

Reactions of Wheland complexes: base catalysis in re-aromatization reaction of σ complexes obtained from 1,3,5-tris(*N,N*-dialkylamino)benzene and arenediazonium salts

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ABSTRACT: The usual idea on the two-steps mechanism of aromatic electrophilic substitution reactions is that the first step (the attack of the electrophilic reagent on the activated substrate) is rate limiting, while the driving force of the reaction is the fast proton departure to recover the resonance energy of the aromatic substrate. The now examined systems allow the formation of stable σ cationic complexes (Wheland intermediates) which may be investigated by simple procedures. Data here reported represent a clear and simple instance of a measurement of the rate of the proton abstraction from a Wheland intermediate and they indicate that this proton abstraction occurs by base catalysis in a rate determining step. Probably, this feature is more frequent than that usually conceived in the mechanism of electrophilic aromatic substitution reactions, because these reactions are often carried out in reaction mixtures containing large amounts of proton acceptor species which might mask the possible base catalysis. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: base catalysis; Wheland intermediates; electrophilic aromatic substitution; rate-determining step

INTRODUCTION

In common textbooks of organic chemistry¹ aromatic electrophilic substitution reactions are indicated to occur (See Scheme 1) by a two-steps mechanism, which involves firstly the attack of the electrophilic reagent producing a hybridization change (from sp^2 to sp^3) of the carbon atom center of the reaction. Consequently, a charged σ complex (the so-called Wheland² intermediate (**W**)) is formed. In Kochi³ treatment, the first interaction between the aromatic substrate and the electrophilic reagent is a donor-acceptor interaction (**DA**).

In principle, the formation of σ complexes may be indicated to be reversible, but for the present reactions, this subject needs more detailed investigations.

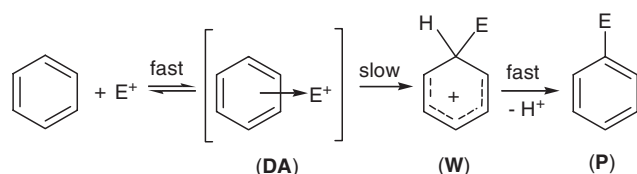
The second step concerns the elimination of a proton (by C—H bond breaking) and the formation of reaction products (**P**) with the consequent change in the hybridization of carbon atom (from sp^3 to sp^2). The re-aromatization process is usually reported as a fast step because of the resonance energy gain from **W** to **P**. Also in

this step, probably, the formation of a **DA** complex between the proton and the aromatic substrate of the reaction precedes the formation of the final product **P**. In contrast, the departure of the proton in a rate-limiting step was firstly studied and recognized by Zollinger and Effenberger. In particular, some works have reported the observation of a primary isotope effect in reactions between diazonium salts and naphthol derivatives^{4,5} or indole derivatives.⁶ Effenberger⁷ states: "Deprotonation of the σ complexes...requires base".

In this framework we examined the behavior of the reactions of 1,3,5-tris(*N*-piperidyl)benzene (**1**) and 1,3,5-tris(*N*-morpholinyl)benzene (**2**) with 4-substituted benzenediazonium tetrafluoroborates which give the formation of stable σ -adducts (Wheland-like intermediates).⁸ Recently,⁹ we reported the characterization of complexes (prepared by reaction between 4,6-dinitrobenzofuroxan and 1,3,5-tris(*N,N*-dialkylamino)benzenes) of special interest because they can be regarded at the same time as σ -adducts for contemporary S_NAr and S_EAr processes.

These are rare cases of σ complexes, which not only may be characterized by spectroscopic method (mainly NMR and UV/Vis spectroscopy), but their reactivity may be quantitatively investigated by usual kinetic procedures.

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Scheme 1

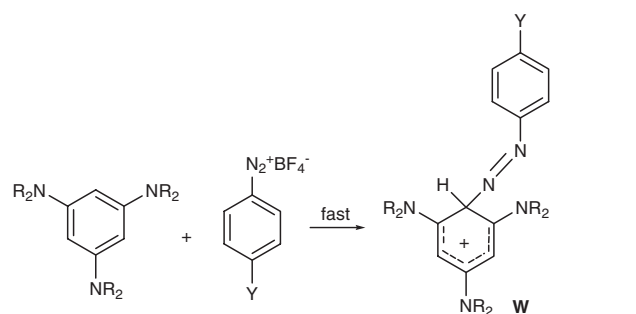
In the present work, we are reporting a kinetic investigation about the second step of the reaction of Scheme 1, in acetonitrile, (from **W** to **P**) toward the final product of the azo-coupling reaction.

RESULTS AND DISCUSSION

When equimolar amounts of **1** (or **2**) in acetonitrile, and diazonium tetrafluoroborate (**3**, **4**, **5**) are mixed at 20°C, an orange colour develops, related to the formation of σ cationic complexes $6^+ - 11^+$, as we have previously ascertained on the basis of NMR spectral data.⁸ UV/Vis spectroscopic data, immediately recorded after mixing, agree with the complete and instantaneous formation of complexes **W** starting from tris(*N,N*-dialkylamino)benzenes and diazonium salts, as reported in Scheme 2 (see Experimental section).

Decomposition of **W** complexes ($6^+ - 11^+$) leading to azoderivatives **12H–17H** (Scheme 3) may spontaneously occur in some days, or may occur in a few minutes by the action of bases providing compounds **12–17**.⁸ Scheme 3 represents a picture of the main possible reaction pathways.

These findings are in agreement with the fact that in 1,3,5-tris-(*N,N*-dialkylamino)benzenes the three NR_2 groups make the system particularly basic, thus the **W** complex is a weak acid. For this reason the first transition state depicted in Scheme 1 is at a lower energy level with respect to the second one, and this make the second step



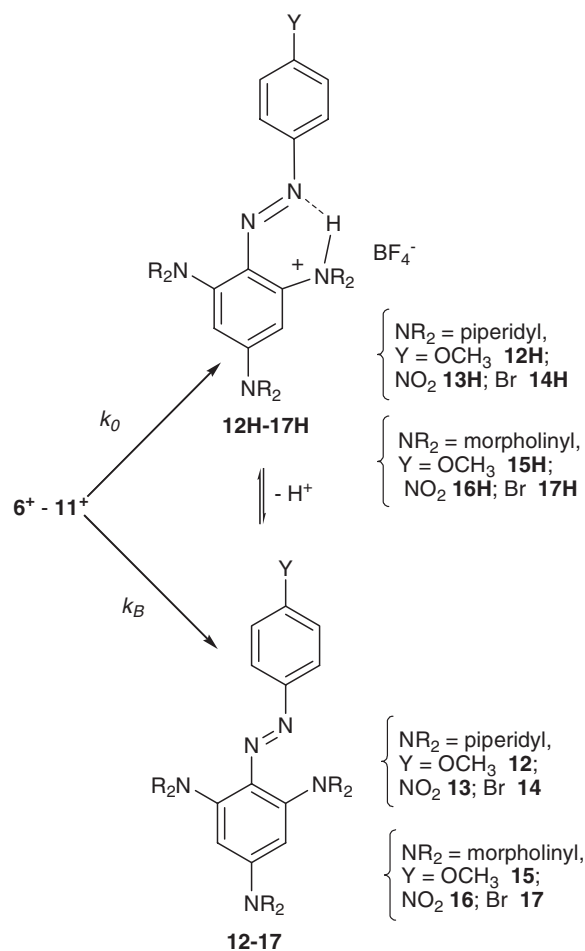
$\text{NR}_2 = \text{piperidyl}$ **1**
 $\text{NR}_2 = \text{morpholinyl}$ **2**

$\text{Y} = \text{OCH}_3$ **3**
 $\text{Y} = \text{NO}_2$ **4**
 $\text{Y} = \text{Br}$ **5**

$\left\{ \begin{array}{l} \text{NR}_2 = \text{piperidyl}, \\ \text{Y} = \text{OCH}_3 \text{ } 6^+; \text{NO}_2 \text{ } 7^+; \text{Br } 8^+ \end{array} \right.$

$\left\{ \begin{array}{l} \text{NR}_2 = \text{morpholinyl}, \\ \text{Y} = \text{OCH}_3 \text{ } 9^+; \text{NO}_2 \text{ } 10^+; \text{Br } 11^+ \end{array} \right.$

Scheme 2



Scheme 3

of reaction rate-determining: then it could be affected by base catalysis. Thus, we started a study in order to measure such an effect.

Tables 1 and 2 report sets of data concerning the transformation of **W** (**6** and **9**) into **P** in the presence of variable amounts of DABCO.

The experimental data clearly indicate that the rates of formation of azo-coupling products (**P**) from Wheland intermediate are increased by increasing the amounts of the base. The dependence is linear and it may be expressed by the Eqn. 1,

$$k = k_0 + k_B [\text{B}] \quad (1)$$

where k_0 (s^{-1}) refers to the spontaneous transformation reaction of **W** into **12H–17H** salts, assisted by the solvent or *via* an intramolecular base-catalysis, and k_B ($\text{s}^{-1} \text{mol}^{-1} \text{dm}^3$) is related to the proton abstraction process from sp^3 carbon of **W** by the base added as a catalyst to afford **12–17** bases.

Table 3 reports the data obtained by Eqn. 1. A similar behavior has been also observed when the counter ion of the benzenediazonium salt (and, consequently, of **W**) is the *o*-benzenedisulfonylimidate instead of tetrafluoroborate (entry 10 of Table 3).

Table 1. Rate of reaction of complex **6**⁺ at 20 °C, in CH₃CN and in the presence of variable amounts of DABCO. [1]₀ = 5.3 × 10⁻⁵ mol dm⁻³, [3]₀ = 5.1 × 10⁻⁵ mol dm⁻³

[DABCO] × 10 ⁵ mol dm ⁻³	3.32	4.16	4.98	5.82	6.65	7.48	8.32	9.38
<i>k</i> (s ⁻¹) × 10 ³	3.00	3.26	4.32	4.37	4.42	4.41	4.70	6.00
[DABCO] × 10 ⁴ mol dm ⁻³	1.36	1.70	2.04	2.39	3.40	—	—	—
<i>k</i> (s ⁻¹) × 10 ³	7.70	8.30	9.20	11.0	13.5	—	—	—

Table 2. Rate of reaction of complex **9**⁺ at 20 °C in CH₃CN and in the presence of variable amounts of DABCO. [2]₀ = 4.6 × 10⁻⁵ mol dm⁻³, [3]₀ = 4.9 × 10⁻⁵ mol dm⁻³

[DABCO] × 10 ⁵ mol dm ⁻³	3.32	4.99	6.65	8.31	9.98	11.6	13.3
<i>k</i> (s ⁻¹) × 10 ³	0.830	1.30	1.81	2.10	2.20	2.55	2.99
[DABCO] × 10 ⁵ mol dm ⁻³	15.0	16.6	18.3	—	—	—	—
<i>k</i> (s ⁻¹) × 10 ²	3.15	3.92	4.65	—	—	—	—

Table 3. *k*₀ and *k*_B values (see text) for the transformation of Wheland complex **6**⁺ (unless otherwise indicated) into final products, at 20 °C, in the presence of different added bases

Entry	Amine	p <i>K</i> _a ^a	<i>k</i> ₀ ^b (s ⁻¹)	<i>k</i> _B ^b (s ⁻¹ mol ⁻¹ dm ³)	<i>r</i> ^c	<i>n</i> ^d
1	Pyridine	12.33	(1.23 ± 0.05) × 10 ⁻⁴	0.150 ± 0.006	0.9950	8
2	Imidazole	14.20	(2.42 ± 0.2) × 10 ⁻⁴	3.32 ± 0.10	0.9970	8
3	Morpholine	16.61	(7.10 ± 1) × 10 ⁻⁴	14.6 ± 0.6	0.9970	6
4	DABCO	18.29	(2.10 ± 0.2) × 10 ⁻³	37.1 ± 1	0.9982	13
5	Triethylamine	18.70	(1.48 ± 0.05) × 10 ⁻³	40.7 ± 1	0.9982	5
6	Piperidine	18.92	(7.10 ± 0.7) × 10 ⁻⁴	54.0 ± 3.0	0.9932	6
7	Quinuclidine	19.51	(4.30 ± 1) × 10 ⁻⁴	133 ± 6	0.9951	7
8	Morpholine ^e	16.61	(6.27 ± 0.5) × 10 ⁻³	193 ± 5	0.9985	6
9	DABCO ^f	18.29	(1.68 ± 1) × 10 ⁻³	21.7 ± 1.0	0.9889	10
10	DABCO ^g	18.29	(1.76 ± 0.3) × 10 ⁻³	293 ± 14	0.9953	6

^a Data from References.^{10,11}^b Errors are standard deviation.^c Correlation coefficient.^d Number of points.^e Wheland complex **7**⁺, obtained from 1,3,5-tris(*N*-piperidyl)benzene (**1**) and *p*-nitrobenzenediazonium tetrafluoroborate (**4**).^f Wheland complex **9**⁺, obtained from 1,3,5-tris(*N*-morpholinyl)benzene (**2**) and *p*-methoxybenzenediazonium tetrafluoroborate (**3**).^g Wheland complex, obtained from 1,3,5-tris(*N*-piperidyl)benzene (**1**) and *p*-methylbenzenediazonium *o*-benzenedisulfonylimidate (**18**).

Generally, when the base catalysis is investigated (such as in S_NAr reactions) there are complications arising from the fact that the intermediate is formed “in situ” in non-known amount, and the kinetic equation takes into account the possible return back to the starting materials of the complex.

In contrast, the present study starts from solutions containing known amount of **W** intermediate and *k* value is a simple measurement of the formation of **P** from **W**. *k*_B is a measure of the proton abstraction from sp³ carbon atom by the nitrogen atom of the catalyst. *k*₀ is a measure of the spontaneous re-aromatization process, without the intervention of an external base; it should be independent from the catalyst used and represents a less important pathway.

Vice-versa, we have observed that the *k*₀ value ranges from 1 × 10⁻⁴ to 2 × 10⁻³ mol⁻¹ dm³. We think that the variations reported in Table 3 may depend on the high *k*_B/*k*₀ ratio, which is an indication that the formation of **P** is almost wholly base-catalysed; it is well known that when a straight line shows a very high slope, the true

uncertainty of the intercept may be high even if the statistical errors (calculated as standard deviation) are in an acceptable range.

As expected, *k*_B value (which is related to base catalyzed processes) is dependent on the basicity of the catalyst. For this reason, Table 3 reports also the p*K*_a values (in acetonitrile) of the used bases.

The dependence of *k*_B value on p*K*_a values obeys the Brønsted relation¹² (Eqn. 2) (in partial agreement with previous reports of Zollinger¹³):

$$\log_{10} k_B = \beta pK_a + C \quad (2)$$

giving Eqn. 3 (*r* = 0.977).

$$\log_{10} k_B = (0.36 \pm 0.04) \times pK_a + (-4.93 \pm 0.60) \quad (3)$$

Linear and non-linear Brønsted equations have been observed: in the present study, notwithstanding the large p*K*_a range (8 p*K*_a units) examined and the structural variability of the used amines, the linearity is more than

acceptable. Even if the Brønsted analysis is only a plug in the study of mechanistic problems, because the present reaction is quite simple, it is reasonable to state that there is a relevant base catalysis step which represents the major pathway for the system in reaching **P**.

The use of Brønsted relationship, especially in solvents different from water, has been criticized and questioned. The measurement of the isotopic kinetic effect (K_H/K_D ratio) could be a better tool to investigate the course of the C—H bond breaking on the reaction coordinates.¹⁴

Base catalysis was reported to be operating in azo-coupling reaction of citrazinic acid and 4-methoxybenzenediazonium chloride.¹⁵ In contrast, in the 2,6-dihydropyridine/4-methoxybenzenediazonium chloride system no evidence of base catalysis was reported.¹⁶

Azo-coupling of *N,N*-dimethylaniline shows evidence of self catalysis.¹⁷ Moreover, evidence of base catalysis in reactions of naphthol derivatives and diazonium salts was also reported.¹⁸

The use of **2** (the morpholinyl derivative) instead of **1** shows a small decrease of k_B value (from 37 to 22 s⁻¹, see entries 4 and 9 of Table 3). This difference is minor and it may be hardly explained because several parameters of difficult evaluation can be operative (for instance, difference in conformational structure, difference in solvation, inductive electron-withdrawing effect of the oxygen and the related difference in basic strengths).

More relevant difference is observed (more than one order of magnitude) by changing Y from OCH₃ (entry 3 of Table 3) to NO₂ (entry 8). Even if the distance between Y and the reaction center is quite large, the electron-withdrawing resonance effect of the nitro group is operating in enhancing the acidic character of the C—H bond.

CONCLUSIONS

In conclusion, the data reported for the examined electrophilic aromatic substitutions, are a clear indication that the Wheland intermediate is formed in a fast step, and the rate determining step is the proton abstraction to produce the re-aromatized final compound; this situation occurs because of the stability of the **W** complexes.⁸ Obviously, these conclusions could not be extended to the whole of the aromatic electrophilic reactions. Anyway, it is important to emphasize that often the experimental conditions of reaction, involving the formation of the electrophilic reagents in the reaction mixtures including bases, could mask the base catalysis process. For this reason a “saturation” phenomenon can occur and the importance of the C—H bond breaking in a rate-determining step could be evidenced only from the measurement of kinetic isotopic effect.

We can emphasize that the present reaction is exceptionally suitable (owing the stability of **W** com-

plexes) to give a simple and strong indication that the C—H bond breaking can occur in a rate determining re-aromatization step.

EXPERIMENTAL

General remarks

UV/Vis spectrophotometric data were recorded with a Perkin-Elmer (model Lambda 12) spectrophotometer.

The compounds **1**, **2**, **6⁺**, **7⁺**, **9⁺**, **12H**, **13H**, **15H**, and **12**, **13**, **15** were prepared as reported in Reference 8, compounds **3** and **4** are commercially available, compound **18** was synthesized as reported.¹⁹

When solutions of **1** (or **2**) in acetonitrile are mixed with the diazonium salts **3–4** in equimolar amount, an orange color immediately develops, related to the formation of Wheland complexes **6⁺**, **7⁺**, and **9⁺**, as recently reported on the bases of ¹H-NMR spectral data.⁸ Their formation may be considered instantaneous and complete, as tested by measurements of the experimental absorbance values obtained from mixtures of different concentrations of **1** and **3**. The observed absorbance values are stable at 20 °C for 10–20 minutes. Thus, UV/Vis spectral data confirm the observation obtained by ¹H NMR data: the formation of σ cationic complexes is a fast process and the equilibrium reported in Scheme 1 is completely shifted toward the right.

The spontaneous conversion of σ cationic complexes **6⁺**, **7⁺**, and **9⁺** into azo compounds **12H**, **13H**, and **15H** (or **12**, **13**, and **15**) occurs in long reaction times: about 1–2 days to reaching the 50% of conversion. Our attempts to realize direct measurements of k_o at different concentrations of **1** and **3** have furnished data unsatisfactorily reproducible, in the range (1.4–5.4)10⁴ s⁻¹.

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