Articles

Mechanism of the Gibbs Reaction. Part 4.[1] Indophenol Formation via *N*-Chlorobenzoquinone Imine Radical Anions. The Aza-$S_{RN}2$ Chain Reaction Mechanism. Chain Initiation with 1,4-Benzoquinones and Cyanide Ion

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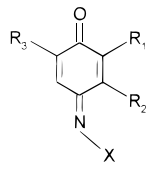
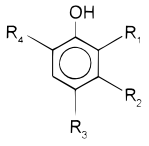
The mechanism of the Gibbs reaction, a colorimetric phenol assay that applies *N*-chlorobenzoquinone imines **1** in an aqueous basic medium, was investigated. It is concluded that *N*-chloroimine radical anion **7** generated in a single electron transfer (SET) from the anion of phenol **4** to *N*-chloroimine **1** can produce indophenol dye **3** in three distinct routes. For more reactive reagent−substrate pairs, a route is proposed that involves a fast combination of the radical pair in the solvent cage and, consequently, the total rate of which exhibits a pH-independent second-order kinetics, as does the preceding SET itself. For less reactive reagents, a route is proposed in which the *N*-chloroimine radical anion **7** escapes from the solvent cage to initiate a chain reaction, evidenced by its characteristic kinetics. It has been found in the kinetic experiments that during propagation the chlorine of the chain carrier *N*-chloroimine radical anion **7** is substituted by the anion of **4** in a bimolecular rate-determining step. Therefore, the mechanism of the chain reaction is termed $S_{RN}2$. In the case when the anion of **4** is less active, a competitive reaction along a third route can proceed in which the *N*-haloimine radical anion **7** yields benzoquinone imine **6** by the elimination of halogenide and the abstraction of an H-atom from the medium. Compound **6** is also known to give indophenol **3** with a second-order but pH-dependent rate that is considerably faster than the rate in the first route. On the basis of the different kinetic characteristics outlined above a clear distinction can be made among these three pathways. In this paper, evidence is also presented for the initiating SET. Furthermore, it is of high importance that the *N*-haloimine radical anion **7** can also be generated from reagent **1** using external electron donors and, independently of its origin, it can be spin trapped with 2,2,6,6-tetramethylpiperidine-*N*-oxyl.

Introduction

Since 1927, when H. D. Gibbs introduced[2] 2,6-dibromobenzoquinone *N*-chloroimine as a phenol assay reagent, the Gibbs reaction has become popular as an analytical tool even though, in most cases, the dibromo reagent has been replaced by the more practical 2,6-dichloro compound **1a**. According to this method, reagent **1a** reacts quantitatively with phenoxide ion (**2a**) in an alkaline solution to form the blue-colored anion of indophenol **3a**, the concentration of which is determined by colorimetric methods[3] (Scheme 1).

This assay is usually efficient even in those cases where the phenol is *para*-substituted, e.g., with CH_2NH_2, $CH_2N(Me)_2$, CH_2OH, COOH, alkoxy, and halogen, including even fluorine. It is remarkable that some of these *para*-substituents can be eliminated exclusively as a nucleofugal leaving group. Despite the wide-spread application of this reaction and the considerable efforts made to get a deeper insight into its mechanism,[4] none of the mechanisms proposed hitherto have been generally accepted. The mechanisms suggested were disproved in our previous paper[1] on the basis of the following findings. We found that depending on the *para*-substituent (R) of





1a $R_1 = R_3 = Cl$, $R_2 = H$, X = Cl
1b $R_1 = R_2 = R_3 = H$, X = Cl
1c $R_1 = Cl$, $R_2 = R_3 = H$, X = Cl
1d $R_1 = R_2 = R_3 = Cl$, X = Cl
1e $R_1 = R_2 = R_3 = H$, X = Br

4a $R_1 = R_2 = R_3 = R_4 = H$
4b $R_1 = R_2 = R_4 = H$, $R_3 = OH$
4c $R_1 = R_4 = CH_3$, $R_2 = R_3 = H$
4d $R_1 = Cl$, $R_2 = R_3 = R_4 = H$
4e $R_1 = Br$, $R_2 = R_3 = R_4 = H$
4f $R_1 = R_2 = Cl$, $R_3 = R_4 = H$
4g $R_1 = R_4 = Cl$, $R_2 = R_3 = H$
4h $R_1 = R_3 = R_4 = Bu^t$, $R_2 = H$

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(1) Part 3: Pallagi, I.; Toró, A.; Farkas, Ö. *J. Org. Chem.*, **1994**, *59*, 6543−6557.

(2) Gibbs, H. D. *J. Phys. Chem.* **1927**, *31*, 1053−1081.

(3) Kinetics shows that only the anion of phenol reacts with *N*-chloroimines **1** and phenol itself does not (see ref 1).

(4) For a compilation of this assay on various *para*-substituted phenols and for proposed mechanisms see ref 1.

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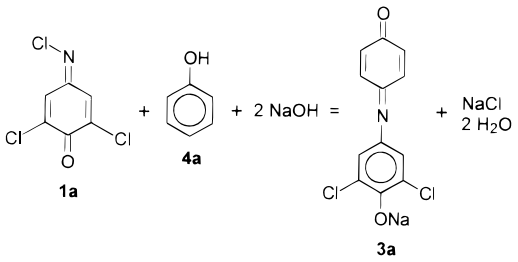
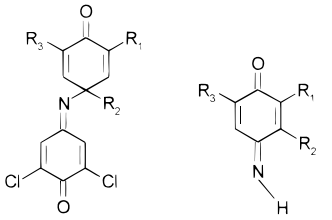
Scheme 1

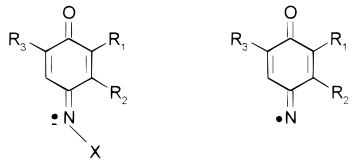


phenol **4** different products were formed in the reaction with *N*-chloroimine **1a**. Thus, if R can leave as an electrofugal leaving group (e.g., R = H, $CH_2N(Me)_2$,CH_2-OH), the reaction yields indophenol **3**, the normal Gibbs product. If R cannot leave as a cation (e.g., R = Me), the final product of the reaction is a compound like **5a**, a 4,4-



5a $R_1 = R_3 = H$, $R_2 = Me$ **6a** $R_1 = R_3 = Cl$, $R_2 = H$
5b $R_1 = R_2 = R_3 = Bu^t$ **6b** $R_1 = R_2 = R_3 = H$
6c $R_1 = Cl$, $R_2 = R_3 = H$
6d $R_1 = R_2 = R_3 = Cl$

disubstituted 2,5-cyclohexadien-1-one. Furthermore, when R is a hydroxyl or an amino group, the phenols are oxidized to the corresponding benzoquinones or benzoquinone imines, respectively, while **1a** is reduced to 2,6-dichlorobenzoquinone imine (**6a**). In all of these cases, the reaction proceeds with a 1:1 stoichiometry. If, however, R can only be eliminated as a nucleofugal group (e.g., R = halogen or alkoxy), the reaction proceeds with a 1:2 stoichiometry. In that case, the reaction yields indophenol **3** via an intermediate of type **5**, and the second mole of phenol gives an oxidation product, which is usually the corresponding benzoquinone when the two *ortho*-positions of the phenol are substituted. The mechanism of the reaction had been studied by kinetic and nonkinetic (NMR) methods. When the reaction followed a second-order kinetics ($v = k$[**1b**][**2**]), a linear correlation was found between the logarithm of the rate constant and the oxidative half-wave potentials of both 4-electrofugal and 4-nucleofugal phenols. According to our observations, independent of the *para*-substituent of the phenol, the first and usually[5,6] rate-determining step of the reaction is always a single electron transfer (SET) from the anion of phenol **4** onto *N*-chloroimine **1**, generating the *N*-chloroimine radical anion **7** and the neutral phenoxy radical **8**. When the reaction could not be characterized by second-order kinetics, a nonlinear acceleration was observed, and this deviation from linearity[7] could be abolished by radical scavengers, indicating that the product was actually formed in a chain reaction. For further progression of the radical reaction to form the indophenol **3**, two pathways were suggested: either a reaction of the radical pair to adduct **9** in the solvent cage or, after an escape of these radicals from the cage, two parallel chain reactions with phenoxyl radical **8** and with benzoquinone imine radical **10**, respectively, as the chain carriers.[1] Although quantum chemical calculations and kinetic experiments verified these suggestions and a phenoxyl radical **8** was even trapped, no conclusive evidence was provided for the actual chain reaction mechanism.



7a $R_1 = R_3 = Cl$, $R_2 = H$, X = Cl **10a** $R_1 = R_3 = Cl$, $R_2 = H$
7b $R_1 = R_2 = R_3 = H$, X = Cl **10b** $R_1 = R_2 = R_3 = H$
7c $R_1 = Cl$, $R_2 = R_3 = H$, X = Cl **10c** $R_1 = Cl$, $R_2 = R_3 = H$
7d $R_1 = R_2 = R_3 = Cl$, X = Cl **10d** $R_1 = R_2 = R_3 = Cl$
7e $R_1 = R_2 = R_3 = H$, X = Br

Moreover, we found that the actual pathway depends on the reactivity of the reaction partners. The chain reaction was characteristic for the less reactive *N*-chloroimines **1**, whereas the reaction of more reactive reagents proceeded via direct combination along with a second-order kinetics.[8]

In this paper, the accelerating effects of two different types of additives, 1,4-benzoquinones **11** and cyanide ion, are investigated in detail, and a chain initiation mechanism is proposed for the former. In addition, direct evidence is presented from spin trapping experiments that the actual chain carrier is generated from *N*-chloroimine **1** and not from phenol **4**. Thus, we describe a technique that is appropriate to investigate the characteristics of the chain reaction in the original Gibbs reaction. Whereas Part 3 of this series had focused on phenols **4** and their influence on the mechanism, in this paper the significance of *N*-chloroimine **1** is emphasized, which widens the insight into the mechanism. Indeed, even without additives, similar spin trapping products were detected in the original Gibbs reaction of the less reactive 1,4-benzoquinone *N*-chloroimine (**1b**). These products were also found during the reinvestigation of the trapping experiments of phenoxyl **8**, affording direct evidence for the initiating SET. Moreover, besides the direct combination and the chain reaction mechanism to form indophenol **3**, a third pathway, involving benzoquinone imine **6**, formed from the chain carrier **7**, was also found. This indicates the complexity of the mechanism investigated. Further kinetic investigations of the Gibbs reaction led to the conclusion that, when chain reactions are involved, both in the original Gibbs reaction and in those initiated by additives, the operative chain carrier is the *N*-chloroimine radical anion **7** and, in respect to this electrophile, the reaction follows an $S_{RN}2$

(5) When the direct combination and the chain reaction run simultaneously, by terminating the latter with 2,2,6,6-tetramethylpyperidine-*N*-oxyl (TEMPO), the much slower former reaction can be monitored, proving that the initiating SET is the slowest step.

(6) In some cases (e.g., R= methoxy), the final oxidation involving the second mole of phenol is the rate-determining step.

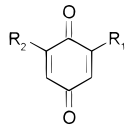
(7) The hypothetical second-order rate vs time function was found to be an excellent indicator. Its horizontal straight line or a deviation from that reflects reliably the nature of the reaction, the acceleration, and the influence of the additives. The acceleration is termed linear when the virtual rate of the accelerated reaction remains second-order.

(8) The second-order kinetics alone does not confirm the direct combination. To comply with this requirement, the reaction rate should not be affected by radical scavenger TEMPO, i.e., identical rate constants in the presence and absence of TEMPO indicate an exclusive direct combination for the dye formation reaction.

chain mechanism. This finding is in accordance with a proposal for certain radical aromatic nucleophile substitutions where the same type of mechanism was suggested.[9−11]

Results and Discussion

Gibbs Reaction in the Presence of Benzoquinones. The effect of 1,4- benzoquinones **11** on the reaction of phenol **4a** and *N*-chloroimines **1** was monitored by UV−vis and ^{1}H NMR methods. According to UV−vis spectra, 1,4-benzoquinone (**11a**) and 2,6-dichloro-1,4-benzoquinone (**11b**) accelerated the formation of indophenols **3** in the reaction of **4a** with several *N*-chloroimines **1**.[12] When plotting the hypothetical second-order rate constant vs time, a deviation from the kinetics of the original Gibbs reaction, i.e., a nonlinear acceleration characteristic for a chain reaction, is observed in the reaction of phenol **4a** with *N*-chloroimine **1b** or 2-chloro-1,4-benzoquinone *N*-chloroimine (**1c)** induced with quinone **11a** and in that with *N*-chloroimines **1a**−**c** with quinone **11b** (Figures 1 and 2).[7] In constrast, the acceleration with quinone **11a** was almost linear in the reaction of phenol **4a** with *N*-chloroimine **1a** and 2,3,6-trichloro-1,4-benzoquinone *N*-chloroimine (**1d**)[13] (14% and 12% decrease of the rate constant, respectively, until 85% conversion)[14] and with quinone **11b** in the reaction of *N*-chloroimine **1d**. These accelerating effects could be terminated by the free radical scavenger 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO).



11a $R_1 = R_2 = H$
11b $R_1 = R_2 = Cl$

The influence of 1,4-benzoquinones **11** on the Gibbs reaction was also monitored by ^{1}H NMR. With this technique, the reaction could be investigated without preparative steps. Applying this method, it was found that the only product of the Gibbs reaction is indophenol **3**. Furthermore, in a spin trapping experiment in the presence of TEMPO as the radical scavanger, besides indophenol **3**, compounds **12**, **13**, and **14** were also detected.[15] This observation verifies that the acceleration has been induced by a radical reaction and the operating radical derives from *N*-chloroimine **1b**.

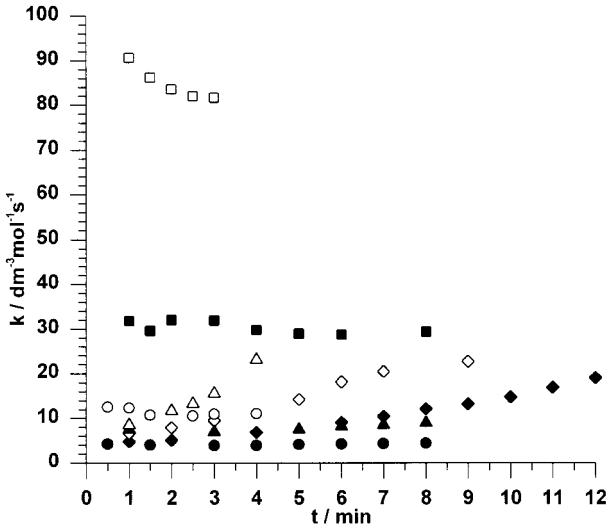


Figure 1. Hypothetical second-order rate constants vs time plot of the Gibbs reaction of *N*-chloroimines **1a**−**d** with phenol **4a** in the presence of quinone **11a** (empty symbols) and the blank reaction (filled symbols) in borate buffer (pH = 9.2) at 295 K. Because of the great differences of the *k* values of the individual compounds, a factor *f* was defined*: f* is the ratio of the observed and depicted *k* values. [**1a**−**d**] = 6.0×10^{-5} mol dm^{-3}. [**11a**] = 2.4×10^{-4} mol dm^{-3} except for the reaction of **1d**, where it was 3.0×10^{-5} mol dm^{-3}. [**4a**] = 6.6×10^{-3} mol dm^{-3} *N*-chloroimine **1a** (●) and (○), $f = 1$; [**4a**] = 1.5×10^{-1} mol dm^{-3} *N*-chloroimine **1b** (♦) and (◊), $f = 10^{-2}$; [**4a**] = 3.6×10^{-2} mol dm^{-3} *N*-chloroimine **1c** (▲) and (△), $f = 10^{-1}$; [**4a**] = 1.1×10^{-3} mol dm^{-3} *N*-chloroimine **1d** (■) and (□), $f = 1$.

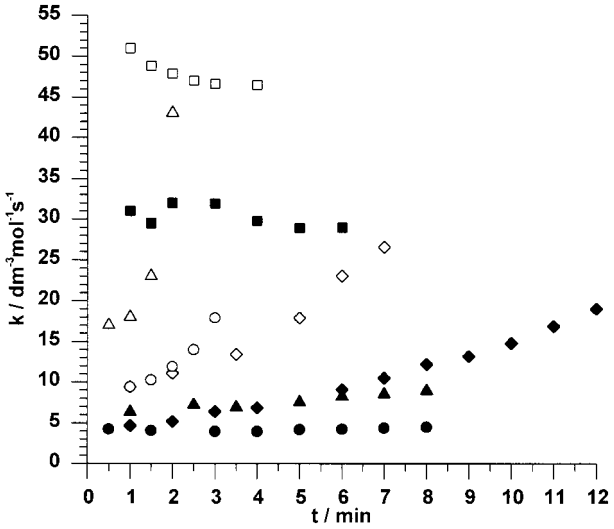


Figure 2. Hypothetical second-order rate constants vs time plot of the Gibbs reaction of *N*-chloroimines **1a**−**d** with phenol **4a** in borate buffer in the presence of quinone **11b**. [**1a**−**d**] = 6.0×10^{-5} mol dm^{-3}. [**11b**] = 3.0×10^{-5} mol dm^{-3}. For legend and [**4a**] see Figure 1. **1a**, $f = 1$ (●) and (○); **1b**, $f = 10^{-2}$ (♦) and (◊); **1c**, $f = 10^{-1}$ (▲) and (△); **1d**, $f = 1$, (■) and (□).

(9) (a) Denney, D. B.; Denney, D. Z. *Tetrahedron* **1991**, *47*, 6577−6600. (b) Denney, D, B.; Denney, D, Z.; Perez, A., J. *Tetrahedron* **1993**, *49*, 4463−4476. (c) Denney, D, B.; Denney, D, Z. *Tetrahedron* **1997**, *53*, 9835−9846.

(10) The $S_{RN}1$ mechanism was proposed in 1966 by Kornblum and Russell for aliphatic systems (Kornblum, N.; Michel, R. E.; Kerber, R. C. *J. Am. Chem. Soc.* **1966**, *88*, 5662−5663. Russell, G. A.; Danen, W. C. *J. Am. Chem. Soc.* **1966**, *88*, 7463−7464) and in 1970 by Bunnett for aromatic systems (see ref 39a).

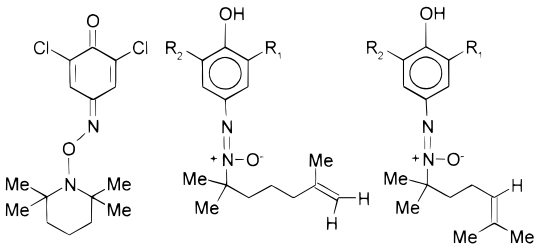
(11) For opposing $S_{RN}2$ in haloaryl systems, see, for example: (a) Bunnett, J. F. *Tetrahedron* **1993**, *49*, 4477−4484. (b) Rossi, R. A.; Palacios, S. A. *Tetrahedron* **1993**, *49*, 4485−4494. (c) Marquet, J.; Jiang, Z.; Gallardo, I.; Battle, A.; Cayón, E. *Tetrahedron Lett.* **1993**, *34*, 2801−2804. (d) Mir, M.; Espín, M.; Marquet, J.; Gallardo, I.; Tomasi, C. *Tetrahedron Lett.* **1994**, *35*, 9055−9058. (e) Niat, M.; Marquet, J.; Gallardo, I.; Cervera, M.; Mir, M. *Tetrahedron Lett.* **1994**, *35*, 9059−9062. (f) Saveant, J.-M. *Tetrahedron* **1994**, *50*, 10117−10165

(12) For conversion plots, see Supporting Information.

(13) Later we show that there are two reasons why the rate constant is increased. First, a chain reaction resulting in a nonlinear acceleration and second, in certain cases, the chain carrier, in a terminating step, produces imine **6**, which is more reactive than *N*-chloroimine **1** but reacts along the same second-order kinetics, resulting in an increase of the rate constant, i.e., linear acceleration is observed (see ref 7).

(14) The observed slight decrease of the rate constant in time is caused by a side reaction of quinone **11** with imine **6** formed dominantly in the case of the more reactive *N*-chloroimines **1**.

(15) The increase of the intensities of ^{1}H NMR signals upon addition to the NMR solutions of spin trapping adducts prepared in a different way proved their structure. (For the preparation, isolation and identification of these products see Experimental Section).



12 **13a** $R_1 = R_2 = Cl$ **13b** $R_1 = R_2 = H$ **14a** $R_1 = R_2 = Cl$ **14b** $R_1 = R_2 = H$

The ^1H NMR signal of quinone **11a** is broad in an alkaline solution (pH = 9.2, borate buffer, argon atmosphere) (Figure 3). When the alkaline solution of **11a** was quickly acidified, a small (~2%) amount of 1,4-hydroquinone (**4b**) was also detected.[16] When *N*-chloroimine **1a** is added to a solution of quinone **11a** (pH = 9.2) in the NMR tube, a small amount of imine **6a** could be observed immediately. According to the ^1H NMR spectra, the signal of **1a** was broad while that of **11a** sharpened strikingly. These observations prove that, under our experimental conditions, a quinone → hydroquinone transformation takes place, which is known to produce also the semiquinone radical anion (**15a**).[17] The great influence of the strong electron-acceptor **1a** ($E_{1/2} = -0.04$ mV; **11a**: $E_{1/2} = 0.10$ mV) on the ^1H NMR signal of quinone **11a** and the broadening of the signal of *N*-chloroimine **1a** suggest a SET from radical anion **15a** to *N*-chloroimine **1a** to produce 2,6-dichloro-1,4-benzoquinone *N*-chloroimine radical anion (**7a**), the same radical anion that is generated by phenoxide **2** in the normal Gibbs reaction. We propose that this SET initiates the chain reaction, i.e., semiquinone radical anion **15a** acts as an external electron donor. For further progression, radical anion **7a** may have three ways to react: it either initiates a chain by itself ($S_{RN}2$ mechanism) or by producing neutral imine radical **10** ($S_{RN}1$ mechanism) or

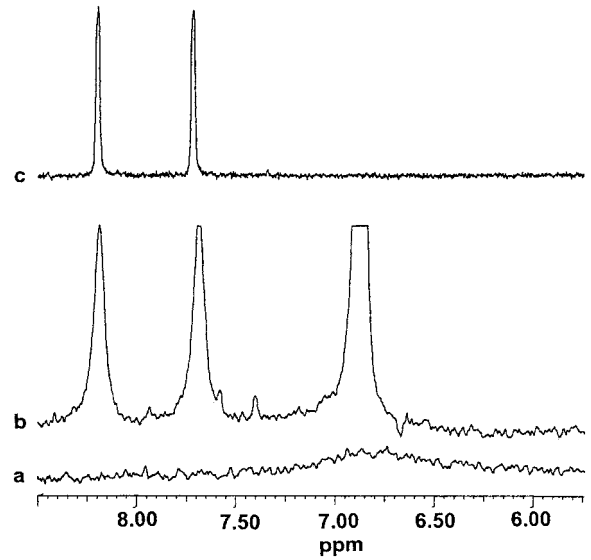
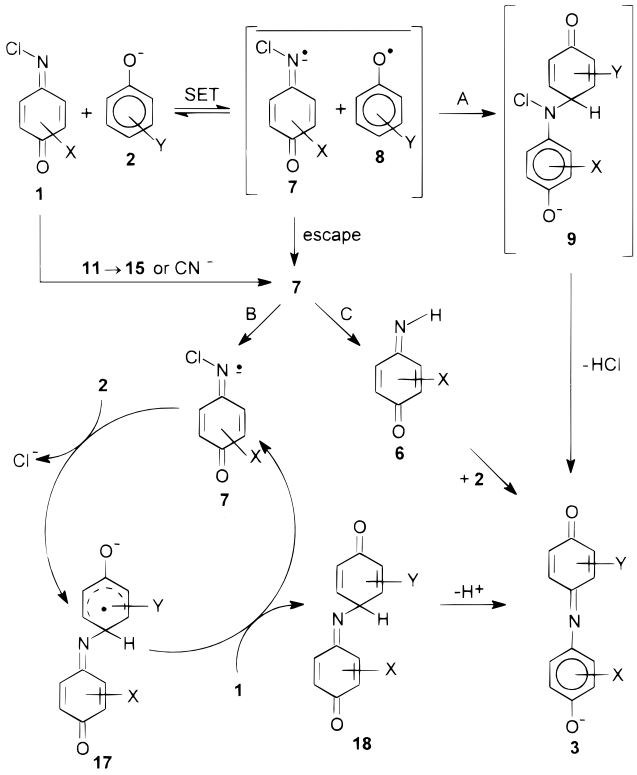


Figure 3. (a) ^1H NMR spectrum of quinone **11a** in borate buffer. (b) ^1H NMR spectrum of the 1:1 mixture of *N*-chloroimine **1a** and quinone **11a**. (c) ^1H NMR spectrum of *N*-chloroimine **1a** in borate buffer.

Scheme 2



it is transformed to imine **6**[18,19] (see Scheme 2). In the first two cases, as a result of the chain reaction, a nonlinear acceleration is experienced. In the third case, because imines **6** react with phenols **4** in the same

(16) The disproportionation can also occur in an acidic medium (see: Patai, S. *The Chemistry of the Quinonoid Group. Part 2.* John Wiley & Sons: New York, 1974; pp 746−769). Formation of more 1,4-hydroquinone (**4b**) within a prolonged time in an alkaline medium before acidifying the solution ruled out this potential artifact.

(17) (a) Fomin, G. V.; Blyumenfel'd, L. A.; Sukhorukov, V. I. *Dokl. Akad. Nauk SSSR* **1964**, *157*, 1199−1201; *Chem. Abstr.* **1964**, *61*, 12824. (b) Bishop, C, A.; Tong, L. K. J. *Tetrahedron Lett.* **1964**, *41*, 3043−3048. (c) Bishop, C. A.; Tong, L, K. *J. Am. Chem. Soc.* **1965**, *87*, 501−505. (d) Lazarov, St.; Trifonov, A.; Popov, Tz. *Z. Phys. Chem. (Leipzig)* **1968**, *238*, 145−160; *Chem. Abstr.* **1968**, *69*, 95717a. (e) Endo, T.; Miyazawa, T.; Shiihashi, S.; Okawara, M. *J. Am. Chem. Soc.* **1984**, *106*, 3877−3878. (f) Roberts, J. L., Jr.; Sugimoto, H.; Barrette, W. C., Jr.; Sawyer, D. T. *J. Am. Chem. Soc.* **1985**, *107*, 4566−457. (g) Endo, T.; Miyazawa, T.; Shiihashi, S.; Okawara, M. *J. Am. Chem. Soc.* **1984**, *106*, 3877−3878. (h) Fukuzumi, S.; Nakanishi, I.; Maruta, J.; Yorisue, T.; Suenobu, T.; Itoh, S.; Arakawa, R.; Kadish, K. M. *J. Am. Chem. Soc.* **1998**, *120*, 6673−6680.

(18) In analogy to radical aromatic nucleophile substitutions, the reaction is termed $S_{RN}1$ when the chain carrier is the neutral imine radical **10** and $S_{RN}2$ when it is the *N*-chloroimine radical anion **7**. For the sake of clarity, structures of imine radicals **10** are also included.

(19) For the formation of imine **6** from *N*-haloimine radical anion **7**, two alternatives have to be considered: either the elimination of a halogen anion and a subsequent H-atom abstraction via imine radical **10** or the reverse order of these steps. According to our semiempirical quantum chemical calculations (PM3 method), *N*-chloroimine radical anion **7** is a π-radical having considerable spin density only at the orbitals suitable for π-bonding (spin density of orbital p_z on nitrogen atom of **7a** is 0.28 while that of p_y and p_x, suitable for σ-bonding, are almost zero). On the other hand, the σ-type imine radical **10** has a large spin density on orbital p_x. (Spin densities of orbitals p_x, p_y, and p_z on *N*-atom of imine radical **10a** are 0.48, 0.08, and 0.28, respectively). However, an intramolecular $\pi \rightarrow \sigma$ transformation on *N*-haloimine radical anion **7** may also be presumed, as a similar intramolecular $\pi \rightarrow \sigma$ transformation has already been reported for haloaryl radical anions (see ref 24).

(20) Corbett, J. F. *J. Chem. Soc. B* **1970**, 1502−1509.

(21) The linear accelerating effect of quinones **11** were perfectly simulated by in situ generated imines **6** (see Supporting Information).

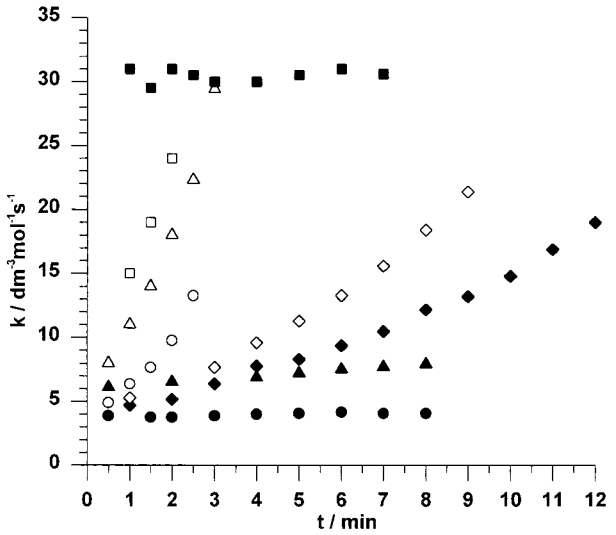


Figure 4. Hypothetical second-order rate constants vs time plot of the Gibbs reaction of *N*-chloroimines **1a**−**d** with phenol **4a** in the presence of cyanide ions. For [**4a**] see Figure 1. [**1a**−**d**] = 6.0×10^{-5} mol dm^{-3}. [KCN] = 1.7×10^{-5} mol dm^{-3}. **1a**, $f = 1$ (●) and (○); **1b**, $f = 10^{-2}$ (♦) and (◊); **1c**, $f = 10^{-1}$ (▲) and (△); **1d**, $f = 1$ (■) and $f = 10$ (□).

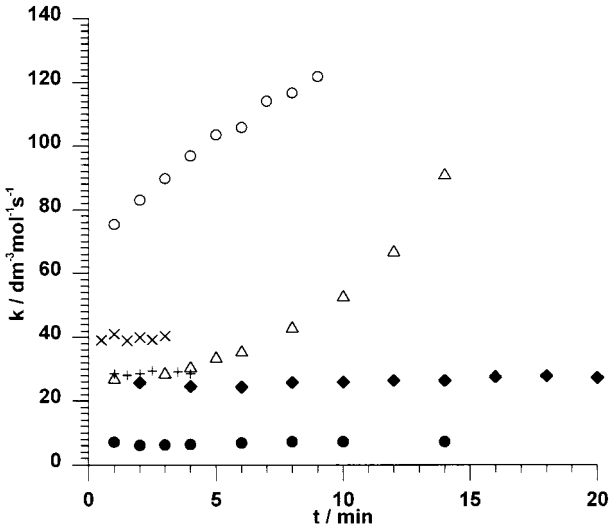


Figure 5. Hypothetical second-order rate constants vs time plot of the Gibbs reaction of *N*-chloroimine **1b** ($f = 1$) and *N*-bromoimine **1e** ($f = 10$) with phenol **4c**, blank experiments (**1b**: ♦; **1e**: ●), in the presence of quinone **11a** (**1b**: ○; **1e**: +), or cyanide ion (**1b**: △; **1e**: ×). [**1b,e**] = 6.0×10^{-5} mol dm^{-3}, [**4c**] = 1.0×10^{-3} mol dm^{-3}, [**11a**] = 6.0×10^{-4} mol dm^{-3}, [KCN] = 1.7×10^{-5} mol dm^{-3} (see ref 23).

second-order kinetics[20] but with higher rates than *N*-chloroimines **1**,[1] their participation in the dye formation results in a linear acceleration.[21]

Reaction of Phenols with *N*-Chlorobenzoquinone Imines in the Presence of Cyanide Ion. When KCN is added to an alkaline solution of *N*-chloroimine **1a** in an NMR tube, a fast (partial) transformation of **1a** to imine **6a** can be observed. When TEMPO is also present, instead of this transformation, the formation of compounds **12**, **13a**, and **14a** is detected. When monitoring the Gibbs reactions of *N*-chloroimines **1** with phenol **4a** in the presence of cyanide ion by UV−vis spectroscopy, an acceleration occurred which could be prevented by radical scavenger TEMPO (Figure 4). The UV spectra of *N*-chloroimines **1**, in the presence of cyanide ion in borate buffer, indicate that, during the time needed for indophenol formation, the transformation to the corresponding imines **6** was negligible or very small (e.g., **1d**). This supports that, upon cyanide initiation, *N*-chloroimine radical anion **7** is formed only in a low concentration.

The radical anion **7** could be more effectively generated by adding cyanide anion, and furthermore, no *organic* compounds had to be added. Therefore, cyanide was applied in most of the experiments, even if the exact mechanism of this initiation is still unknown.[22a,b]

Mechanistic Implications. To determine which one is the operating chain reaction mechanism, kinetic methods were applied. The reactions of benzoquinone *N*-bromoimine (**1e**) and *N*-chloroimine **1b** with 2,6-dimethylphenol (**4c**), in the presence of quinones **11** or cyanide ion (see later) as chain initiators, were compared.[12] In absence of the initiator, this phenol reacts with both *N*-haloimines, affording indophenols **3** with a second-order rate constant stable in time (Figure 5).[7] However, when initiators are applied a substantial difference is observed: while a nonlinear acceleration, characteristic for a chain reaction mechanism, occurs in the reaction of **4c** with *N*-chloroimine **1b**, the reaction with *N*-bromoimine **1e** is linearly accelerated, demonstrating the effect of imine **6b** (Figure 5). The different reactivities of these two *N*-haloimines are in controversy with an $S_{RN}1$ mechanism, according to which both *N*-haloimines should react via the same intermediate, imine radical **10b**. However, this observation can be readily rationalized when considering an $S_{RN}2$ mechanism, where the intermediates are different, i.e., *N*-chloroimine **1b** reacts via the radical anion **7b** in a chain reaction while *N*-bromoimine **1e** affords an imine by H-atom abstraction from the medium. Because bromide anion is a much better leaving group as described for arylhalogenide radical anions,[24c] the explanation seems to be obvious: while *N*-bromo radical anion **7e**, being unstable, is transformed into imine **6b**, the stability of *N*-chloro radical anion **7b** allows both chain initiation and propagation.

The chain carrier was identified using kinetic experiments on the basis of the following considerations. In case of an $S_{RN}1$ mechanism (imine radical **10** as the chain carrier), similarly to the ionic S_N1 mechanism, a slow monomolecular dissociation is followed by fast addition of the nucleophile. In an $S_{RN}2$ mechanism (*N*-chloroimine radical anion **7** as the chain carrier), similarly to the ionic S_N2 mechanism, the slow, rate-determining step is the bimolecular reaction of the chain carrier and the nucleo-

(22) (a) In our previous paper (ref 1), we reported that acetonitrile accelerated the Gibbs reaction. Because this solvent may be contaminated with cyanide ions, we determined the cyanide concentration[22b] of the reaction mixture ($(1.6-6) \times 10^{-6}$ mol dm^{-3}) and found that the acceleration effect caused by the cyanide contamination was equal to that caused by the same quantity of cyanide added directly to cyanide-free acetonitrile. Thus, the observed acceleration caused by acetonitrile was clearly due to its cyanide contamination. (b) Cyanide contamination of the acetonitrile used in earlier experiments was 3.2×10^{-3} mol dm^{-3}. (Determined according to *Standard Methods for the Examination of Water and Wastewater* APHA, AWWA, and WPCF: 1989; XVII edition, pp 4−31.

(23) Ninety percent of conversion was achieved in a blank experiment with *N*-chloroimine **1b** in 40 min. During this time, the second-order rate constant was found to be steady.

(24) (a) Behar, D.; Neta, P. *J. Am. Chem. Soc.* **1981**, *103*, 103−106. (b) Behar, D.; Neta, P. *J. Am. Chem. Soc.* **1981**, *103*, 2280−2283. (c) Kimura, N.; Takamuku, S. *J. Am. Chem. Soc.* **1995**, *117*, 8023−8024.

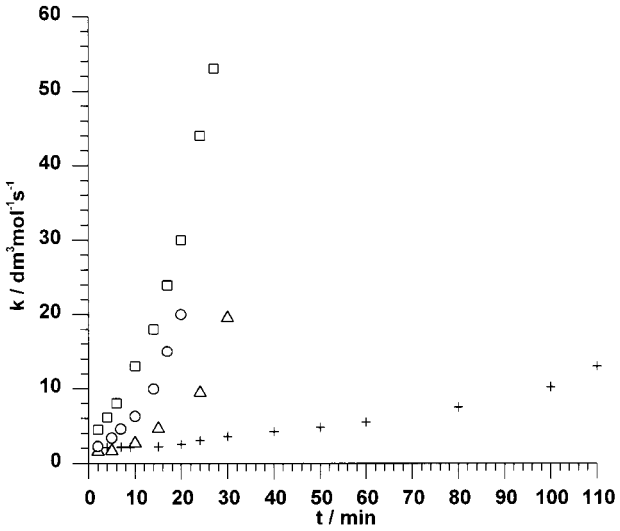


Figure 6. Hypothetical second-order rate constants vs time plot of the Gibbs reaction of *N*-chloroimine **1b** with phenols **4d**−**g** in the presence of KCN at $T = 293$ K (pH = 10.0). [**1b**] = 6.0×10^{-5} mol dm^{-3}, [KCN] = 3.6×10^{-5} mol dm^{-3}. [**4d**] = 7.72×10^{-2} mol dm^{-3}, $f = 10^{-3}$, (△); [**4e**] = 1.04×10^{-1} mol dm^{-3}, $f = 10^{-3}$, (○); [**4f**] = 2.45×10^{-1} mol dm^{-3}, $f = 10^{-4}$, (□); [**4g**] = 2.45×10^{-1} mol dm^{-3}, $f = 10^{-4}$, (+).

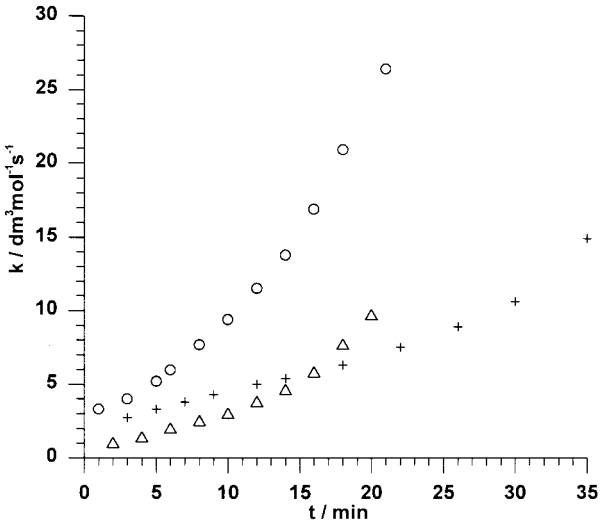


Figure 7. Hypothetical second-order rate constants vs time plot of the reaction of *N*-chloroimine **1b** with phenol **4a** as a function of the concentration of **4a** at 295 K. [**1b**] = 4.24×10^{-3} mol dm^{-3}, [**4a**] = 3.90×10^{-1} mol dm^{-3}, (pH = 9.33), $f = 10^{-3}$, (+). [**1b**] = 6.18×10^{-4} mol dm^{-3}, [**4a**] = 1.47×10^{-1} mol dm^{-3}, (pH = 9.25), $f = 10^{-2}$, (△). [**1b**] = 6.14×10^{-5} mol dm^{-3}, [**4a**] = 5.86×10^{-2} mol dm^{-3}, (pH = 9.15), $f = 10^{-2}$, (○).

phile. Consequently, in an $S_{RN}1$ mechanism, the rate depends *only* on the chain carrier and its concentration, whereas when an $S_{RN}2$ mechanism is operating, the rate is *also* dependent on the nucleophile and its concentration. The Gibbs reactions of *N*-chloroimine **1b** and four phenols, 2-chloro- (**4d**) ($pK_a = 8.56$),[25a] 2-bromo- (**4e**) ($pK_a = 8.45$),[25b] 2,3-dichloro- (**4f**) ($pK_a = 7.70$),[25c] and 2,6-dichlorophenol (**4g**) ($pK_a = 6.80$),[25b] were investigated in these experiments. The chain reaction was always maintained by the same concentration of the additive (KCN),[26] and the pH was always adjusted to 10.0. Depicting the hypothetical second-order rate constant as a function of time, it can be seen that the initial rates depend on the kind of phenol (Figure 6). This fact alone does not verify the phenol dependence of the chain reaction because the direct reaction is also depending on the kind of phenol.[27a,b] To eliminate the latter, the quotients of these two rates were calculated. These were 3.9, 3.1, 1.6, and 2.2, respectively, indicating the phenol dependence of the relative initial rates. It is also noteworthy that from the relative rates calculated for 90% conversion (51, 31, 24, and 14, respectively) for the reaction of phenols **4d**−**g** with *N*-chloroimine **1b**, the same conclusion can be drawn. Thus, the higher the reactivity of the phenol, the greater the observed acceleration.[27b]

These results are incompatible with an $S_{RN}1$ mechanism but comply with an $S_{RN}2$ mechanism.[28] Another requirement of the latter is the dependence of the rate constant on the concentration of the nucleophile. This is also true, demonstrated by the increasing hypothetical second-order rate constant with increasing concentration of phenol **4a** in its reaction with *N*-chloroimine **1b** (Figure 7).

Beyond the direct combination in the solvent cage, there are two other ways of dye formation involving the escaped radical anion **7**, the reactions via chain reaction or via imine **6**. To determine the contribution of these two competitive pathways and to establish whether the actual nucleophile is the phenol or its anion, the pH dependence of the Gibbs reactions of *N*-chloroimine **1b** and three phenols, **4a**, **4c**, and **4g**, of considerably different reactivities were investigated. In the case of phenol **4a**, in the pH range of 7.6−10.0, the increase of the hypothetical second-order rate constant was observed with decreasing pH (Figure 8). It is known[29] that the reactivity of imine **6b** shows similar pH dependence; thus, a new pathway in which the chain carrier abstracted an H-atom from the medium to give imine **6b** is concluded. The results with the other two phenols cor-

(25) (a) Patai, S. *The Chemistry of the Hydroxyl Group. Part 1*; John Wiley & Sons: New York, 1971; pp 373−392. (b) Fischer, A.; Leary, G. J.; Topsom, R. D.; Vaughan, J. *J. Chem. Soc. B* **1967**, 686−687 (c) Williams, S. G.; Norrington, F. E. *J. Am. Chem. Soc.* **1976**, *98*, 508−516.

(26) The products from the reaction of these phenols and *N*-chloroimine **1b** are formed partially by a chain reaction mechanism even without initiators at this pH, but as a result of the low reactivity of the nucleophile, the decomposition of radical anion **7** is significant, resulting in a lower conversion. When initiators were applied the rate increased and the products were formed quantitatively.

(27) (a) Rates of the direct combination in the reaction of phenols **4d**−**g** with *N*-chloroimine **1b** in dm^3 mol^{-1} s^{-1} were 3.8×10^{-4}, 6.4×10^{-4}, 2.2×10^{-4}, and 9.0×10^{-5}, respectively. (b) The proportions of chain reaction mechanism for phenols **4d**−**g** were found to be 34%, 48%, 52%, and 59%, respectively. Thus, even the higher proportion of chain reaction mechanism cannot compensate the lower reactivity of the phenols **4f,g**.

(28) (a) Reflecting on the comment of one of the referees of this paper, for the sake of clarity, we suggest the use of the $S_{RN}2$ symbol also for those cases when the slowest step of an $S_{RN}1$ reaction is *bimolecular*. (b) Semiempirical calculations are also in accord with an $S_{RN}2$ mechanism thermodynamically favoring *N*-chloroimine radical anion **7a** as an intermediate over imine radical **10a** with ca. 117 kcal/mol. Heat of formations calculated with the PM3 method in kcal/mol are **7a**: −60.8, **7b**: −42.4, **10a**: +56.2, **10b**: +51.8. For a complete energy diagram see ref 1.

(29) Reaction of phenols with imine **6b** proceeds with a second-order kinetics similarly to *N*-chloroimines **1** (direct combination, comparable concentration of reactants), with the difference that its total rate is the sum of the rates of four reactions: (a) reaction of the neutral imine with the anion of **4**, (b) reaction of the neutral imine with phenol **4**, (c) reaction of the protonated imine with the anion of **4**, and (d) reaction of the protonated imine with phenol **4** (see ref 20). The primacy among these reactions depends on pH; thus, in the pH range 6−8, the majority of the dye is formed by reaction *c*. As the protonated imine is by several orders of magnitude more reactive (2.4×10^5 times) than the neutral form, the total rate increases with decreasing pH.

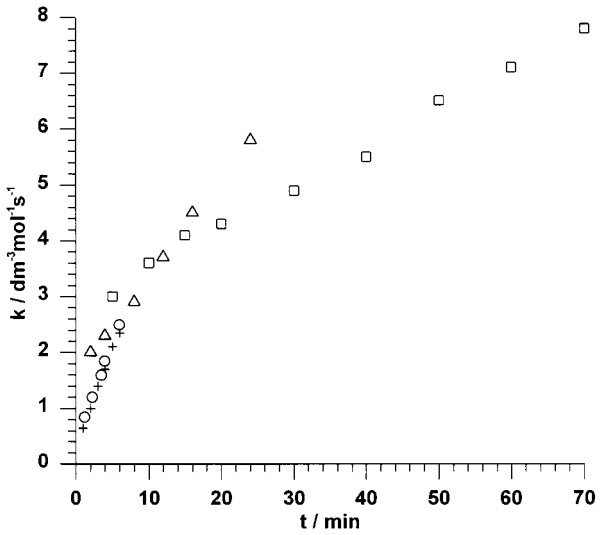


Figure 8. Hypothetical second-order rate constants vs time plot of the Gibbs reaction of *N*-chloroimine **1b** with phenol **4a** at $T = 295$ K. [**1b**] = 6,0 × 10^{-5} mol dm^{-3}. $f = 10^{-1}$. [**4a**] = 1.8 × 10^{-1} mol dm^{-3}, (pH = 7.6) (□); [**4a**] = 1.5 × 10^{-1} mol dm^{-3}, (pH = 8.3) (△); [**4a**] = 1.2 × 10^{-1} mol dm^{-3}, (pH = 9.3) (○); [**4a**] = 9.7 × 10^{-2} mol dm^{-3}, (pH = 9.6) (+).

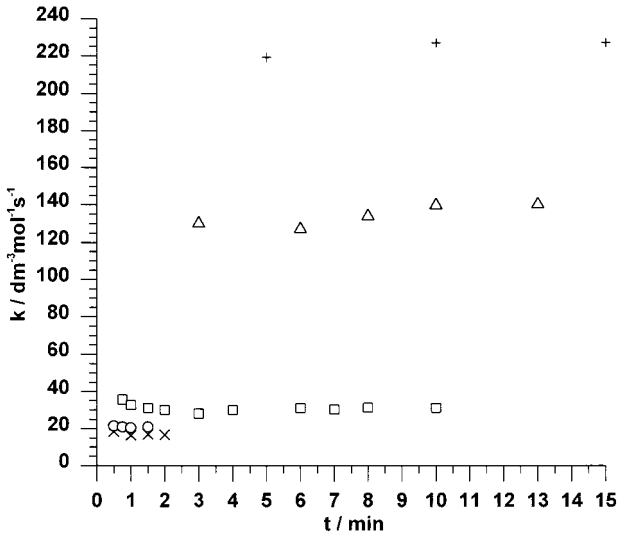


Figure 9. Hypothetical second-order rate constants vs time plot of the Gibbs reaction of *N*-chloroimine **1b** with phenol **4c** at $T = 295$ K. [**1b**] = 6.0 × 10^{-5} mol dm^{-3}. $f = 1$. [**4c**] = 4.0 × 10^{-3} mol dm^{-3}, (pH = 7.4) (+);[31] pH = 8.3 (△), (pH = 9.1) (□); [**4c**] = 2.0 × 10^{-3} mol dm^{-3}, (pH = 10.4) (×); [**2c**] = 1.0 × 10^{-3} mol dm^{-3}, (pH = 12.1) (○).

roborate this assumption. Phenol **4c** (pK_a = 10.7)[25a] showed no chain reaction in the pH range of 7.4−12.1 (α = 5 × 10^{-4} to 9.618 × 10^{-1}) despite the fact that this reaction was moderately (10%) blocked by TEMPO, indicating again the action of another mechanism besides direct combination.[30a,b] An increase of the rate constant with decreasing pH is also observed, and it is even more intense than in the experiments on **4a** (Figure 9). This is in accordance with the fact that phenol **4c** is much more reactive (9 × 10^3 times with *N*-chloroimine **1a**) than phenol **4a**. The pH dependence of the Gibbs reaction of **4g** with *N*-chloroimine **1b** was examined in the pH range of 7.3−9.8 (α = 7.60 × 10^{-1} to 9.99 × 10^{-1}). At nearly neutral pH values in the range of pH 7.3−7.5, **4g** reacted with similar rate constants, which were, however, higher than the rate constant obtained at pH 9.8 in the presence of TEMPO, indicating again the participation of imine **6b** at neutral pH[32] (Figure 10). In the reaction of **4a** in a more basic solution (pH = 10.0−12.8, α = 5.0 × 10^{-1} to 9.98 × 10^{-1}), the quantity of indophenol **3a** decreased gradually and, at pH 12.8, the indophenol was formed

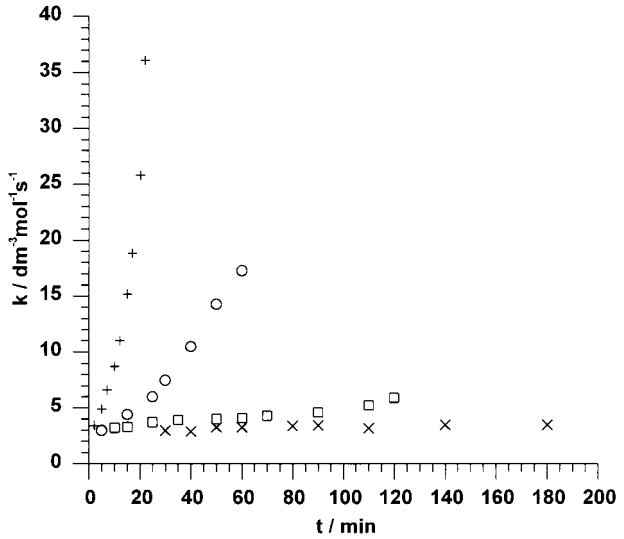


Figure 10. Hypothetical second-order rate constants vs time plot of the Gibbs reaction of *N*-chloroimine **1b** with phenol **4g** at $T = 297$ K. [**1b**] = 6.0 × 10^{-5} mol dm^{-3}. [**4g**] = 6.1 × 10^{-2} mol dm^{-3}, $f = 10^{-3}$, (pH = 7.3) (×);[33a] [**4g**] = 6.1 × 10^{-2} mol dm^{-3}, $f = 10^{-3}$, (pH = 7.9) (□); [**4g**] = 2.45 × 10^{-1} mol dm^{-3}, $f = 10^{-4}$, (pH = 9.8) (○);[33b] [**4g**] = 4.9 × 10^{-2} mol dm^{-3}, [KCN] = 2.4 × 10^{-4} , $f = 10^{-4}$, (pH = 11.2) (+).

in a yield of only 25%. Because 95% of the indophenol is formed via chain reaction mechanism, as has been proven by applying TEMPO in the reaction of *N*-chloroimine **1b** and **4a** at pH 9.2 (see Experimental Section), it was of crucial importance to find an explanation for the suppression of the chain reaction at higher pH.[34]

(30) (a) The rate constant, calculated from the equation $v = k$[**1a**]-[**2c**] for the reaction of *N*-chloroimine **1a** and phenol **4c** at the nearly neutral pH 7.4 was equal to that obtained at the much higher pH of 9.5, despite the low degree of dissociation (α = 5 × 10^{-4}) at the neutral pH. This indicates that, for *N*-chloroimine **1a**, only 2,6-dimethylphenoxide ion (**2c**) can be the donor in the initiating SET and the neutral phenol **4c** cannot. Anion of **4** was reported to be 10^3 to 5 × 10^4 times more reactive than neutral phenol in their reaction with *p*-benzoquinone diimine (see ref 20). (b) The rate of this reaction was the same at pH 12.1 with or without TEMPO. The conversion was also the same, but in both cases, it was about 5% lower than in the blank experiment conducted in borate buffer. This suggests that, similarly to the reaction of phenol **4a**, at high pH imine **6b** is not formed because of the fast decomposition of radical anion **7b**.

(31) Upon monitoring the reaction until 90% conversion for about 8 h, the second-order rate constant was found to be steady.

(32) Indophenol **3a** can also be prepared by the reaction of *N*-chloroimine **1a** and phenol **4a**, and this reaction was used for calculating the amount of the dye in these experiments. Thus, in the presence of TEMPO, at pH 9.57, 41% of indophenol **3a** is observed, indicating that the chain reaction was also a significant route (59%) in the case of this phenol. It was also established that in the pH range 9.0−9.7 the yield of indophenol **3a** was only 74% as a result of the decomposition of *N*-chloroimine radical anion **7b**. A formation of 100% dye was detected when applying cyanide additive.

(33) (a) Monitoring the reaction until 90% conversion for about 20 h, the rate constant was found to be steady. (b) The rate constant calculated was corrected with the decay of the *N*-chloroimine radical anion **7b**.

(34) Though the stability of the other two possible reactants *N*-chloroimine **1b** and imine **6b** is somewhat lowered by increasing the pH, the extreme decrease of the dye formation cannot be explained only by this reduced stability. However, it indicates the role of the chain reaction mechanism.

We have chosen phenol **4g** to determine whether the phenol or its anion is the reactive nucleophile in the substitution reactions of *N*-chloroimine radical anion **7b** during propagation. An important characteristic of phenol **4g** is that it is by 3 orders of magnitude more acidic than phenol **4a**. This fact enables the examination of the anion of **4g** in the relatively low pH range of 9.4−9.8, where the stability of the chain carrier is still reasonable and the dissociation of the phenol is almost complete ($\alpha = 9.975 \times 10^{-1}$ to 9.987×10^{-1}). Chain reaction is observed,[35] suggesting the reaction of *N*-chloroimineradical anion **7b** with 2,6-dichlorophenoxide ion (**2g**) as the substitution step in the chain (Figure 10). It is noteworthy that with increasing pH, the indophenol yield dropped here, also, but even at pH 11.2 ($\alpha = 9.9996 \times 10^{-1}$) the reaction could be accelerated successfully with KCN, which indicates that the *N*-chloroimine radical anion **7b** reacts with 2,6-dichlorophenoxide ion **2g** in the chain reaction (Figure 10).[36]

This and the earlier observations suggest that, of the dye formations via chain reaction and via imine **6b**, the latter may influence notably the rate constant only if the reaction of the chain carrier with the anion of **4** is decelerated as a result of the $S_{RN}2$ mechanism to such an extent that the transformation of the chain carrier to imine **6b** becomes competitive. If this condition is achieved in a medium where the formed imine **6b** can be protonated[29] (pH = 7.3−8.5), the highly reactive imine cation will cause a significant but *linear* acceleration.

All of these results suggest that *N*-chloroimine radical anion **7** can produce indophenol dye **3** in two pathways, independently of whether it has been induced by additives (quinones **11** or cyanide ion) or generated by the starting SET in the original Gibbs reaction. Either it eliminates a halogenide ion and abstracts an H-atom from the medium to produce imine **6**, which then reacts with phenoxide **2** to give indophenol **3** and aminophenol **16**[37] or, more preferably, it starts a radical chain reaction. According to this second pathway, its *N*-halogen is displaced by phenoxide **2** in a bimolecular nucleophilic substitution yielding the adduct radical **17**, which then transfers an electron to *N*-chloroimine **1** to yield adduct **18** and radical anion **7**, respectively. By this second SET, the chain propagation can also be maintained because adduct **18** can easily be deprotonated to form indophenol **3** and radical anion **7** can enter the cycle again when substituted with another phenoxide **2** (Scheme 2).[38]

Because the chain carrier reacts with the nucleophile in a bimolecular fashion in the rate determining step during the chain propagation, this mechanism is termed $S_{RN}2$.

A similar anionic radical $S_{RN}2$ chain reaction mechanism was invoked for the reaction of aryl radical anions with nucleophiles[9] to explain the contradictions between experimental results and the widely accepted $S_{RN}1$ mechanism.[11,39] Accordingly, after reviewing the literature and on the basis of their experimental results and ab initio calculations, D. B. Denney and D. Z. Denney[9] concluded that, in certain aromatic nucleophilic substitutions initiated by electron injection, it was not the neutral aryl radical but the aromatic radical anion itself that reacted with the nucleophile. Thus, the reaction became bimolecular because the propagation shifted from elimination to substitution and so the $S_{RN}1$ chain reaction mechanism changed to $S_{RN}2$.

The similarity between the Gibbs chain reaction mechanism and that proposed for the nucleophilic substitution of aryl radical anions is striking. Even if the latter is a substitution on a carbon atom instead of a nitrogen and the radical anion is generated by an external electron donor instead of the nucleophile itself, the operating chain is highly analogous. It means that our findings afford further evidence supporting the existence of this type of mechanism.

Phenoxide ion is also known to be applied as a nucleophile in aromatic radical nucleophilic substitutions, though the early results were somewhat controversial. For example, halobenzenes were reported to react with phenoxide ion in aqueous *tert*-butyl alcohol upon initiation by sodium amalgam, yielding diphenyl ethers,[40a] but these experiments could not be reproduced.[40c] There were some other unsuccessful attempts to make phenoxide ion react,[40b,d−f] whereas later, aryl radicals generated with

(35) The chain reaction was anticipated as *N*-chloroimine **1b** reacts even with phenol **4a** in this way (>95%) to form indophenol **3**. Because phenol **4g** is less reactive than phenol **4a**, after the SET, the direct combination in the cage is suppressed and the escape becomes favored.

(36) (a) Applying the more reactive *N*-chloroimine **1a**, all three phenols, even **4g**, reacted with direct combination. Repeating the reaction in the presence of KCN as initiator, the reaction rate increased though without pH dependence in the range of 7.5−10.5.[36b] (b) The linear acceleration is indicative of the influence of imine **6a** on the rate. The pH independence can be rationalized by the decreased basicity caused by the negative inductive effect of the chlorine substituents in imine **6a** (in contrast with imine **6b**), which inhibits protonation at this pH.

(37) (a) It is known (see ref 20) that the stoichiometry of the reaction of imine **6** with 4-electrofugal phenols is 2:1. The first imine **6** gives leuko-indophenol, which is further oxidized by the second imine **6** to indophenol **4** while **6** is reduced to 4-aminophenol. However, it is also known[37b,c] that the more reactive *N*-chloroimines **1** give 2 equiv of imine **6** with 4-aminophenols, resulting in the regeneration of imine **6**. In our case, the involvement of the large excess of *N*-chloroimine **1** in the oxidation step is also possible despite its lower redox potential (**1a** $E_{1/2}$= −0.04 mV, **6a** $E_{1/2}$ = 0.04 mV). (b) Bonastre, J.; Castetbon, A.; Andrieu, X. *Bull. Soc. Chim. Fr.* **1981**, 283−289. (c) Pallagi, I.; Dvortsák, P. *J. Chem. Soc., Perkin Trans. 2* **1986**, 105−110.

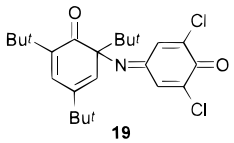
(38) A small quantity of hydroquinone **4b** is always present in an alkaline solution of benzoquinone, therefore, a third alternative should also be considered. Because **4b** is quickly oxidized by *N*-chloroimines to quinone along with the formation of an imine (via imine radical **10**, as this reaction could also be terminated by TEMPO), it might also be a source of the accelerator imines **6** or imine radicals **10**. However, in the reaction of *N*-chloroimine **1b** and phenol **4a** in the presence of hydroquinone **4b**, no such effect was observed. Therefore, this alternative was ruled out.

(39) (a) Kim, J. K.; Bunnett, J. F. *J. Am. Chem. Soc*, **1970**, *92*, 7463−7466. (b) Amatore, C.; Pinson, J.; Savéant, J. M.; Thiébault, A. *J. Am. Chem. Soc.* **1981**, *103*, 6930−6937. (c) Galli, C.; Bunnett, J. F. *J. Am. Chem. Soc.* **1981**, *103*, 7140−7147.(d) Amatore, C.; Pinson, J.; Savéant, J. M.; Thiébault, A. *J. Am. Chem. Soc.* **1982**, *104*, 817−826. (e) Carver, D. R.; Hubbard, J. S.; Wolfe, J. F. *J. Org. Chem*. **1982**, 47, 1036−1040. (f) Tolbert, L. M.; Martone, D. P. *J. Org. Chem*. **1983**, *48*, 1185−1190. (g) Carver, D. R.; Greenwood, T. D.; Hubbard, J. S.; Komin, A. P.; Sachdeva, Y. P.; Wolfe, J. F. *J. Org. Chem*. **1983**, *48*, 1180−1185. (h) Rossi, R. A.; Rossi, R. H. *Aromatic Nucleophilic Substitution by the $S_{RN}1$ Mechanism;* ACS Monograph 178; American Chemical Society: Washington, DC, 1983. (i) Amatore, C.; Oturan, M. A.; Pinson, J.; Savéant, J. M.; Thiébault, A. *J. Am. Chem. Soc.* **1984**, *106*, 6318−6328. (j) Penenory, A. B., Pierini, A. B., Rossi, R. A. *J. Org. Chem*. **1984**, *49*, 3834−3835. (k) Amatore, C.; Oturan, M. A.; Pinson, J.; Savéant, J. M.; Thiébault, A. *J. Am. Chem. Soc.* **1985**, 107, 3451−3459. (l) See ref 11.

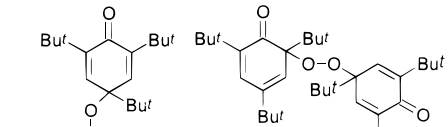
(40) (a) Rajan, S.; Sridaran, P. *Tetrahedron Lett*. **1977**, 2177−2180. (b) See ref 39c. (c) Rossi, R. A.; Pierini, A. B. *J. Org. Chem*. **1980**, *45*, 2914−2115. (d) Rossi, R. A.; Bunnett, J. F. *J. Org. Chem*. **1973**, *38*, 3020−3025. (e) Ciminale, F.; Bruno, G.; Testaferri, L.; Tiecco, M. *J. Org. Chem*. **1978**, *43*, 4509−4512. (f) Semmelhack, M. F.; Bargar, T. *J. Am. Chem. Soc.* **1980**, *102*, 7765−7774. (g) Amatore, C.; Combellas, C.; Pinson, J.; Savéant, J. M.; Thiébault, A.; Verpeaux, J. N. *J. Chem. Soc., Chem. Commun*. **1988**, 7−8. (h) Alam, N.; Amatore, C.; Combellas, C.; Pinson, J.; Savéant, J. M.; Thiébault, A.; Verpeaux, J. N. *J. Org. Chem*. **1988**, *53*, 1496−1504. (i) Beugelmans, R.; Bois-Choussy, M. *Tetrehedron Lett*. **1988**, *29* 1289−1292. (j) Beugelmans, R.; Bois-Choussy, M.; Tang, Q. *Tetrehedron Lett*. **1988**, *29*, 1705−1708. (k) Pierini, A. B.; Baumgartner, M. T.; Rossi, R. A. *J. Org. Chem*. **1991**, *56*, 580−586.

electron injection[40g,h] or with photostimulation[40i−k] could be trapped by phenoxide or 2-naphthoxide ions.

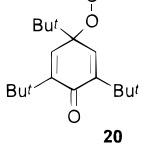
In the introduction, the spin trapping of phenoxy radical **8** reported in the previous paper of this series[1] was mentioned. Namely, in the Gibbs reaction of 2,4,6-tri-*tert*-butylphenol (**4h**) and *N*-chloroimine **1a**, besides compounds **5b** and **19**, peroxy dimers **20** and **21** were



19



21



20

isolated when the reaction medium had not been deoxygenated.[1] This experiment supplied clear evidence of the presence of phenoxy radical **8** as it was trapped by dioxygen. Because the small dioxygen molecule can easily enter the radical cage to prevent the direct combination, which has already been decelerated by steric hindrance, it was doubtful whether these findings also proved a chain reaction mechanism with phenoxy radical **8** as its carrier. In view of the new results, these reactions were reinvestigated with varying oxygen concentrations and in the presence of TEMPO in the medium. Accordingly, a higher oxygen concentration increased not only the concentration of peroxy dimers **20** and **21** but also that of compounds **12**, **13a**, and **14a** formed by spin trapping of the *N*-chloroimine radical anion **7a**, at the expense of compounds **5b** and **19**. In addition, a decrease in oxygen concentration resulted in proportionally less peroxy dimers **20** and **21** and compounds **12**, **13a**, and **14a** but more **5b** and **19**. An important observation was made when a higher concentration of acetonitrile was applied in the solvent: only traces of peroxy dimers **20** and **21** were detected (even at oxygen saturation!) and the amounts of compounds **12**, **13a**, and **14** decreased also proportionally. We believe that these experiments clearly demonstrate that 2,4,6-tri-*tert*-butylphenoxy radical **8** is not a chain carrier but instead, when being trapped by dioxygen, its decay enables the escape of an equivalent of *N*-chloroimine radical anion **7** from the cage, which supports evidence of a SET from 2,4,6-tri-*tert*-butylphenoxide ion (**2h**) to *N*-chloroimine **1a**.

We believe that these findings confirm that both quinones and cyanide ion catalyze the transformation of *N*-chloroimines **1** to *N*-chloroimine radical anions **7**, which initiate and propagate a chain reaction even in an alkaline aqueous solution.

The above results prompted us to reinvestigate the original Gibbs chain reaction, exemplified by the reaction of *N*-chloroimine **1b** and phenol **4a**. In the presence of TEMPO, compounds **13b** and **14b** were produced. This experimental result and those presented above confirm that in the original Gibbs reaction the *same* $S_{RN}2$ mechanism is operating as in those generated by additives.

Experimental Section

The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 250 spectrometer at frequencies of 250.1 and 62.9 MHz, respectively. Spectroscopic measurements in the UV−vis region were performed on an LKB Ultrochrom II and a Varian Cary 3E spectrophotometer. Mass spectra (EI, 70 eV) were taken on a Finnigan MAT 8430 instrument. Polarographic measurements were carried out on a PAR 174-A polarographic analyzer (glassy carbon, PT and SCE electrodes) in an aqueous 2×10^{-4} mol dm^{-3} solution of the test compound buffered with $Na_2B_4O_7$, at dc operation. *N*-Chloroimine **1a** was purchased from Merck (Darmstadt, Germany), and further *N*-chloroimines were prepared by known methods.[41] For kinetic experiments, see the Supporting Information; for further information on materials and methods, see Part 3 of this series.[1]

Reaction of *N*-Chloroimine 1a with Quinone 11a. Compound **1a** (53 mg, 0.25 mmol) was dissolved in CD_3CN (1.9 mL), and D_2O (0.6 mL) was added (solution *A*). Then, 0.2 mL of this solution was transferred into an NMR tube, and CD_3CN (0.1 mL), D_2O (0.3 mL), borate buffer (0.2 mL), and a solution of **11a** [0.2 mL of a solution of **11a** (27 mg, 0.25 mmol) dissolved in CD_3CN (2.5 mL)] were added (solution *B*). The ^{1}H NMR spectra was recorded immediately.[42] **1a**: ^{1}H NMR δ 8.22 (s, br, 1H), 7.71 (s, br, 1H). **6a**: 7.61 (1H), 7.42 (1H).[43] **11a**: 6.89 (s, br, 4H).

Reaction of *N*-Chloroimine 1a with Quinone 11a in the Presence of TEMPO. Solution *A* (0.2 mL) was transferred into an NMR tube, and CD_3CN (0.1 mL), D_2O (0.2 mL), borate buffer (0.2 mL), a solution of TEMPO [0.1 mL of a solution of TEMPO (39 mg, 0.25 mmol) dissolved in CD_3CN (0.5 mL) and D_2O (4.5 mL), (solution *C*)] and solution *B* (0.2 mL) were added. After 2−3 min, the mixture was extracted with $CDCl_3$ (0.5 mL). According to the ^{1}H NMR spectrum, no **6a** was formed.

Reaction of *N*-Chloroimine 1a with Phenol 4a in the Presence of Quinone 11a and TEMPO. Solution *A* (0.2 mL) was transferred into an NMR tube, and borate buffer (0.3 mL), CD_3CN (0.1 mL), solution *C* (0.1 mL), solution *B* (0.2 mL), and a solution of phenol **4a** [0.2 mL of a solution of **4a** (46 mg, 0.50 mmol) dissolved in CD_3CN (0.4 mL) and D_2O (2.1 mL)] were added. According to ^{1}H NMR spectra, a quantitative formation of indophenol **3a** was observed in 15 min at 25 °C (during the reaction, the signal of **1a** was broad). **3a**: ^{1}H NMR δ 7.45 (d, J = 9.9 Hz, 2H), 7.26 (s, 2H), 6.67 (d, J = 9.9 Hz, 2H). **12**: 8.65 (s, br, 1H), 7.74 (s, br, 1H). **13a**: 8.08 (s, 2H), 4.73 (s, br, 1H), 4.69 (s, br, 1H). **14a**: 8.08 (s, 2H), 5.08 (m, 1H). **4a**: 7.30 (dd, $J_1 = J_2 = 7.8$ Hz, 2H), 6.96 (dd, $J = 7.8$ Hz, 1H), 6.87 (d, $J = 7.8$ Hz, 2H). Quinone **11a** could not be identified because of its broad signal. (The spectra were recorded with suppression of the water signal).

Partial Transformation of Quinone 11a into Hydroquinone 4b in an Alkaline Solution. Solution *B* (0.2 mL) was transferred into an NMR tube, D_2O (0.3 mL) and borate buffer (0.2 mL) were added, and the ^{1}H NMR spectra were recorded without delay.[44] **11a**: ^{1}H NMR (internal reference CD_3CN, 2.05 ppm) δ 7.3−6.2 (br). In another experiment, after addition of borate buffer to the solution of **11a**, the mixture was acidified with trifluoroacetic acid (50 μL). **11a**: ^{1}H NMR δ 6.65 (s, 4H), 1,4-Hydroquinone **4b**: 6.58 (s, 4H). ([**11a**]/[**4b**] $\approx$ 98/2). The experiment was repeated with the modification that the mixture was allowed to stand for 3 min ([**11a**]/[**4b**] $\approx$ 96/4) or 6 min ([**11a**]/[**4b**] $\approx$ 77/23) before acidification.

Reaction of *N*-Chloroimine 1b with Quinone 11b. A solution of **1b** [1.50 mL of a solution of *N*-chloroimine **1b** (21.3 mg, 0.15 mmol) dissolved in acetonitrile (2.5 mL) and the volume filled to 250.00 mL with water (solution *D*)] was

(41) Venuvanalingam, P.; Chandra Singh, U.; Subbaratnam, N. R.; Kelkar, V. K. *Spectrochim. Acta, Part A* **1980**, *36*, 103−107.

(42) When in the NMR experiments the FID acquisition took longer than 3−4 min, a decomposition of imine **6a** was observed.

(43) Because of the low concentration and instability of imine **6a**, we were unable to determine its coupling constants.

(44) The solvents were deoxygenated by argon.

transferred in a 25 mL normal flask, and borate buffer (5.0 mL), water (15 mL), and a solution of quinone **11b** [0.30 mL of asolution of **11b** (26.9 mg, 0.15 mmol) dissolved in acetonitrile (5 mL) and filled to 25 mL with water)] were added. The volume was brought to 25 mL with water. The reaction was monitored by UV where quinone **11b** was also in the reference solution. The conversion of *N*-chloroimine **1b** to imine **6b** was 70% after 30 min (**6b** λ_{max}: 258 nm[20]).

Preparation of Spin Trapping Adduct 12. *N*-chloroimine **1a** (84 mg, 0.4 mmol) was dissolved in acetonitrile (10 mL) and diluted with water (120 mL), and borate buffer (30 mL) was added. A solution of TEMPO (25 mg, 0.16 mmol) in acetonitrile (2 mL) and a solution of KCN (78 mg, 1.2 mmol) in borate buffer (5 mL) were added. After 25 min at 25 °C, the mixture was extracted with hexane (2 × 100 mL), the combined organic extracts were washed with NaOH (0.1 M, 2 × 100 mL) (separation of the layers was facilitated by addition of solid NaCl) and water (3 × 50 mL), dried, and evaporated. Crude **12** was purified by preparative TLC (silica, benzene). **12** was contaminated with **13a** and **14a** according to ^{1}H NMR. **12**: ^{1}H NMR ($CDCl_3$) δ 8.56 (d, J = 2.5 Hz, 1H), 7.42 (d, J = 2.5 Hz), 1.9−1.3 (m, 6H), 1.46 (s, 6H), 1.39 (s, 6H); ^{13}C NMR δ 172.4 (s), 138.9 (d), 131.7 (s), 129.2 (s), 127.4 (d), 127.3 (s), 88.6 (s), 74.6 (s), 42.3 (t), 39.5 (t), 27.7 (q, br), 19.5 (t). MS (EI) *m*/*z* (rel intensity) 330/332 ($[M]^{+\bullet}$, 65/47), 315/317 ($[M - {}^{\bullet}CH_3]^+$, 52/37), 69 (100).

Preparation of Spin Trapping Adducts 13a and 14a. *N*-chloroimine **1a** (147 mg, 0.7 mmol) was dissolved in acetonitrile (5 mL) and diluted with water (10 mL), and TEMPO [109 mg, 0.7 mmol in acetonitrile (5 mL) and in water (5 mL)] and KCN (182 mg, 2.8 mmol in borate buffer (20 mL) were added. After 10 min at 25 °C, the pH was adjusted to 5−6 with HCl. The reaction mixture was extracted with chloroform (2 × 25 mL), and the combined organic extracts were washed with borate buffer (2 × 20 mL) and water (2 × 30 mL), dried, and concentrated. The crude product (the ratio of **13a/14a** was ∼1/1) was purified on preparative TLC (silica, benzene). **13a** and **14a** were isolated as a mixture and characterized with UV, ^{1}H and ^{13}C NMR, and mass spectrometry. The pH dependence of the UV spectrum in a basic medium suggests that both compounds have a phenolic hydroxyl group. The dissociation is considerable in both water and 95% ethanol, showing that the aromatic nucleus carries substituents with negative inductive effect. Both the neutral and the dissociated form show a pronounced bathochromic effect compared to the spectrum of 2,6-dichlorophenol **4g**. This indicates that the *para* substituent is in donor−acceptor interaction with the phenolic hydroxyl which facilitates delocalization. λ_{max} (95% ethanol) 315 and 367 nm; λ_{max} 306 nm (with one drop of 0.1 N HCl added to the solution (4 mL) in the cuvette); and λ_{max} 363 nm (with one drop of triethylamine added). (The corresponding data for phenol **4g** are 282 and 302 nm in neutral, 282 nm in acidic, and 302 nm in basic media, respectively.) According to the ^{1}H and ^{13}C NMR spectra, in **13a** and **14a**, the part derived from *N*-chloroimine **1a** was reduced into a phenol derivative and the piperidine ring of TEMPO was cleaved in both cases; however, whereas in the structures of **13a** one of the methyl groups was turned into a terminal double bond, in **14a** a CH═C$(CH_3)_2$ group was formed. ^{1}H homo decoupling and ^{1}H NOE difference experiments made the identification of the characteristic signals of **13a** and **14a** possible. **13a**: ^{1}H NMR (C_6D_6, T = 318 K) δ 8.17 (s, 2H, overlapping with the signal **14a**),[45] 5.47 (br, 1H, exchangeable with D_2O; overlapping with the signal **14a**), 4.75 (s, br, 1H), 4.71 (s, br, 1H), 1.57 (s,br, 3H), 1.39 or 1.38 (s, 6H). **14a**: 8.17 (s, 2H), 5.47 (br, 1H, exchangeable with D_2O; overlapping with the signal **13a**), 5.07 (t, br, J = 6.9 Hz and ∼1 Hz with two methyls), 1.60 (s, br, 3H), 1.47 (s, br, 3H), 1.39 or 1.38 (s, 6H). **13a** and **14a** :^{13}C NMR ($CDCl_3$, 298 K) δ 147.7 (s), 145.0 (s), 137.6 (s), 132.4 (s), 125.4 (d), 123.0 (d), 120.4 (s), 110.4 (t), 80.7 (s), 80.6 (s), 41.1 (t), 40.8 (t), 37.6 (t), 26.4 (q), 26.4 (q), 25.6 (q), 22.9 (t), 22.2 (q), 21.9 (t), 17.6 (q). MS (EI) *m*/*z* (rel intensity) 330/332 ($[M]^{+\bullet}$, 0.4/0.2), 313/315 ($[M - {}^{\bullet}OH]^+$, 11/8), 69 (100).

Reaction of *N*-Chloroimine 1a with KCN. Solution *A* (0.2 mL) was transferred into an NMR tube, and borate buffer (0.2 mL), CD_3CN (0.1 mL), and a solution of KCN [0.2 mL of a solution of KCN (16 mg, 0.25 mmol) was dissolved in borate buffer (0.2 mL) and D_2O (2.3 mL)] were added. **1a**: ^{1}H NMR δ 8.20 (s, br, 1H), 7.71 (s, br, 1H). **6a**: 7.62 (s, br, 1H), 7.42 (s, br, 1H) (the spectra should be recorded within 8 min). After recording the spectra, the solution was extracted with $CDCl_3$ (0.5 mL), and the ^{1}H NMR spectra was recorded again. **1a**: ^{1}H NMR δ 8.02 (d, J = 2.6 Hz, 1H), 7.55 (d, J = 2.6 Hz, 1H). **6a**: 7.51 (d, J = 2.3 Hz, 1H), 7.21 (d, J = 2.3 Hz, 1H) (the ratio of **1a**/**6a** was ≈ 55/45). Then, 0.1 mL of the dried $CDCl_3$ layer was diluted with *n*-hexane (4 mL) to record the UV spectrum of the mixture: **1a** (λ_{max} 301 and 310 nm) and **6a** (λ_{max} 278 nm, shoulder at 270 nm). When a mixture of 2-propanol (0.1 mL), water (2 mL), and borate buffer (0.1 mL) was added to the $CDCl_3$ solution (0.1 mL), the unreacted *N*-chloroimine **1a** was transformed into imine **6a** immediately.[37b,c]

Reaction of *N*-Chloroimine 1a with KCN in the Presence of TEMPO. Compound **1a** (21 mg, 0.1 mmol) was dissolved in CD_3CN (2 mL). Then, 0.2 mL of this solution was transferred into an NMR tube, and CD_3CN (0.1 mL), borate buffer (0.2 mL), TEMPO [0.1 mL of a solution of TEMPO (15.6 mg, 0.1 mmol) dissolved in CD_3CN (0.1 mL) and D_2O (1.9 mL)], and KCN [0.4 mL of solution of KCN (6.5 mg, 0.1 mmol) dissolved in borate buffer (0.2 mL) and D_2O (1.8 mL)] were added. Monitoring the reaction with ^{1}H NMR, the consumption of **1a** (s,br) was observed, but in the presence of TEMPO **1a** gave compounds **12**, **13a**, and **14a** instead of **6a**. When the experiment was repeated without KCN, although **1a** was decomposed in a radical reaction again in the alkaline solution, compounds **12**, **13a**, and **14a** were formed, but in a significantly lower exítent.

Reaction of *N*-Chloroimine 1b with Phenol 4a in the Presence of TEMPO. To a solution of **1b** (26 mg, 0.2 mmol) in acetonitrile (1 mL) were added a solution of phenol **4a** (67 mg, 0.7 mmol) in acetonitrile (0.5 mL), borate buffer (5 mL, 50 mM, D_2O), and a solution of TEMPO (31 mg, 0.2 mmol) in acetonitrile (0.5 mL) and D_2O (3 mL) (with D_2O the rate was higher than with H_2O). After 5 h at 25 °C, water (10 mL) was added, and the pH was adjusted to 5.5−6.5 with HCl. The mixture was extracted with $CHCl_3$ (2 × 10 mL), and the combined organic layers were washed with water (l0 mL), dried, and concentrated to 0.5−1 mL at reduced pressure (water bath temperature 30−35 °C). Then *n*-hexane (25 mL) was added, and the organics were washed with HCl (0.1 M, 2 × 20 mL) and water (2 × 10 mL) to separate from indophenol **3** and the excess of phenol, dried and evaporated. **1b**: ^{1}H NMR (acetone-d_6, T = 323 K, reference standard TMS) δ 7.72 (dd, J_1 = 10.2 Hz, J_2 = 2.7 Hz, 1H), 1H), 7.21 (dd, J_1 = 10.2 Hz, J_2 = 2.7 Hz), 6.54 (dd, J_1 = 10.2 Hz, J_2 = 1.3 Hz, 1H), 6.44 (dd, J_1 = 10.2 Hz, J_2 = 1.3 Hz, 1H). **13b**: 8.35 (s, br, OH), 7.82 (d, J = 8.0 Hz, 2H), 6.74 (d, J = 8.0 Hz, 2H), 4.78 (s, br, 2H). **14b**: 8.35 (s, br, OH), 7.82 (d, J = 8.0 Hz, 2H), 6.74 (d, J = 8.0 Hz, 2H), 5.0 (br, 1H). MS (EI) *m*/*z* (rel intensity) 262 ($[M]^{+\bullet}$, 2), 245 ($[M - {}^{\bullet}OH]^+$, 28), 121 (10), 69 (100).

Reaction of *N*-Chloroimine 1a with 2,4,6-Tri-*tert*-butylphenol 4h. Method *a* (reaction without deoxigenation, in 17 vol % aqueous acetonitrile). To a solution of *N*-chloroimine **1a** (105 mg, 0.5 mmol) in acetonitrile (20 mL) and water (200 mL) were added borate buffer (20 mL), TEMPO (6 mg, 0.04 mmol) in acetonitrile (1 mL), and **4h** (39 mg, 0.15 mmol) in acetonitrile (25 mL). After shaking and standing for 25 min at room temperature, the mixture was neutralized with HCl and extracted with chloroform (2 × 100 mL). The organic phase was washed with water (100 mL), dried (Na_2SO_4), and concentrated to 5 mL (water pump, max. 30 °C). Then, 2−3 drops of 1,1,2,2-tetrachloroethane-d_2 (TCE-d_2) were added, and after the removal of the rest of the chloroform, $CDCl_3$ (0.5 mL) was added. **1a**: ^{1}H NMR δ (reference, the signal of TCE-d_2, 6.00 ppm) 7.97 (d, J = 2.6 Hz, 1H), 7.49 (d, J = 2.6 Hz, 1H). **13a** and **14a**: 8.02 (s, br, 2 × 2H), 5.04 (br, 1H, overlapping

(45) The chemical shifts (δ) of the aromatic protons of **13a** and **14a**, respectively, were 8.07 and 8.08 in $CDCl_3$ (or tetrachloroethane-d_2).

with a signal of hydroxy protons of **4h**, **13a**, and **14a**), 4.68 (s, br, 1H). 4.64 (s, br, 1H); **5b**: 7.36 (d, $J = 2.5$ Hz, 1H), 7.27 (d, $J = 2.5$ Hz, 1H), 6.54 (s, 2H). **19**: 7.39 (d, $J = 2.5$ Hz, 1H), 7.05 (d, $J = 2.4$ Hz, 1H), 6.37 (d, $J = 2.5$ Hz, 1H), 5.92 (d, $J = 2.4$ Hz, 1H). **20**: 6.66 (s, 4H). **21**: 6.83 (d, $J = 2.7$, 1H), 6.80 (d, $J = 2.5$ Hz, 1H), 6.63 (d, $J = 2.7$ Hz, 1H), 6.07 (d, $J = 2.5$ Hz, 1H). The ratio of **1a/(13a + 14a)/5b/19/20/21** was ~1:0.08:0.14:0.10:0.07:0.04. **Method *b* (argon atmosphere, in 17 vol % aqueous acetonitrile).** The same as method ***a***, but the solvents used were purged with argon for 10 min and the reaction was carried out under argon. The ratio of **1a/12/(13a + 14a)/5b/19/20/21** was ~1:0.03:0.04:0.22:0.14:0.02:0.04. **Method *c* (oxygen atmosphere, in 63 vol % aqueous CD_3CN).** The solvents used were purged with oxygen for 15 min. To a solution of *N*-chloroimine **1a** (1.30 mg, 6.2×10^{-3} mmol) in CD_3CN (0.30 mL) were added borate buffer (0.30 mL, $Na_2B_4O_7$ in D_2O) and phenol **4h** (1.05 mg, 4×10^{-3} mmol) in CD_3CN (0.20 mL) into an NMR tube. After the mixture was shaken and allowed to stand for 10 min, TCE-d_2 (~0.5 mL) was added. After further shaking, the NMR spectrum of the lower layer was recorded. The ratio of **1a/3b/5b/19** was ~1:0.18:0.92:0.65 (only traces of peroxide dimer **20** could be detected and contained no **13a** and **14a**). **Method *d* (argon atmosphere, 65 vol % aqueous CD_3CN).** The solvents used were purged with argon for 15 min. To a solution of *N*-chloroimine **1a** (1.30 mg, 6.2×10^{-3} mmol) in CD_3CN (0.30 mL) were added TEMPO [0.05 mL of a solution of TEMPO (0.54 mg, 3.5×10^{-3} mmol) in CD_3CN (0.20 mL)], borate buffer (0.30 mL, $Na_2B_4O_7$ in D_2O), and phenol **4h** (0.90 mg, 3.4×10^{-3} mmol) in CD_3CN (0.20 mL) into an NMR tube. After the mixture was shaken and allowed to stand for 10 min, $CDCl_3$ (~0.5 mL) was added. After further shaking and separation of the layers, an NMR spectrum of the lower layer was recorded. The ratio of **1a/3b/12/(13a + 14a)/5b/19/ 20/21** was ~1:0.07:0.10:0.03:0.68:0.22:0.03:0.04.

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Supporting Information Available: The kinetic data in graphical form, copies of the ^1H and ^{13}C NMR spectra, and mass spectra.

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