is now possible to predict unprecedented reactions of quinones with nucleophiles by combining the  $E$  parameters reported in this work with the manifold of  $N$  and  $s_N$  parameters listed in our database.<sup>7</sup>

Hydride abstractions belong to the most important applications of quinones.<sup>3</sup> In a subsequent article, we will demonstrate that the  $E$ -parameters reported in this work can furthermore be used to analyze the mechanisms involved in these reactions and to predict the corresponding rate constants.

## EXPERIMENTAL SECTION

**Materials.** Commercially available **1a** was purified by sublimation before use. **1b** was prepared by chlorination and subsequent oxidation of 1,4-dimethoxybenzene as reported in the literature.<sup>31</sup> Commercially available **1c** was recrystallized from chloroform. Silyl ketene acetals **2(a, a', b, d, e)** were prepared by silylation of the deprotonated esters according to ref 32. Silyl enol ether **2f** was prepared from acetophenone as reported in the literature.<sup>33</sup> Enamines **2g** and **2h** were synthesized by condensation of the cycloalkanones with morpholine according to a literature procedure.<sup>34</sup>  $N$ -deuterated-morpholine was synthesized by deuterium exchange of morpholine with  $D_4$ -methanol followed by evaporation of the remaining methanol (3 $\times$ ) before it was dried with sodium. All other chemicals were purchased from commercial sources and used without further purification.

**Kinetics.** Most rates of reactions were determined photometrically in dry acetonitrile or in freshly distilled dry  $CH_2Cl_2$ . Fast reactions were determined by using the stopped-flow technique. Slow reactions were measured by conventional photodiode array UV–vis spectrometers or  $^1H$  NMR. The temperature was kept constant at  $20 \pm 0.1$  °C by using a circulating bath thermostat.

## ASSOCIATED CONTENT

### Supporting Information

Details of the kinetic experiments, synthetic procedures, X-ray crystal structure determination, and quantum chemical calculations as well as NMR spectra of all characterized compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

### Corresponding Author

herbert.mayr@cup.uni-muenchen.de

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We thank the China Scholarship Council (fellowship to X.G.) and the Deutsche Forschungsgemeinschaft (SFB 749, Project

B1) for financial support. We are grateful to Dr. Peter Mayer for the X-ray diffraction experiments. Furthermore, we thank Dr. Armin R. Ofial for help during preparation of this manuscript. Dedicated to Professor Johann Mulzer on the occasion of his 70th birthday.

## REFERENCES

- (1) Wöhler, F. *Justus Liebigs Ann. Chem.* **1844**, *51*, 145–163.
- (2) (a) Thiele, J. *Chem. Ber.* **1898**, *31*, 1247–1249. (b) Suida, H.; Suida, W. *Justus Liebigs Ann. Chem.* **1918**, *416*, 113–163. (c) *The Chemistry of the Quinoid Compounds, Parts 1 and 2*; Patai, S., Ed.; Wiley: Chichester, U. K., 1974. (d) *The Chemistry of the Quinoid Compounds Vol. 2, parts 1 and 2*; Patai, S.; Rappoport, Z., Eds.; Wiley: Chichester, U. K., 1988. (e) Moody, C. J.; Nawrat, C. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 2–24. (f) Kuttyrev, A. *Tetrahedron* **1991**, *47*, 8043–8065. (g) *Methoden der Organischen Chemie (Houben-Weyl)*; Grundmann, C., Ed; Chinone I und II Vol. 7/3a und Vol. 7/3b; Thieme: Stuttgart, 1977–1979. (h) *Science of Synthesis*; Griesbeck, A. G., Ed., Quinones and Heteroatom Analogues, Vol. 28; Thieme: Stuttgart, 2006.
- (3) (a) Conant, J. B.; Fieser, L. F. *J. Am. Chem. Soc.* **1923**, *45*, 2194–2218. (b) Conant, J. B.; Fieser, L. F. *J. Am. Chem. Soc.* **1924**, *46*, 1858–1881.
- (4) (a) *Biochemistry of Quinones*; Morton, R. A., Ed.; Academic Press Inc.: New York–London, 1965. (b) Nohl, H.; Jordan, W.; Youngman, R. J. *Adv. Free Radical Biol.* **1986**, *2*, 211–279. (c) *Enzyme-Catalyzed Electron and Radical Transfer*; Holzenburg, A., Scrutton, N. S., Eds.; Kluwer: New York, 2000.
- (5) Guo, X.; Mayr, H. *J. Am. Chem. Soc.* **2013**, *135*, 12377–12387.
- (6) (a) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938–957. (b) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66–77. (c) Mayr, H.; Ofial, A. R. *Pure Appl. Chem.* **2005**, *77*, 1807–1821. (d) Mayr, H.; Ofial, A. R. *J. Phys. Org. Chem.* **2008**, *21*, 584–595.
- (7) For a comprehensive database of nucleophilicity parameters  $N$  and  $s_N$  as well as electrophilicity parameters  $E$ , see [www.cup.lmu.de/oc/mayr/DBintro.html](http://www.cup.lmu.de/oc/mayr/DBintro.html).
- (8) (a) 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. (b) Lucius, R.; Loos, R.; Mayr, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 91–95. (c) Richter, D.; Hampel, N.; Singer, T.; Ofial, A. R.; Mayr, H. *Eur. J. Org. Chem.* **2009**, 3203–3211. (d) Ammer, J.; Nolte, C.; Mayr, H. *J. Am. Chem. Soc.* **2012**, *134*, 13902–13911.
- (9) Fukuzumi, S.; Fujita, M.; Matsubayashi, G.; Otera, J. *Chem. Lett.* **1993**, 1451–1454.
- (10) Fukuzumi, S.; Fujita, M.; Otera, J.; Fujita, Y. *J. Am. Chem. Soc.* **1992**, *114*, 10271–10278.
- (11) Renaud, P.; Schubert, S. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 433–434.
- (12) Liu, W.-Z.; Bordwell, F. G. *J. Org. Chem.* **1996**, *61*, 4778–4783.
- (13) Bourdelande, J. L.; Gallardo, I.; Guirado, G. *J. Am. Chem. Soc.* **2007**, *129*, 2817–2821.
- (14) (a) Ott, R.; Pinter, E. *Monatsh. Chem.* **1997**, *128*, 901–909. (b) Tandon, V. K.; Maurya, H. K. *Tetrahedron Lett.* **2009**, *50*, 5896–5902.
- (15) Chapyshev, S. V.; Ibata, T. *Mendeleev Commun.* **1994**, *4*, 150–152.
- (16) Koch, A. S.; Harbison, W. G.; Hubbard, J. M.; Kort, M.; Roe, B. *A. J. Org. Chem.* **1996**, *61*, 5959–5963.
- (17) (a) Terrier, F. *Modern Nucleophilic Aromatic Substitution*; Wiley-VCH: Weinheim (Germany), 2013. (b) Makosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282–289. (c) Makosza, M.; Kwast, A. *J. Phys. Org. Chem.* **1998**, *11*, 341–349.
- (18) Throughout this article we define “partial rate constants” as the sum of the reactivities of all equivalent positions.
- (19) Ofial, A. R.; Ohkubo, K.; Fukuzumi, S.; Lucius, R.; Mayr, H. *J. Am. Chem. Soc.* **2003**, *125*, 10906–10912.
- (20) Frisch, M. J.; Trucks, G. W.; Schlegel, H.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; 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.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.02; Gaussian, Inc.: Wallingford, CT, 2009.
- (21) It can be assumed that the reactions of  $\pi$ -nucleophiles at C-Cl positions proceed analogously but from the higher reactivities of the C-F positions in **1d** compared with the C-Cl positions in **1c** one can derive that breaking of the C-F bond in the reactions of **1d** cannot be far advanced in the transition state.
- (22) (a) Fischer, H.; Treibs, A.; Zaucker, E. *Chem. Ber.* **1959**, *92*, 2026–2029. (b)  $N$  for 2-ethylpyrrole can be assumed to be in between those for pyrrole and 2,4-dimethylpyrrole.
- (23) Ribo, J. M.; Acero, C. *Liebigs Ann.* **1995**, 509–514.
- (24) Horner, L.; Spietschka, W. *Justus Liebigs Ann. Chem.* **1955**, *591*, 1–20.
- (25) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1977**, *18*, 4041–4044.
- (26) Mukaiyama, T.; Sagawa, Y.; Kobayashi, S. *Chem. Lett.* **1987**, 2169–2172.
- (27) Saraswathy, V. G.; Sankaraman, S. *J. Org. Chem.* **1995**, *60*, 5024–5028.
- (28) Ulrich, H.; Richter, R. In *Methoden der Organischen Chemie (Houben-Weyl)*, Vol. 7/3a; Grundmann, C., Ed; Thieme: Stuttgart, 1977; pp 683–686.
- (29) Ott, W.; Formacek, V.; Seidenspinner, H.-M. *Liebigs Ann. Chem.* **1984**, 1003–1012.
- (30) Equation 1 has been parametrized for reactions in which only one new bond is formed in the rate-determining step; that is, it is not applicable to concerted cycloadditions. As eq. 1 does not include a steric parameter, it cannot explain subtle changes, as discussed in Figure 5.
- (31) López-Alvarado, P.; Avendaño, C.; Menéndez, J. C. *Synth. Commun.* **2002**, *32*, 3233–3239.
- (32) Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644–5645.
- (33) (a) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075–2088. (b) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2089–2100.
- (34) Hünig, S.; Lücke, E.; Brenninger, W. *Org. Synth.* **1961**, *41*, 65.