Reactive Intermediates

Evidence for Carbon–Carbon Meisenheimer–Wheland Complexes between Superelectrophilic and Supernucleophilic Carbon Reagents**

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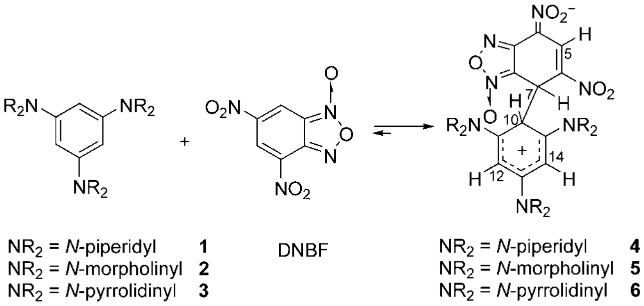
The observation, or the isolation (when it is possible), of intermediates in nucleophilic aromatic substitution[1a] (S_NAr; the so-called Meisenheimer complexes M) and in electrophilic aromatic substitution[1b,c] (the so-called Wheland complexes W) reactions is an important confirmation of the proposed mechanisms. Our interest has, in the past, focused on intermediates in the S_NAr reaction[2] and, more recently, also on electrophilic aromatic substitution reactions[3] (Wheland intermediates). Both kinds of σ complexes (M and W) have appreciable stability when a number of strong electron-withdrawing groups or electron-donating groups, respectively, are present on the aromatic ring. 4,6-Dinitrobenzofuroxan (DNBF) is a powerful carbon electrophilic reagent[4] and 1,3,5-tris(*N*,*N*-dialkylamino)benzenes are powerful carbon nucleophilic reagents.[5] Herein, we report that these couples act as superelectrophilic[6,7] and supernucleophilic reagents, thus providing evidence of a carbon–carbon coupling reaction with formation of Meisenheimer–Wheland zwitterionic complexes. This kind of adduct was, up until now, only proposed,[7] but not observed experimentally.

Addition of solutions of 1,3,5-tris(*N*-piperidyl)benzene (**1**), 1,3,5-tris(*N*-morpholinyl)benzene (**2**), or 1,3,5-tris(*N*-pyrrolidinyl)benzene (**3**) in CD_2Cl_2 to a solution of DNBF in CD_2Cl_2 at −70 °C in an NMR tube resulted in the signals of the starting materials in the ^1H NMR spectra disappearing and the appearance of new signals, which are ascribed to compounds **4**, **5**, and **6** (Scheme 1). Acidification of solutions of **4** in $[D_6]$DMSO by addition of DCl afforded a spectrum containing exclusively the signals of the starting materials, namely **1** (in a protonated form) and DNBF.



Scheme 1. Reaction of 1,3,5-tris(*N*,*N*-dialkylamino)benzenes with 4,6-dinitrobenzofuroxan to produce carbon–carbon zwitterionic complexes.

Scheme 1 illustrates the observed reactions with formation of Wheland–Meisenheimer complexes **4**–**6**, whose structures are in agreement with the spectral data obtained at low temperature. Detailed analyses of the reaction products **4**–**6** by variable-temperature NMR spectroscopy revealed an unexpected behavior of these W–M compounds which deserves some special consideration. We describe herein the study carried out on compound **6** in detail; similar behavior was obtained with **4** and **5** (full spectral data for compounds **4**–**6** are shown in Tables 1 and 2).

The mixing of cooled (−70 °C) solutions of DNBF and 1,3,5-tris(*N*-pyrrolidinyl)benzene (**3**) in CD_2Cl_2 afforded a new product (**6**) immediately. The ^1H NMR spectrum of this solution (maintained at −70 °C) shows four separate signals in the range $\delta = 4.3$–5.1 ppm, three of which correspond to the three hydrogen atoms belonging to the tris(*N*-pyrrolidinyl)benzene moiety and one ascribed to the furoxanic ring. The other hydrogen atom, which is hydrogen bonded to the furoxanic ring, was found at $\delta = 8.60$ ppm (Table 1).

Direct proton to carbon correlation (gHSQC sequence, Figure 1, left) obtained at −70 °C shows that two of the four hydrogen atoms which resonate at $\delta = 4.61$ and 4.43 ppm are connected to two carbon atoms at $\delta = 87.22$ and 88.28 ppm; these chemical shifts are in the range typical for sp^2-hybridized carbon atoms of 1,3,5-tris(*N*-pyrrolidinyl)benzene. In contrast, the two remaining proton signals ($\delta = 4.32$ and 5.00 ppm) are connected directly to carbon atoms resonating at $\delta = 45.09$ and 40.87 ppm, respectively, which is clear evidence for the sp^3 hybridization of these carbon atoms.

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Table 1: ^{1}H NMR spectral data in CD_2Cl_2.

Compound	T [°C]	δ_{H5}	δ_{H7}	δ_{H10}	δ_{H12}[a]	δ_{H14}[a]	δ_{NCH_2}	$\delta_{others\ CH_2}$
1	+25			6.00			3.00–3.10 (m, 12 H)	1.60–1.70 (m, 12 H), 1.46–1.56 (m, 6 H)
2	+25			6.00			3.05–3.10 (m, 12 H)	3.75–3.82 (m, 12 H)
3	+25			5.18			3.19–3.27 (m, 12 H)	1.88–1.98 (m, 12 H)
DNBF	+25	9.11 (d, J = 1.9 Hz)	8.84 (d, J = 1.9 Hz)					
4	−70	8.77	4.97 (d, J = 4.7 Hz)	4.68 (d, J = 4.7 Hz)	5.26	5.11	2.70–4.25 (m, 12 H)	1.30–1.95 (m, 18 H)
4	+ 25	8.78	5.15	5.22[b]	5.22[b]	5.22[b]	3.28–3.52 (m, 12 H)	1.60–1.80 (m, 18 H)
5	−70	8.81	5.05 (d, J = 3.8 Hz)	4.66	5.16	5.30		2.85–4.25 (m, 24 H)
5	−25	8.83	5.30	5.23[b]	5.23[b]	5.23[b]		3.10–4.00 (m, 24 H)
6	−70	8.60	5.00 (d, J = 3.6 Hz)	4.32 (d, J = 3.6 Hz)	4.61	4.43	2.70–4.25 (m, 12 H)	1.60–2.20 (m, 12 H)
6	+25	8.67 (d, J = 0.9 Hz)	5.14	4.58[b]	4.58[b]	4.58[b]	3.15–3.60 (m, 12 H)	1.80–2.15 (m, 12 H)

[a] Interchangeable assignments. [b] Broad singlet.

Proton to proton correlation obtained at −70 °C (gCOSY sequence, Figure 1, right) shows that the signal at δ = 5.00 ppm is correlated with the furoxanic hydrogen atom at δ = 8.60 ppm and to one of the three tris(N-pyrrolidinyl)benzene hydrogen atoms at δ = 4.32 ppm (J = 3.6 Hz).

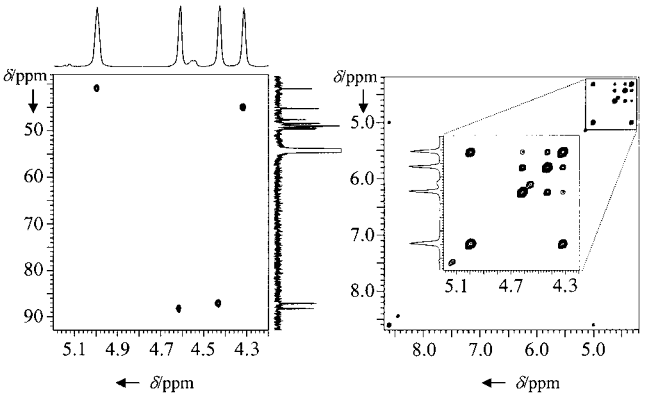


Figure 1. Left: gHSQC spectrum of compound **6** in CD_2Cl_2 at −70 °C. Right: gCOSY spectrum of compound **6** in CD_2Cl_2 at −70 °C.

All the mentioned NMR data, recorded at −70 °C, agree with a Wheland–Meisenheimer (W–M) structure that is produced in the reaction between DNBF and tris(N-pyrrolidinyl)benzene.[8]

In the Wheland–Meisenheimer structure (Scheme 1) C12 and C14 are sp^2 hybridized, while C10 and C7 are sp^3 hybridized, thus accounting for the two high-field ^{13}C NMR signals at δ = 45.09 and 40.87 ppm, respectively. The presence of two distinct hydrogen (and carbon) signals for the two other CH groups (C12 and C14) of the tris(N-pyrrolidinyl)benzene can be easily explained because of the presence of an asymmetric carbon center (C7) and a "C_2 center" (C10);[9] under these conditions the two CH atoms are diastereotopic and thus appear as anisochronous signals in both the ^{1}H and ^{13}C NMR spectra. The same effect can be observed for the aromatic quaternary carbon atoms, which show three separated signals, and for the pyrrolidinic rings (six signals for the six α-nitrogen carbon atoms).

On raising the temperature, neither the ^{13}C nor ^{1}H NMR spectra change until −30 °C (−30 °C and −40 °C for **4** and **5**, respectively). Above −30 °C the three signals ascribed to the hydrogen atoms of the tris(N-pyrrolidinyl)benzene moiety show line broadening as a result of an exchange process. The signals coalesce at −1 °C and appear as a single signal at +20 °C (Figure 2). In contrast, the other signal (H7) always remains sharp.

It is worth noting that the dynamic process observed is reversible: warming the solution from −30 °C to room temperature and cooling again to −30 °C gives a spectrum that is identical to the starting one. Satisfactory line-shape simulation (Figure 2) was obtained using only one rate constant, which shows that ΔG^{+} is not constant with temperature and indicates that the ΔS^{+} value is not negligible. An accurate analysis by means of the Eyring equation[10] yields $\Delta H^{+} = 22.7 \pm 0.2$ kcal mol^{-1} and $\Delta S^{+=}32 \pm 5$ e.u. for **6** ($\Delta H^{+} = 17.6 \pm 0.2$ kcal mol^{-1}, $\Delta S^{+=}18 \pm 6$ e.u. for **4** and $\Delta H^{+} = 10.4 \pm 0.3$ kcal mol^{-1}, $\Delta S^{+=}10 \pm 6$ e.u. for **5**).

The same dynamic process can also be observed in the ^{13}C NMR spectra: the coalescence of the three quaternary carbon atoms C11, C13, and C15 can be clearly seen above −30 °C, and they appear as a single line above −1 °C. However, the coalescence and the single averaged line cannot be observed for the three carbon atoms at δ = 87.22, 88.28, and 45.09 ppm because of the very large chemical shift difference between the signals (a line width of about 3 KHz is expected assuming $\Delta G^{+} \approx 13$ kcal mol^{-1} at room temperature). As in the proton spectra, the fourth signal, belonging to the C7 atom of the furoxanic ring, is always sharp irrespective of the temper-

Table 2: ^{13}C NMR spectral data in CD_2Cl_2.

Comp.	T [°C]	$\delta_{C4,C6,C8,C9}$[a]	δ_{C5}	δ_{C7}	δ_{C10}	$\delta_{C12,C14}$[a]	$\delta_{C11,C13,C15}$[a]	δ_{NCH_2}	$\delta_{NCH_2CH_2}$ and $NCH_2CH_2CH_2$
1	+25				99.32	99.32, 99.32	154.80	52.15	25.29, 26.94
2	+25				97.64	97.64, 97.64	154.06	50.72	67.69
3	+25				86.67	86.67, 86.67	150.67	48.46	26.12
DNBF	+25	116.65, 138.46, 145.19, 151.19	126.42	120.14					
4	−70	109.61, 113.43, 119.28, 150.43	135.47	41.99	39.47	88.24, 90.09	158.51, 159.85, 159.89	48.33, 48.76 49.08, 49.80(2 sig. ov.), 49.85	23.78, 24.22, 24.26, 24.56, 24.88, 26.15, 26.26, 26.51, 27.33
4	+25	110.92, 114.21, 120.00, 151.21	135.70	43.75			160.34	50.44	26.53, 24.72
5	−70	109.44, 113.44, 118.34, 150.33	135.51	42.94	39.17	89.52, 91.23	159.87, 160.27, 160.94	46.75, 47.36, 47.60, 47.90, 48.37, 48.71	65.00, 65.56, 66.12, 66.20, 66.56, 66.97
6	−70	109.36, 113.62, 119.16, 150.95	133.78	40.87	45.09	87.22, 88.28	154.91, 155.29, 157.94	47.54, 48.37, 48.86, 49.03, 49.37, 49.55	24.83, 24.97, 25.01, 25.43, 25.88, 26.17
6	+25	110.25, 114.54, 119.46, 151.79	134.60	42.28			157.86[b]	49.79	25.96

[a] Interchangeable assignments. [b] Broad signals.

ature, thus showing that the furoxanic anion is still present at room temperature.[11]

Hence, the dynamic NMR data suggest the existence, above the coalescence temperature, of a Wheland–Meisenheimer complex in three homomeric structures (Scheme 2) with bonds C7/C10, C7/C12, and C7/C14 rapidly exchanging. The positive value of $\Delta S^{\neq}$ also agrees with a mechanism in which a bond involved in the W–M complex is broken. It should be noted that the activation parameters obtained for **6** are quite different from those obtained for **4** and **5**. A possible explanation can be hypothesized by considering the different steric environments involved in the W–M complexes: although the steric effects of the six-membered rings are almost the same in **4** and **5**, the smaller and more flexible five-membered rings in **6** lead to a stabilization of the W–M structure and hence affords greater $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values.

The existence of a π–π charge-transfer (CT) complex between DNBF and tris(amino)benzene derivatives could also occur, but experimental spectral data obtained for

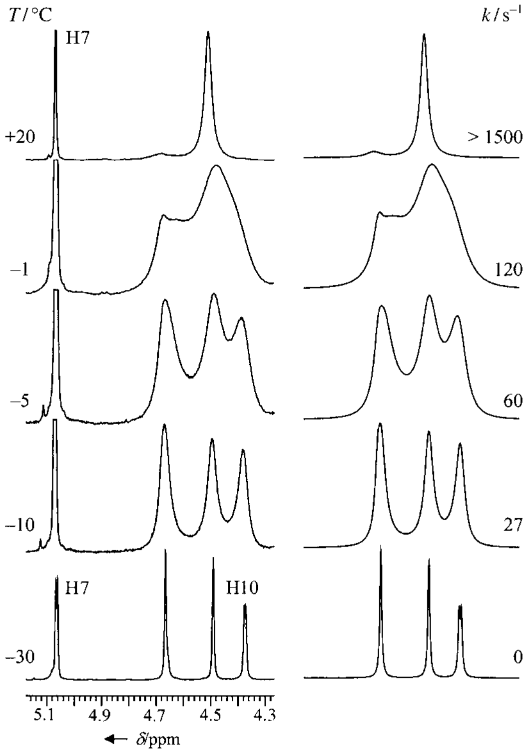
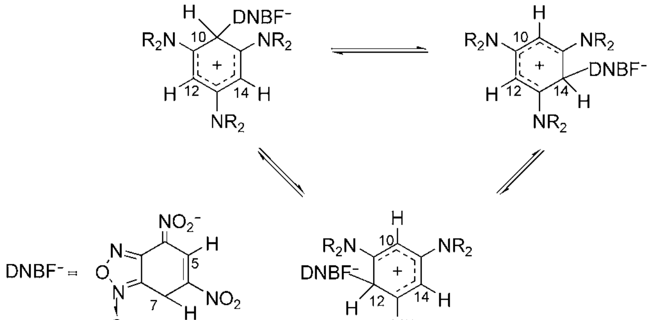


Figure 2. Left: experimental variable-temperature NMR spectra of **6**. Right: line-shape simulation obtained with the rate constant indicated. NR_2 = piperidyl, morpholinyl, pyrrolidinyl.



Scheme 2. Proposed interconversion pathway for the observed reversible and temperature-dependent transformation of W–M structures **4**–**6**.

compounds **4** and **6** clearly show (also at room temperature) the presence of sp^3 hybridization at the C7-position of the DNBF moiety (^{13}C NMR signal at $\delta = 40.87$ ppm). If such a CT complex existed, this carbon atom should revert back to sp^2 hybridization and hence a ^{13}C NMR signal at around $\delta = 90$ ppm would be observed in the ^{13}C NMR spectrum at +25 °C.

In conclusion, the reaction between a superelectrophilic reagent such as DNBF and powerful carbon nucleophilic reagents such as 1,3,5-tris(*N*,*N*-dialkylamino)benzenes have given the possibility to characterize, for the first time, zwitterionic carbon–carbon Meisenheimer–Wheland complexes, whose structures were ascertained by one- and two-dimensional NMR experiments. A dynamic NMR study of these species also showed, through observation of coalescence, that increasing the temperature results in the formation of a Wheland–Meisenheimer complex in three homomeric structures with bonds C7/C10, C7/C12, and C7/C14 rapidly exchanging. Very strongly activated systems often give unexpected results, and this is the case here.

Experimental Section

Compounds **1** and **2** were prepared as reported in ref. [3]. Compound **3** was prepared in a similar manner from 1,3,5-trichlorobenzene and pyrrolidine. DNBF was prepared as reported in ref. [8]. NMR spectra were recorded on Varian Gemini 300, Mercury 400, or Inova 600 spectrometers operating at 300, 400, or 600 MHz (for ^{1}H NMR) or 75.46, 100.56, or 150.80 MHz (for ^{13}C NMR), respectively. Signal multiplicities were established by DEPT experiments. Chemical shifts were referenced to the solvent [($\delta = 5.30$ and 54.2 ppm for CD_2Cl_2), ($\delta = 7.27$ and 77.0 ppm for $CDCl_3$), ($\delta = 2.0$ and 0.3 ppm for CD_3CN), ($\delta = 2.6$ and 39.5 ppm for [D$_6$]DMSO) for ^{1}H and ^{13}C NMR, respectively]. The variable-temperature NMR spectra and 2D low-temperature spectra were recorded on the Inova 600 with a direct PFG Probe. The temperatures were calibrated by substituting the sample with a precision Cu/Ni thermocouple before the measurements. Complete fitting of dynamic NMR line shapes was carried out using a PC version of the DNMR-6 program.[12]

The low-temperature samples for NMR experiments were prepared directly in the NMR tube by mixing two cooled (−70 °C) solutions of DNBF (0.006 M) and **1**, **2**, or **3** (0.006 M) in CD_2Cl_2.

The behavior observed for compounds **4**–**6** on changing the temperature and the reversibility of the process was also observed in $CDCl_3$ solutions.

Mixing **1**, **2**, or **3** with DNBF in acetonitrile at low temperature (−30 °C) resulted in the precipitation of a coral-red solid. Heating the resulting solids, which were isolated by filtration, in a melting point apparatus resulted in them gradually darkening (133–140 °C, 118–125 °C, and 129–135 °C for compounds **4**–**6**, respectively) then decomposing. However, their ^{1}H and ^{13}C NMR spectra were identical to those obtained for compounds **4**–**6**, formed directly in an NMR tube and recorded at 25 °C.

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[8] Recently, we studied the formation of σ complexes between nitrobenzofuroxans and amines and found that reaction of DNBF with 1,4-diazabicyclo[2.2.2]octane (DABCO) or piperidine affords Meisenheimer complexes which show ^{1}H NMR signals (in [D$_6$]DMSO) corresponding to protons bonded to the sp^3-hybridized C7 atom at $\delta = 6.8$ ppm and 6.2–6.4 ppm, respectively. When DNBF reacts with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) the positive charge is delocalized over the two nitrogen atoms, and the ^{1}H NMR signal of the proton on the sp^3-hybridized C7 atom appears at $\delta = 5.3$ ppm, which is very similar to values reported here for **4–6**; see C. Boga, L. Forlani, *J. Chem. Soc. Perkin Trans. 2* **2001**, 1408–1413.
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[11] This observation also excludes the hypothesis that the starting reagents could be involved in the transition state because, if this is true, an exchange between the H7 signal of the W–M complex and the H7 signal of DNBF should be observed.
[12] QCPE program no. 633, Indiana University, Bloomington, IN, USA.