Photoreactions of *N*-Methyl-1,8-naphthalimide with Methylbenzenes: [3+3]-Additions and Water-Incorporated Additions

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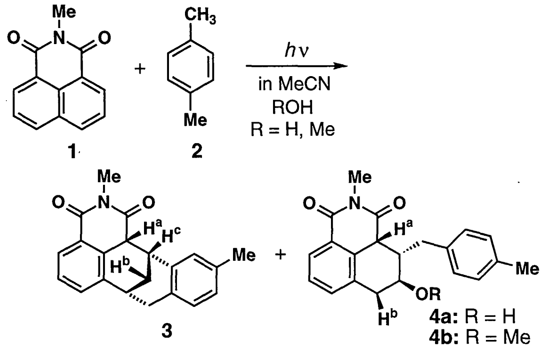
Novel [3+3]-additions and water (methanol)-incorporated additions were observed in the photoreactions of *N*-methyl-1,8-naphthalimide with methylbenzenes, such as xylenes, mesitylene, and durene, in acetonitrile. A mechanism for the reactions is proposed on the basis of the fluorescence quenching examinations, calculations of ΔG associated with the electron transfer, and deuteration studies.

1,8-Naphthalimide derivatives have been reported to be very promising anticancer and antiviral agents possibly due to their ability to intercalate into DNA with high affinity and sequence specificity, and to be used in a variety of biological and medicinal applications.[1] Combined with the high photoactivity, some of naphthalimides have been used as sequence-specific DNA-photonucleases,[2] and for the mechanisms generation of the carbocation,[2a] electron-transfer from guanine residues,[2b] hydrogen abstraction from thymine,[2c] and hydroxyl radical formation[2d] have been proposed. On the other hand, photophysical properties of naphthalimides have also attracted considerable interest in recent years.[3] Whereas, fundamental photoreactions of naphthalimides have not yet fully elucidated, and to our knowledge reactions with alkenes[4] and amines,[5] and other reactions[2,6] are the only examples reported so far. In this letter, we report on photoreactions of *N*-methyl-1,8-naphthalimide (**1**) with simple methylbenzenes, in which novel [3+3]-additions and water (methanol)-incorporated additions proceed possibly from the singlet excited state of **1**.

Irradiation of a dried acetonitrile solution, containing <0.005% H_2O, of **1** (2.4×10^{-3} mol/dm^3) and *p*-xylene (**2**, 4×10^{-1} mol/dm^3) with a high-pressure Hg lamp through about 1 cm path length saturated $CuSO_4$ aqueous filter (50% transmittance at 340 nm) under a nitrogen atmosphere gave a [3+3]-adduct **3** in 36% yield (eq 1). When the reactions were carried out in the presence of water (ROH, R = H) and in the presence of methanol (ROH, R = Me) 1:1:1-adducts (**4a,b**) of **1**, **2**, and ROH were obtained together with **3**. The yields of **3** and **4a** were 23% and 31% in the presence of 0.2% H_2O, and those of **3** and **4b** were 24% and 30% in the presence of 0.5% methanol, respectively.



1 **2**

3

4a: R = H
4b: R = Me

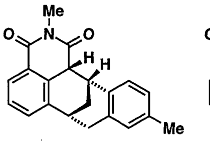
(1)

The products **3,4a,b** were isolated by column chromatography on silica gel. Their structures were determined by their spectral properties, especially by their ^{1}H NMR spectra.[7] The observed ^{1}H NMR coupling constants of **3,4a** corresponded well to the predicted values on the basis of the dihedral angles obtained from MM2 calculations. The formations of **3** and **4a** were not sensitized by Michler's ketone (E_T = 260 kJ/mol, E_T (**1**) = 220 kJ/mol)[3a] in MeCN and also in 0.2% H_2O-MeCN.

To clarify the source of the transferred hydrogens in the reactions deuteration studies were carried out. Thus, the photoreaction with **2** in 0.5% D_2O-MeCN led to deuteration of H^a (47%) and H^b (84%) in **3**, and of H^a (53%) and H^b (87%) in **4a**, and no deuterations of H^a and H^b in **3** and **4a** were observed in the reaction with **2**-d_{10} in 0.5% H_2O-MeCN. However, the deuterations of H^a in **3** and **4a** during the photoreactions were found to be obscure, since the H^a protons in **3** and **4a** were slowly deuterized in 0.5% D_2O-MeCN in the dark possibly due to enolization.

Other photoreactions of **1** with simple methylbenzenes are summarized in Table 1. Thus, both of [3+3]-adducts **5,6a-c**

Table 1. Photoreactions of **1** with methylbenzenes in MeCN and in 2.5% H_2O-MeCN[a]



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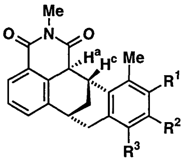
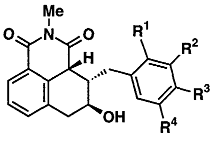


6a: R^1=R^2=R^3=H
6b: R^1=R^3=H, R^2=Me
6c: R^1=R^3=Me, R^2=H



7a: R^1=Me, R^2=R^3=R^4=H
7b: R^1=R^3=R^4=H, R^2=Me
7c: R^1=R^3=H, R^2=R^4=Me
7d: R^1=R^3=R^4=Me, R^2=H

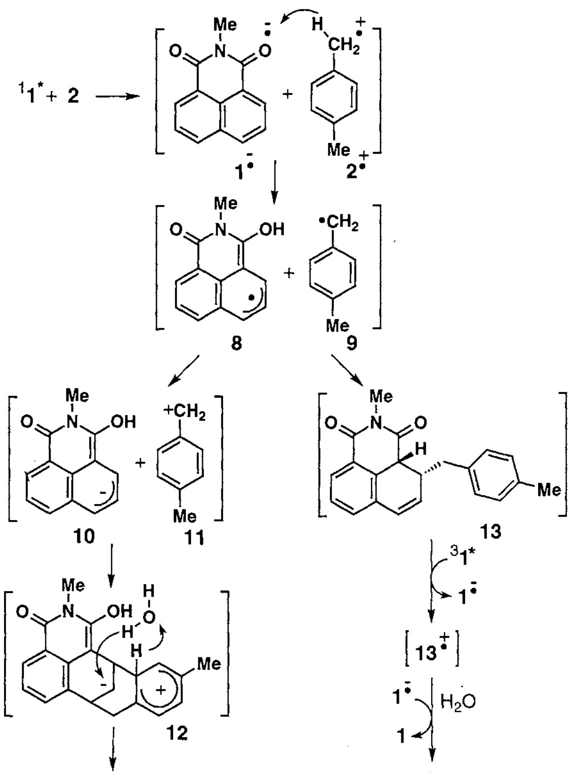
methylbenzene	E^{ox}[b] / V	ΔG[c] / kJ/mol	products (yield/%)[d]	**5+6**[e] / **7**
toluene	2.272	+1.6	no reaction	
o-xylene	2.234	-2.1	**7a**(—,34)	0
m-xylene	2.230	-2.4	**5**(9,3), **6a**(8,2), **7b**(—,29)	0.2
p-xylene	2.124	-12.7	**3**(36,20), **4a**(—,38)	0.5[f]
mesitylene	2.104	-14.6	**6b**(38,35), **7c**(—,19)	1.8
durene	1.860	-38.1	**6c**(47,37), **7d**(—,8)	4.6

[a]Irradiation conditions: [**1**] = 2.4×10^{-3} mol/dm^3, [methylbenzene] = 4×10^{-1} mol/dm^3. [b]Experimental conditions: [methylbenzene] = 1×10^{-3} mol/dm^3 in 0.1 mol/dm^3 Bu_4NClO_4/MeCN, at an ambient temperature, with a carbon electrode vs. Ag/0.01 mol/dm^3 $AgClO_4$, normalized as E^{ox}(ferrocene) = 0.428 V. [c]ΔG value associated with the electron transfer from methylbenzene to the singlet excited state of **1** calculated by $\Delta G = 96.39[E^{ox} - E^{red}(\mathbf{1})] - E_S(\mathbf{1}) - C$,[8] where $E^{red}(\mathbf{1}) = -1.244$ V, $E_S(\mathbf{1}) = 331.9$ kJ/mol,[4b] and C = 5.4 kJ/mol. [d]Yield obtained in MeCN and that in 2.5% H_2O-MeCN, respectively. [e]Based on the yields obtained in 2.5% H_2O-MeCN. [f]**3**/**4a**.

and water-incorporated adducts **7b-d** were obtained in the reactions with *m*-xylene, mesitylene, and durene, and the ratio (**5**+**6**)/**7** increased with decrease of the ΔG values associated with the electron transfer from the methylbenzenes to the singlet excited state of **1**, while no products were observed in the reactions with toluene and the only water-incorporated adduct **7a** was found in those with *o*-xylene. The structures of **6a-c** were supported by the smaller ^{1}H NMR coupling constants between H^a and H^c (~0 Hz) compared with those in **3** (3.7 Hz). The MM2 calculations showed that the structures of **6a-c** with trans configuration between H^a and H^c were more stable than those with cis configuration probably due to the steric repulsion between the imide carbonyl group and the methyl substituent.

There was no evidence from the UV spectra for a preformed ground-state complex between **1** and **2**. On the other hand, fluorescence of **1** (τ = 170 ps) in MeCN was quenched by **2** at a rate of 2.8×10^{10} dm^3 mol^{-1} s^{-1}, which was comparable to the diffusion controlled rate constant in MeCN, and implied that 74% of the singlet excited state of **1** was quenched by **2** under the photoreaction conditions. Along with the quenching an rather strong exciplex emission was observed even in MeCN. From the solvent effect on the maximum wavelength of the exciplex emission the dipole moment of the exciplex was calculated to be 10.4 D, indicating the highly polar nature of the exciplex.[9]

From these results, we propose a tentative mechanism for the [3+3]-addition and the water-incorporated addition (Scheme 1). The both reactions seem to proceed from the singlet excited state of **1**, as shown by the triplet sensitization and fluorescence quenching examinations. The interaction between the singlet excited state of **1** and **2** can afford an exciplex or a radical ion pair, in which proton transfer may proceed to give a radical pair of **8** and **9**. Two types of reactions, electron transfer from **9** to **8** and radical coupling reaction between **8** and **9**, may be opened for the radical pair. In the electron transfer pathway thermally allowed [3+3]-cycloaddition of the anion **10** to the cation **11**, followed by water-mediated proton transfer and enol-keto tautomerization, may finally give the [3+3]-adduct **3**.[10] Alternatively, in the radical coupling pathway anti-Markovnikov addition[4a] of water to the double bond of an adduct **13** possibly sensitized by the long-lived triplet excited state of **1**,[11] may afford the water-incorporated adduct **4a**.



Scheme 1.

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7 ^{1}H NMR for **3** (CDCl$_3$, 270 MHz) δ 2.23 (s, 3H), 2.35 [m, 2H, these signals appeared at 1.71 (dddd, J = 2.0, 2.0, 3.9, 12.9 Hz, 1H) and 1.81 (ddd, J = 2.0, 4.4, 12.9 Hz, 1H) in C$_6$D$_6$], 2.69 (dd, J = 4.0, 16.5 Hz, 1H), 3.27 (dd, J = 5.1, 16.5 Hz, 1H), 3.32 (s, 3H), 3.51 (m, 1H), 4.17 [br s, 2H, these signals appeared at 3.32 (d, J = 3.7, 1H) and 4.05 (m, 1H) in C$_6$D$_6$], 6.79 (d, J = 7.9 Hz, 1H), 6.87 (dd, J = 1.5, 7.9 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.35 (d, J = 1.5 Hz, 1H), 7.48 (dd, J = 1.2, 7.6 Hz, 1H), 7.96 (dd, J = 1.2, 7.6 Hz, 1H) ppm. ^{1}H NMR for **4a** (CDCl$_3$, 270 MHz) δ 1.99 (dd, J = 11.2, 13.7 Hz, 1H), 2.35 (s, 3H), 2.68 (dd, J = 5.1, 13.7 Hz, 1H), 2.92 (d, J = 18.4 Hz, 1H), 3.16 (ddd, J = 2.9, 4.2, 5.1 Hz, 1H), 3.27 (dd, J = 5.4, 18.4 Hz, 1H), 3.36 (s, 3H), 4.13 (m, 1H), 4.41 (d, J = 4.2 Hz, 1H), 7.04 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 7.42 (dd, J = 7.2, 8.2 Hz, 1H), 7.44 (dd, J = 2.4, 8.2 Hz, 1H), 8.12 (dd, J = 2.4, 7.2 Hz, 1H) ppm.

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11 The high reactivity of the triplet excited state of 1,8-naphthalimides toward electron donors has been reported.[2d,5]