Photogeneration of 1,5-naphthoquinone methides via excited-state (formal) intramolecular proton transfer (ESIPT) and photodehydration of 1-naphthol derivatives in aqueous solution[1]

Matthew Lukeman, Duane Veale, Peter Wan, V. Ranjit N. Munasinghe, and John E.T. Corrie

Abstract: The photochemistry of naphthols **1**, **2**, **4**, **5** and **9**, and phenol **10** has been studied in aqueous solution with the primary aim of exploring the viability of such compounds for naphthoquinone and quinone methide photogeneration, along the lines already demonstrated by our group for phenol derivatives. 1-Naphthol (**1**) is known to be substantially more acidic than 2-naphthol (**2**) in the singlet excited state (pK_a^* = 0.4 and 2.8, respectively) and it was expected that this difference in excited-state acidity might be manifested in higher reactivity of 1-naphthol derivatives for photochemical reactions requiring excited-state naphtholate ions, such as quinone methide formation. Our results show that three types of naphthoquinone methides (**26a**, **26b**, and **27**) are readily photogenerated in aqueous solution by irradiation of 1-naphthols. Photolysis of the parent 1-naphthol (**1**) in neutral aqueous solution gave 1,5-naphthoquinone methide **26a** as well as the non-Kekulé 1,8-naphthoquinone methide **26b**, both via the process of excited-state (formal) intramolecular proton transfer (ESIPT), based on the observation of deuterium exchange at the 5- and 8-positions, respectively, on photolysis in D_2O–CH_3CN. A transient assignable to the 1,5-naphthoquinone methide **26a** was observed in laser flash photolysis experiments. The isomeric 2-naphthol (**2**) was unreactive under similar conditions. The more conjugated 1,5-naphthoquinone methide **27** was formed efficiently via photodehydroxylation of **4**; isomeric **5** was unreactive. The efficient photosolvolytic reaction observed for **4** opens the way to design related naphthol systems for application as photoreleasable protecting groups by virtue of the long-wavelength absorption of the naphthalene chromophore.

Key words: photosolvolysis, excited-state intramolecular proton transfer, quinone methide, photorelease, photoprotonation.

Résumé : Opérant en solution aqueuse, on a étudié la photochimie des naphtols **1**, **2**, **4**, **5** et **9** et du phénol **10** afin de déterminer la viabilité de tels composés pour la photogénération de méthides de naphtoquinone et de quinone suivant les voies déjà mises de l'avant par notre groupe pour les dérivés du phénol. Il est bien connu que, dans l'état excité singulet, le 1-naphtol (**1**) est beaucoup plus acide que le 2-naphtol (**2**) (pK_a^* de 0,4 et 2,8, respectivement) et on s'attendait à ce que cette différence d'acidité dans l'état excité pourrait se manifester par une plus grande réactivité des dérivés du 1-naphtol pour les réactions photochimiques impliquant des ions naphtanolates dans l'état excité, tel que la formation de méthide. Nos résultats démontrent que l'irradiation des 1-naphtols en solutions aqueuses conduit facilement à la formation de trois types de méthides de naphtoquinones (**26a**, **26b** et **27**). L'irradiation du 1-naphtol fondamental (**1**), en solutions aqueuses neutres, conduit au méthide de 1,5-naphtoquinone (**26a**) ainsi qu'au méthide de 1,8-naphtoquinone (**26b**), une structure qui ne répond pas aux normes de Kekulé; sur la base d'expériences de photolyse dans un mélange de D_2O–CH_3CN qui conduisent à un échange de deutérium dans les positions respectivement 5 et 8, ces deux méthides se produisent par un processus de transfert intramoléculaire de proton dans l'état excité (formel). Lors d'expériences de photolyse éclair au laser, on a observé une entité transitoire attribuable au méthide de la 1,5-naphtoquinone. Dans des conditions semblables, le 2-naphtol (**2**) isomère n'est pas réactif. Le méthide de la 1,5-naphtoquinone (**27**) qui est plus conjuguée se forme facilement par photodéhydroxylation du composé **4**; son isomère **5** n'est pas réactif. La réaction efficace de photosolvolyse du composé **4** ouvre la voie au développement de systèmes de naphtols qui pourraient être utilisés comme groupes protecteurs qui pourraient être éliminés photochimiquement en

Received 23 June 2003. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 30 January 2004.

M. Lukeman, D. Veale, and P. Wan.[2] Department of Chemistry, Box 3065, University of Victoria, Victoria, BC V8W 3V6, Canada.
V.R.N. Munasinghe and J.E.T. Corrie.[3] National Institute for Medical Research, The Ridgeway, Mill Hill, London, NW7 1AA, U.K.

[1]This article is part of a Special Issue dedicated to Professor Ed Piers.
[2]Corresponding author (e-mail: pwan@uvic.ca).
[3]Corresponding author (e-mail: jcorrie@nimr.mrc.ac.uk).

 doi: 10.1139/V03-184

vertu de la grande longueur d'onde de l'absorption du chromophore du naphtalène.

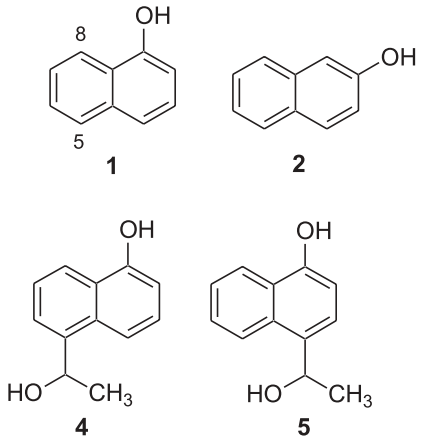
Mots clés : photosolvolyse, transfert intramoléculaire de proton dans l'état excité, méthide de quinone, photoélimination, photoprotonation.

[Traduit par la Rédaction]

Introduction

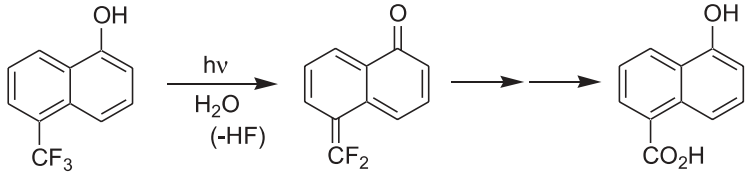
Quinone methides are reactive intermediates of general interest in organic chemistry (1–3). Recent studies from our laboratory (1, 2, 4, 5) have demonstrated that suitably designed simple phenol derivatives give rise to quinone methide-type intermediates efficiently on photolysis in aqueous solution. The substrates that we have investigated so far all possess a phenol and a benzylic-type alcohol or styryl moiety. The enhanced acidity of the phenol moiety in S_1 in these systems is essential for reaction, as previously described (1, 2, 4, 5). We have not investigated simple naphthol derivatives extensively except in some biaryl systems containing a 2-naphthol chromophore, where the quinone methides photogenerated are of the biaryl type (6).

Some time ago, Seiler and Wirz (7) reported the photohydrolysis (to the corresponding carboxylic acids) of a variety of trifluoromethyl-substituted 1-and 2-naphthols (as well as several phenols) and invoked the initial formation of naphthoquinone and quinone methides in their photohydrolysis mechanism (e.g., eq. [1]). Webb et al. (8) have reported a detailed study of the excited-state proton transfer dynamics of 1-naphthol (**1**) and have shown that it is a much stronger acid (in S_1) than 2-naphthol (**2**) (pK_a* values of 0.4 and 2.8, respectively). Moreover, it was shown that the 5- and 8-positions of **1** are much more basic in S_1, as evidenced by deuterium incorporation at these positions when **1** was irradiated in *acidic* D_2O. The formation of two isomeric naphthoquinone methide intermediates was proposed to account for the photoexchange but whether such intermediates were formed via a water-mediated excited-state (formal) intramolecular proton transfer (ESIPT) (from the naphthol OH to the carbon 5- or 8-position) was not explicitly addressed. We have recently reported (9) the first explicit example of an ESIPT from a phenolic OH to an aromatic ring carbon (on the ring not containing the phenolic OH) in 2-phenylphenol (**3**) (eq. [2]). This result led us to investigate whether such a process could operate in the naphthols (**1** and **2**), since naphthols are formally made up of two benzene rings, one of them containing a phenol moiety. Also addressed is whether suitably designed 1-naphthol derivatives **4** and **5** will react in an analogous manner as reported by us (1) for the parent hydroxy-substituted benzyl alcohols with respect to naphthoquinone methide formation. Seiler and Wirz's earlier results (7) suggest that this would indeed be possible.

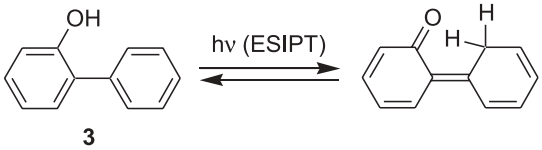


The photochemistry of phenols is also involved in the *p*-hydroxyphenacyl photodeprotection system reported by Givens and co-workers (10). An example designed to photorelease acetic acid from **6** is shown in eq. [3] (11). The essentials of the mechanism involve formation of a spiroketone intermediate **7** from photolysis of *p*-hydroxyphenacyl derivatives bearing good leaving groups, such as *p*-hydroxyphenacyl acetate **6**. Ring opening of **7** by water gives the observed product **8**. Release of the protected moiety (e.g., acetic acid from **6**) is believed to occur in the pri-

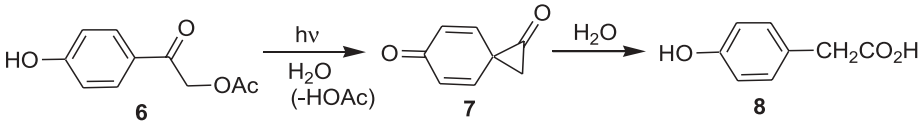
[1]



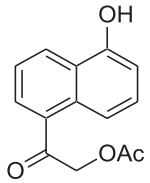
[2]



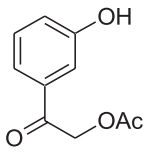
[3]



mary photochemical step. Although the question of triplet vs. singlet state reactivity (which might be dependent on the nature of the leaving group at the α-position) has been a topic of debate (10*c*, 11), the involvement of excited-state (singlet or triplet) deprotonation of the phenol moiety in the reaction sequence for formation of intermediate **7** seems likely. We felt that related substrates **9** and **10** might react similarly. The results of investigations of a variety of naphthols **1**,**2**,**4**, **5** and **9** (and phenol **10**) aimed at providing further insights to all of the above related photochemical reactions are reported herein.



9



10

Results and discussion

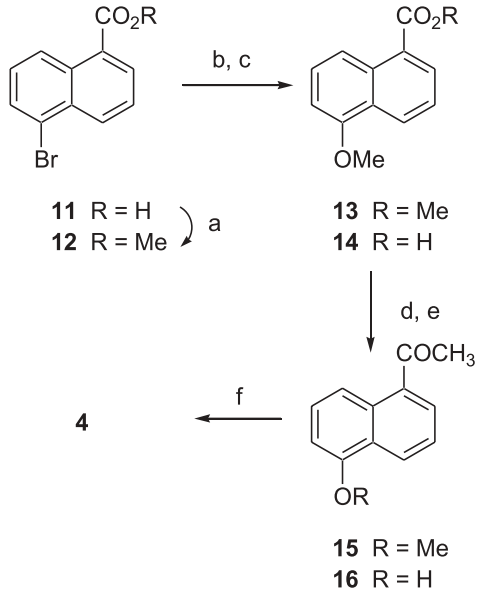
Materials

1- and 2-Naphthols (**1** and **2**) were purchased from Aldrich and were sublimed and recrystallized from hexanes prior to use. The hydroxyethylnaphthols **4** and **5** were synthesized as shown in Schemes 1 and 2. Although the corresponding hydroxyketones are both known compounds, the synthetic routes previously described were not particularly convenient or led to mixtures of regioisomers. The routes shown in the schemes were straightforward but, particularly for the 5-isomer, were only reached after some exploration of other published methods. For synthesis of the 5-isomer **4** (Scheme 1), the readily prepared 5-bromo-1-naphthoic acid **11** (12) was esterified and the 5-bromo group was displaced with methoxide in a copper(I)-catalyzed procedure (13). Further steps to the phenolic ketone **16** and its subsequent reduction readily gave the alcohol **4**. Note however that the work up procedure for the thiophenoxide-mediated demethylation of the methyl ether **15** (and of **17** in the route to the 4-hydroxy compound **5**), which used a literature procedure (14), was modified by addition of hydrogen peroxide to oxidize excess thiophenol, thereby minimizing the odour associated with the procedure. The route to the 4-isomer **5** (Scheme 2) requires no further comment, except to note that direct borohydride reduction of the phenolic ketone **18** gave only dark, uncharacterized material and it was found necessary to protect the phenol as its TBDMS ether **19** during this step. No attempts were made in this study at synthesizing derivatives of **1** with substituents at the 8-position, although these compounds would indeed be worthwhile to investigate in the future. The naphthacyl acetate **9** was prepared as shown in Scheme 3 and the 3-hydroxyphenacyl acetate **10** was made by a route similar to those for the corresponding 4-hydroxy esters previously described (11).

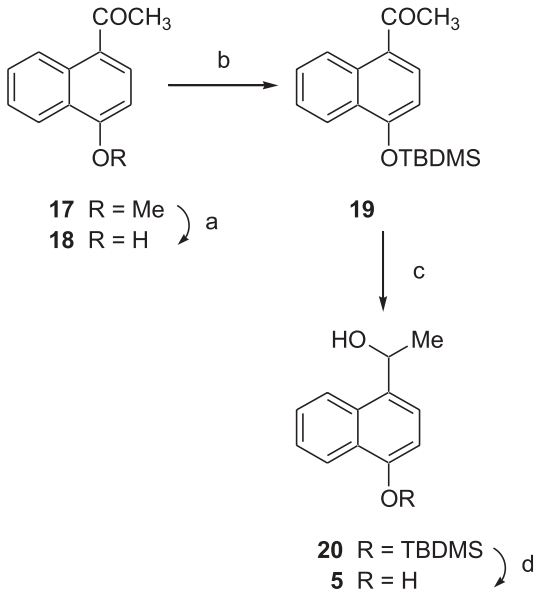
Deuterium exchange studies of 1 and 2

As noted in the *Introduction*, Webb et al. (8) have shown that 1-naphthol (**1**) is considerably more acidic than 2-naphthol (**2**) in S_1, due to the enhanced (localized) charge transfer character available for **1** but not for **2**, the latter

Scheme 1. Reagents: (*a*) MeOH, H_2SO_4, 74%; (*b*) NaOMe, CuBr, MeOH, 70%; (*c*) NaOH, MeOH–H_2O, 85%; (*d*) MeLi, THF–Et_2O, 78%; (*e*) PhSH, K_2CO_3, *N*-methylpyrrolidinone, 72%; (*f*) $NaBH_4$, EtOH, 55%.



Scheme 2. Reagents: (*a*) PhSH, K_2CO_3, *N*-methylpyrrolidinone, 59%; (*b*) TBDMS-Cl, imidazole, DMF, 80%; (*c*) $NaBH_4$, MeOH, 89%; (*d*) TBAF, THF, 88%.



compound having a more diffuse excited state electronic distribution. Moreover, charge transfer from the oxygen to the ring is localized at the 5- and 8-positions of **1**. To demonstrate the enhancement of basicity at these positions of **1**, they irradiated **1** in *acidic* D_2O–CH_3CN and showed that positions 5 and 8 were efficiently exchanged ($\Phi = 0.11$ in 99% D_2O, pD 3; Table 1) while similar irradiation of **2** resulted in no exchange. Photolysis in acidic solution raises the possibility that the exchange may be due to photoprotonation of **1** by hydronium ion, a process that is well known for 1-

Scheme 3. Reagents: (*a*) oxalyl chloride, DMF, CH_2Cl_2, 100%; (*b*) $TMSCHN_2$, CH_2Cl_2–THF–Et_3N, 74%; (*c*) aq. NH_3, THF–MeOH, 47%; (*d*) HCl, HOAc, 82%; (*e*) HOAc, DBU, toluene, 67%.

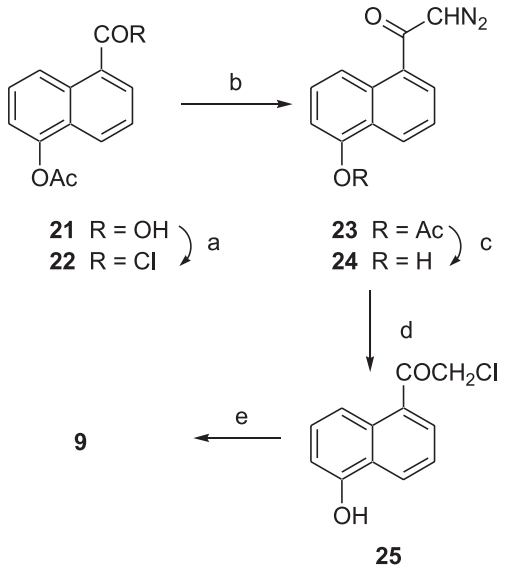


Table 1. Photophysical and photochemical parameters.

Compound	Φ_R	Φ_f[a]	τ[b] (ns)
1	0.11±0.05[c]	0.20 (0.174)	(10.6)
2	<0.001[c]	(0.27)	(13.3)
4	0.84[d]	0.17	5.4
5	<0.001[d]	0.23	5.9

[a]Fluorescence emission quantum yield in neat CH_3CN. Measured relative to the reported fluorescence quantum yield for 1-naphthol in cyclohexane (Φ_f = 0.174) (15) with correction to account for differences in the indices of refraction of the different solvents. Estimated error of ±10% of quoted value. Values in brackets are the fluorescence quantum yields in cyclohexane, from ref 15.

[b]Fluorescence lifetime in neat CH_3CN measured by single photon counting. Lifetimes measured in this way have an estimated error of ±0.2 ns. Values in brackets are the fluorescence lifetimes in cyclohexane from ref. 15.

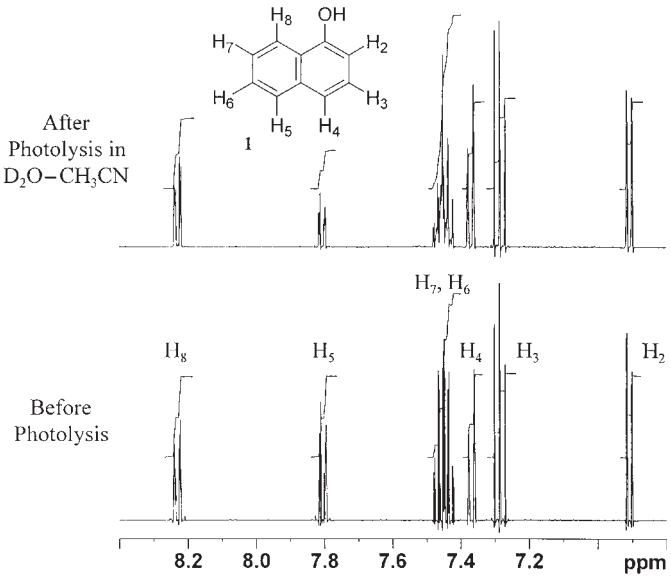
[c]Quantum yield of total deuterium exchange (of all ring positions) in 99% D_2O (pD 3) from ref. 8.

[d]Quantum yield of photomethanolysis in H_2O–CH_3OH (1:1). Estimated error ±10% of quoted value. Measured relative to the quantum yield for photomethanolysis of *o*-hydroxybenzhydrol in the same solvent (5).

methoxynaphthalene (16) and other aromatic compounds (17–19), but does not occur for 2-methoxynaphthalene (16). Therefore, we decided to study photochemical deuterium incorporation of **1** and **2** in aqueous solution, initially under neutral conditions and then over a wide pH range and as a function of water content. To our knowledge, this kind of study has not been previously reported for the naphthols. A similar study for **3** (eq. [2]) (9) resulted in the discovery of a new type of ESIPT (vide infra).

Irradiations of **1** and **2** were carried out in 1:1 D_2O–CH_3CN (~10^{-3} mol L^{-1}, pD 7, Rayonet photochemical reactor, 300 nm lamps, <30 min). Irradiation of **1** for 20 min resulted in efficient incorporation of deuterium at positions 5 (55%) and 8 (20%) to give **1-5D** and **1-8D**, respectively (eq. [4]). This was readily evident by examination of

Fig. 1. 500 MHz ^{1}H NMR spectra of **1** before (bottom), and after (top) 20 min irradiation at 300 nm in D_2O–CH_3CN (1:1), showing decreases in the integrated area of the peaks at 7.80 and 8.22 ppm assigned to ring protons at the 5- and 8-positions, respectively.

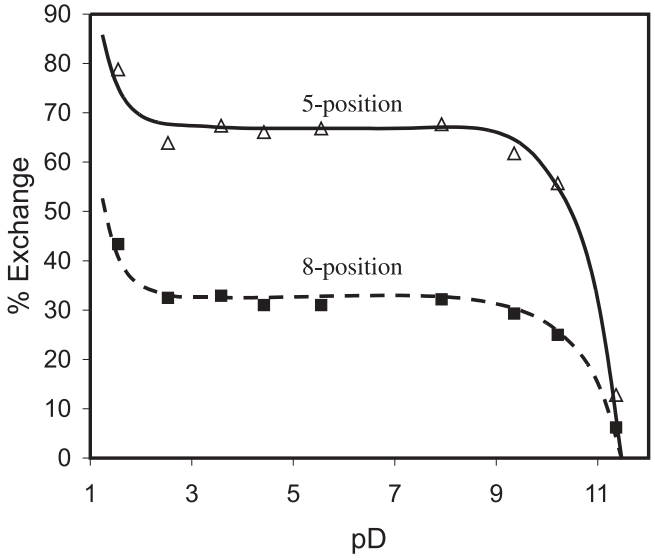


[4] **1** $\xrightarrow[D_2O-CH_3CN]{h\nu}$ **1-5D** + **1-8D**

500 MHz ^{1}H NMR spectra (Fig. 1); the areas of the peaks assigned to protons at the 5- and 8-positions (7.81 and 8.23 ppm, respectively) decreased smoothly with irradiation. The two overlapping triplets at 7.47 and 7.45 ppm assigned to the protons at the 6- and 7- ring positions exhibited changes consistent with diminished coupling to the adjacent protons at the 5- and 8-positions as they are replaced with deuterium. MS analysis of the photolyzed sample indicated an isotope distribution of 37% nondeuterated, 52% monodeuterated, and 11% dideuterated 1-naphthol, consistent with the overall deuterium incorporation measured by NMR. The observation of deuterium incorporation in neutral solution suggests that protonation by acid (D_3O^+) is not responsible for the observed reaction, and that the exchange might be due to an ESIPT process. Formation of **1-5D** and **1-8D** from an ESIPT to the 5- and 8-positions would necessarily proceed via quinone methides **26a-D** and **26b-D**, which have been previously proposed by Webb et al. (8). 2-Naphthol (**2**) did not undergo any observable exchange, even on prolonged irradiation, and the compound was completely recovered.

To better our understanding of the effect of acid on the deuterium incorporation reaction of **1**, photolyses were carried out in which the pD of the aqueous portion was varied over the pD range 1.5–11.4 (Fig. 2). While acid catalysis is observed at pD < 2.5, exchange efficiency was essentially constant from pD 2.5 through to pD 9. Since the hydronium ion concentration varies by many orders of magnitude over

Fig. 2. Plot of % deuterium exchange at the 5- (triangles) and 8- (squares) positions vs. pD (in D_2O–CH_3CN (1:1)) for **1**. Solutions (20 mg substrate in 40 mL solution) were irradiated at 254 nm (16 lamps) for 15 min.



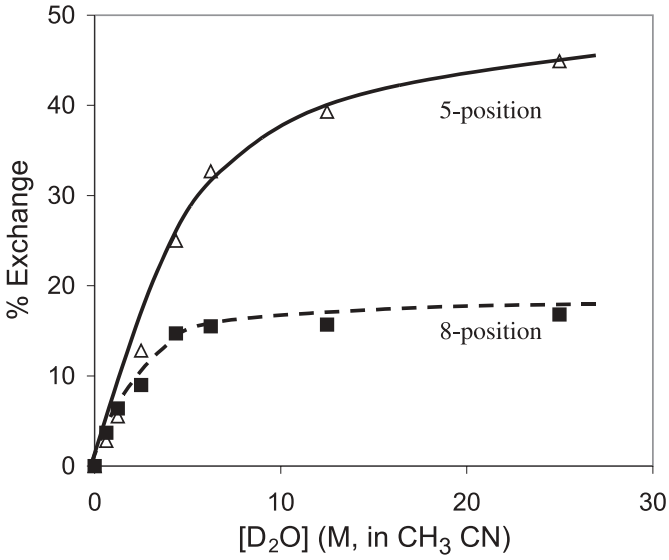
this pH range, it is very unlikely that the deuterium incorporation observed within this range results from protonation by D_3O^+ present in solution. The exchange efficiency decreases above pD 9, which corresponds with the ground state pK_a of **1** (pK_a = 9.2 (8)), indicating that the deprotonated form $\mathbf{1}^-$ does not undergo exchange. Consistent with this, no exchange was observed at high pD. This result rules out a stepwise mechanism in which **1** first undergoes excited-state proton transfer (ESPT) to give excited phenolate ($\mathbf{1}^-$*) that is protonated by D_2O in a subsequent step, since every excitation of $\mathbf{1}^-$ would necessarily lead to an excited phenolate. It is apparent that the naphthol OH is required for reaction, suggesting that an ESIPT might be taking place.

To investigate the role of solvent water in the ESIPT reaction of **1**, photolyses were performed in which the concentration of D_2O (in CH_3CN cosolvent) was varied (Fig. 3). The deuterium exchange efficiency for **1** was negligible at low D_2O concentrations, but increased dramatically as more D_2O was added. The enhancement of reaction efficiency appeared to reach saturation at about 1:1 D_2O–CH_3CN. The need for water to mediate the proton transfer indicates that the ESIPT is not intrinsic, in contrast to the ESIPT observed for **3**. This is probably because the distance between the acidic proton and both basic carbons is too large to allow ground state hydrogen bonding interactions, which are thought to be a prerequisite for intrinsic ESIPTs (9*b*). The efficiency for exchange at the 8-position plateaus at lower water concentrations than does exchange at the 5-position. This could be because the OH functionality is much closer to the 8-position, so less water is required to mediate the proton transfer.

Photodehydroxylation and photodehydration of 4 and 5

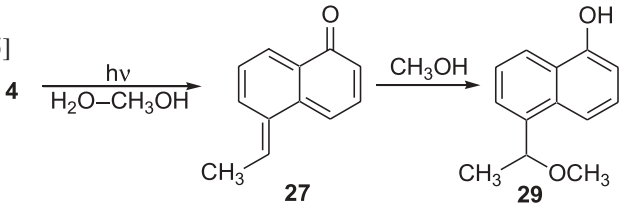
We have previously shown that the photolysis of phenols containing benzylic alcohol groups gives rise to *ortho*-, *meta*-, and *para*-quinone methides in high yield (1). In an attempt

Fig. 3. Plot of % deuterium exchange at 5- (triangles) and 8- (squares) positions vs. D_2O content (pD 7).



to apply this strategy to naphthoquinone methide generation, derivatives **4** and **5** were studied. The naphthoquinone methides produced by net photodehydration of **4** or **5** (**27** and **28**, respectively) were not expected to be sufficiently stable to isolate, so we instead sought to obtain indirect evidence of their presence by isolating their photosubstitution products arising from nucleophilic attack. For example, in methanol–water solutions, the expected photoproduct from **4** is methyl ether **29** (eq. [5]). Although formation of **29** is

[5]



consistent with the presence of **27** as an intermediate, reaction through a cationic intermediate would give the same product and cannot be excluded on the basis of product studies alone.

Irradiation of **4** in 1:1 H_2O–CH_3OH (~10^{-3} mol L^{-1}, Rayonet photochemical reactor, 300 nm lamps, 1 min) did indeed give **29** in 48% yield (eq. [5]), while solutions kept in the dark did not react. The photosubstitution is clean and has a remarkably high quantum yield for production of **29** from **4**, measured to be 0.84 ± 0.04 (Table 1). This value represents the highest reported quantum yield to date for photomethanolysis of benzyl alcohol derivatives. The high quantum yield for formation of **29** implies that attack by water on **27** to regenerate starting material must be very inefficient. This is in line with the known high nucleophilicity of methanol relative to that of water (20). Pure samples of **29** were obtained by chromatographic separation of the photolysate, and photolysis of these samples in 1:1 aqueous acetonitrile regenerated **4**. The methyl ether product can therefore also undergo photosubstitution, presumably through formal

loss of methanol to regenerate **27**. This result shows that ether and ester derivatives of **4** might prove useful as protecting groups for photorelease of alcohols and acids.

Results from the deuterium incorporation studies of **1** show that electron density in singlet excited 1-naphthols is primarily localized at the 5-position, and to a lesser extent at the 8-position. Naphthols **4** and **29** both react through the substituent located at the 5-position. In contrast to these examples, the substituent in **5** is located at the 4-position. No deuterium was incorporated at this position on irradiation of **1**, indicating that minimal charge is transferred to this position on excitation. When **5** was irradiated under similar conditions as **4**, no reaction was observed, showing that photodehydroxylation requires excited state charge transfer from the naphthol OH.

Photochemical studies of 9 and 10

The proposed mechanism for the photosolvolytic rearrangement of **6** (11) that leads to the release of acetic acid appears to require either ESPT to solvent water or an ESIPT from the phenol to the carbonyl oxygen mediated by water, to generate a reactive excited phenolate or a related enol species, respectively, prior to formation of spiroketone **7**. It was of interest to determine whether derivatives such as naphthol **9** and phenol **10** would show similar photosolvolysis. Since the parent 1-naphthol (**1**) has already been shown to undergo a water-mediated ESIPT to the 5- and 8-positions, it seemed reasonable to expect that a similar process could operate in **9**, with the difference that the proton transfer would end up at the carbonyl oxygen. This could activate the compound for release of acetic acid in a manner similar to the reactivity observed for **6**. In the case of phenol **10**, it is well known that there is substantial charge transfer through meta-positions on the benzene ring in S_1 that allows efficient formation of *m*-quinone methides (1, 2, 5). Such charge transfer would be expected to enhance ESIPT from the phenol to the carbonyl moiety of **10**, resulting in a reaction similar to that observed for **6**. To our surprise, both **9** and **10** were found to be completely unreactive in 1:1 H_2O–CH_3CN even on extended irradiation. Complete recovery of the substrates was achieved in all cases. What was surprising was the lack of photodecomposition even on extended photolysis, which leads us to suggest that ESPT or ESIPT processes are occurring for these compounds, but lead to no net chemistry. In the case of **10**, subsequent formation of the non-Kekulé spiroketone intermediate seems to be prohibitive as it would be a ground-state species. For **9**, formation of the requisite spiroketone would seem possible but on closer examination, such a reaction would result in loss of two aromatic rings *and* formation of a strained spiroketone. Moreover, the excited singlet or triplet energy of **9** (a 5-hydroxy-1-acetylnaphthalene) is expected to be substantially lower than that of **6** (a 4-hydroxyacetophenone). One of these factors probably explains the lack of reaction of **9**. No further studies of **9** and **10** were pursued due to their photoinertness in aqueous solution.

Fluorescence measurements

As the ESIPT reaction of **1** is strongly mediated by water, the fluorescence behaviour with respect to water concentration was studied to provide mechanistic insights. If the ESIPT reaction occurs from S_1, as do most ESPTs from phenols, addition of water to the solvent mixture should lead to quenching of the fluorescence intensity by enhancing the proton transfer pathways. Indeed, the fluorescence emission of **1** (in CH_3CN), after an initial red shift from λ_{max} 340 nm to λ_{max} 355 nm on addition of small amounts of water, was progressively quenched by added water, concomitant with a growth in fluorescence intensity at 460 nm. In pure water, the 355 nm band was completely quenched and only emission from the 460 nm band was observed. The band at 460 nm results from emission from the excited 1-naphtholate ion (**1**$^-$), which arises from ESPT from the OH proton of **1** to solvent (water), and is consistent with the previous assignment (8). Relatively large amounts of water were required for efficient formation of **1**$^-$, just as the ESIPT of **1** to give **1-5D** and **1-8D** required large amounts of D_2O. This correlation is not surprising as the two processes are closely related. Thus, quenching of the fluorescence emission of **1** in the presence of water arises from a combination of two competing pathways from S_1, namely ESPT to solvent water and water-mediated ESIPT to the 5- and 8-positions.

The fluorescence behaviour of **5** closely resembled that of **1**. Small amounts of water led to an initial red shift of the fluorescence emission band from λ_{max} 358 nm in neat CH_3CN to λ_{max} 375 nm (Fig. 4). Larger amounts of water led to quenching of this fluorescence band and to a growth in emission at 465 nm (from naphtholate ion **5**$^-$). This information suggests that there are no major pathways that deactivate the singlet excited state of **5** other than those available for **1**.

The fluorescence behaviour of **4** is quite different from that observed for **1** and **5**. Small amounts of water led to a red shift of the fluorescence emission band from λ_{max} 345 nm in neat CH_3CN to λ_{max} 360 nm, though significant quenching of this band was achieved with less water than required for **1** or **5** (Fig. 5). Naphtholate (**4**$^-$) emission (λ_{max} 460 nm) was observed only at high water concentrations and was much weaker than the observed emission of **1**$^-$ or **5**$^-$. Modified Stern–Volmer quenching plots of the emission intensity of **4** and **5** with added water are shown in Fig. 6. The enhanced quenching by water for **4** relative to **5** can be clearly seen. Since the pK_a values for **1**, **4**, and **5** are expected to be approximately equivalent, an additional water-dependent deactivation pathway must be operating for **4**. The net dehydration reaction to give **27** that is available for **4** but not for **1** or **5** can explain this additional quenching if deprotonation of the naphthol and dehydroxylation of the benzylic alcohol are concerted from S_1. This pathway would also compete with ESPT to solvent, explaining the weaker phenolate emission observed. Both Stern–Volmer plots exhibit a squared dependence on water concentration. Our group has previously reported nonlinear fluorescence quenching by water for related phenols, an effect attributable to involvement of water clusters in the ESPT (4).

Fluorescence quantum yields and lifetimes were measured for **4** and **5** in CH_3CN and are listed in Table 1, along with literature values for **1** and **2**. Both **4** and **5** exhibit similar photophysical behaviour to **1** in CH_3CN, indicating that no

Fig. 4. Representative fluorescence quenching traces of **5** by added water in CH_3CN (λ_{ex} 300 nm). Water concentrations are given in the legend. Naphtholate (**5**$^-$) emission grows in at λ_{em} 460 nm with increasing water content.

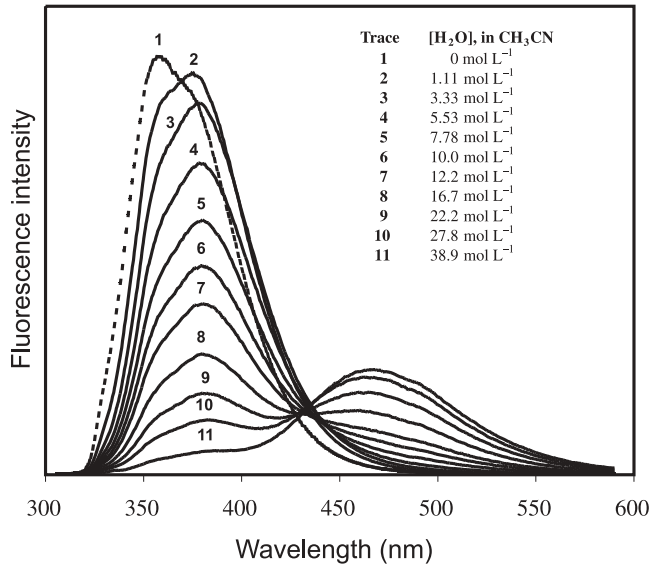
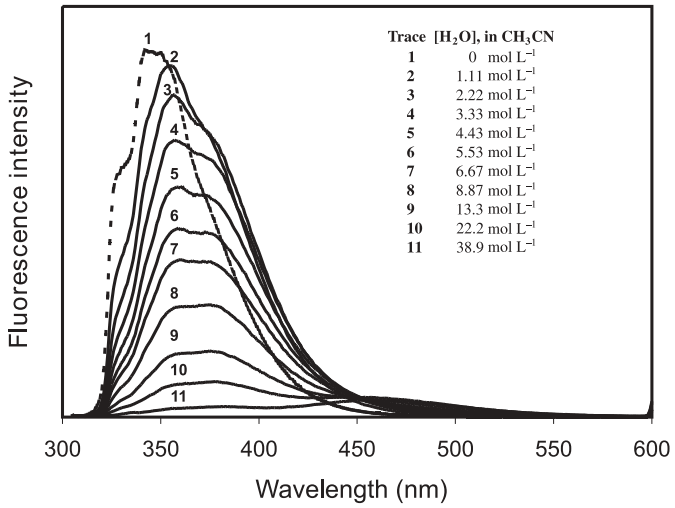


Fig. 5. Representative fluorescence quenching traces of **4** by added water in CH_3CN (λ_{ex} 300 nm). Water concentrations are given in the legend. Naphtholate (**4**$^-$) emission grows in at λ_{em} 465 nm with increasing water content.



major deactivation pathways open up on addition of the hydroxyethyl substituent to the 1-naphthol chromophore except when water is present.

Laser flash photolysis (LFP)

LFP experiments were performed for **1**, **4**, and **5** to gain direct evidence of the suspected naphthoquinone methide intermediates. The resulting data are summarized in Table 2. Mathivanan et al. (19*b*) previously studied 1-methoxynaphthalene by LFP in hexafluoroisopropyl alcohol (HFIP) and observed a transient with a broad absorption band at λ_{max} 550 nm and a second, more narrow band at

Fig. 6. Stern–Volmer plots for steady-state fluorescence quenching of **4** (triangles) and **5** (diamonds) by H_2O (in CH_3CN). The lines drawn are fits to $I_0/I = 1 + K_{SV}[H_2O]^2$.

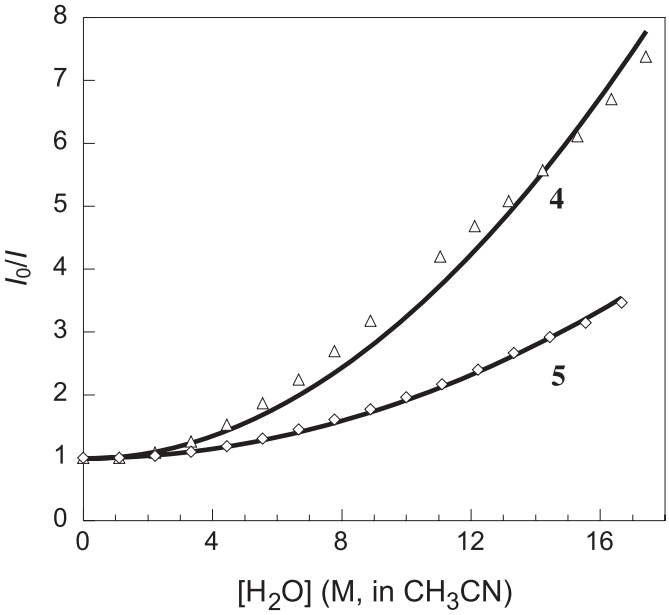


Table 2. Summary of laser flash photolysis transient data.[a]

Transient	λ_{max}[b] (nm)	τ[c] (μs)	k_q[d] (10^6 M^{-1} s^{-1})
26a	350, 530	17	0.90±0.10
27	410, 700	33	1.0±0.1
32	410, 700	1.7	>>50[e]
33	350, 530	45	Not determined

[a]LFP was performed on flowing solutions that were ~10^{-5} mol L^{-1} in the appropriate substrate. Excitation was achieved with an excimer laser (308 nm, ~ 10 ns, <30 mJ/pulse).

[b]Absorption maxima in H_2O–CH_3CN (1:1) solution.

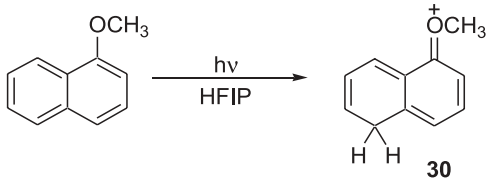
[c]Transient lifetime in H_2O–CH_3CN (1:1) solution, oxygen purged. The estimated error is ±10% of the reported value.

[d]Bimolecular quenching rate constant with added ethanolamine in H_2O–CH_3CN (1:1) solution, according to the following equation: $k_{obs} = k_0 + k_q[Q]$.

[e]Complete quenching was observed with 5.5 mol L^{-1} ethanolamine. Transients with lifetimes as short as 20 ns are readily detectable on the system used, so for complete quenching to be realized with 5.5 mol L^{-1} quencher, k_q must be at least 5×10^7 M^{-1} s^{-1}, and is probably at least an order of magnitude higher.

λ_{max} 360 nm, both of which were assigned to cation **30** obtained via photoprotonation (from HFIP) of 1-methoxynaphthalene at the 5-position (eq. [6]). This tran-

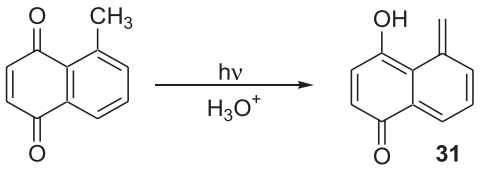
[6]



30

sient could not be detected in aqueous acid, which the authors proposed was because rapid reaction with water reduced the lifetime of the cation to a value shorter than their system could detect. This intermediate bears structural

resemblance to suspected naphthoquinone methide **26a** resulting from ESIPT to the 5-position in **1**. Chiang et al. (21) observed naphthoquinone methide **31** by LFP in dilute aqueous acid solution (generated by γ-hydrogen abstraction in 5-methyl-1,4-naphthoquinone (eq. [7])). This transient had a broad visible absorption band at λ_{max} 600 nm with a lifetime

[7] 

of ≈1 μs (lifetime shortened as pH was decreased), and is structurally related to **27** produced on photodehydration of **4**.

Nanosecond LFP of **1** in 1:1 H_2O–CH_3CN (O_2 saturated) resulted in the formation of a transient with a broad absorption band at 530 nm and a second, more narrow band at 340 nm (Fig. 7). Both peaks appeared immediately after the laser pulse (≈10 ns) and decayed to baseline. The decay kinetics of both peaks fit a monoexponential curve, giving a lifetime of 16 ± 2 μs. This transient spectrum is very similar to that assigned to **30** (19*b*), though blue-shifted by about 20 nm. We assign this absorption to be **26a** formed on ESIPT of **1**. The observed lifetime of 16 ± 2 μs in aqueous solution indicates that this transient is much less reactive with water than **30**, which is expected because of the greater electrophilic nature of **30**. Naphthoquinone methide **26b** is non-Kekulé and is expected to decay within the time of the laser pulse (10 ns). LFP of **1** in neat CH_3CN (O_2 purged) led to formation of a weaker transient (Fig. 7) with a broad visible band (λ_{max} 510 nm) and narrower bands with λ_{max} 390 and 350 nm. We assign this transient to the 1-naphthoxy radical based on the similarity of the observed absorption spectrum to that known for this species (22).

Nanosecond LFP of **4** in 1:1 H_2O-CH_3CN (O_2 saturated) resulted in the formation of a strongly absorbing transient immediately after the laser pulse, with peaks at 410 and 700 nm (Fig. 8). The decay kinetics gave a biexponential fit with a short-lived minor component (τ = 1.5 ± 0.5 μs) and a longer lived major component (τ = 34 ± 2 μs) that both decayed cleanly to baseline. This biphasic decay was observed at all wavelengths, demonstrating that the two decaying species have similar absorbance profiles. The position of the bands is consistent with what is expected for **27**: the red shift relative to **26a** results from the extra unit of conjugation and the extra methyl substituent. The long-wavelength band is similar to that reported for related naphthoquinone methide **31** by Chiang et al. (21). The major (long-lived) component of the observed absorption is assigned to **27** on this basis and on the results of the product studies. The shorter lived species can be assigned to cation **32** that would result from dehydroxylation without prior deprotonation of the phenol, a process well known for methoxy-substituted benzyl alcohols. This cation possesses a similar degree of conjugation as **27**, which would explain its similar absorbance characteristics. Its much shorter lifetime is consistent with the expected enhanced reactivity of a charged species relative to a neutral and closed-shell naphthoquinone methide. No strong transients were observed on LFP of **4** in neat CH_3CN (O_2 purged) in the absence of water. Instead, a weak transient was observed with a broad band at 580 nm, and with narrower bands at 400 and 350 nm (Fig. 8). This species closely resembles the transient observed for **1** in neat CH_3CN in the position, structure, and intensity of the absorption bands. This transient is therefore assigned to the 1-naphthoxy radical of **4**.

A strong transient was also observed on LFP of **5** (in H_2O–CH_3CN (1:1)), which exhibited a broad absorption

Fig. 7. Transient absorption observed on LFP of **1** in H_2O–CH_3CN (1:1) (triangles) and in neat CH_3CN (diamonds) (λ_{ex} 308 nm, O_2 purged for both). For both spectra, the decay trace was taken immediately after the laser pulse (~10 ns).

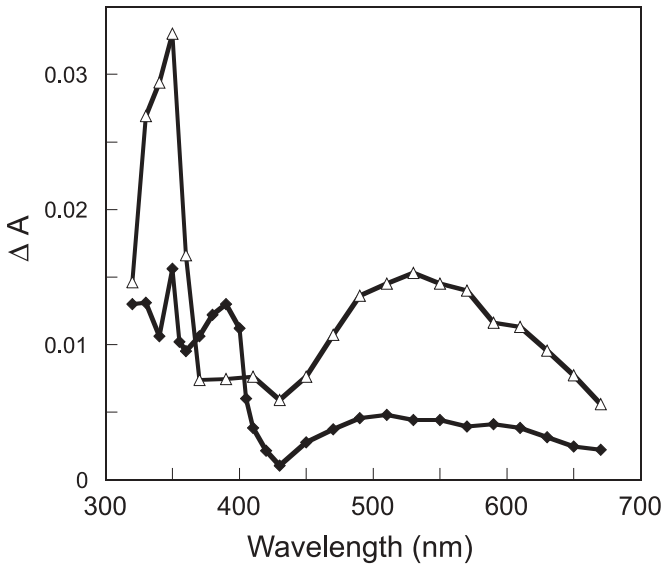
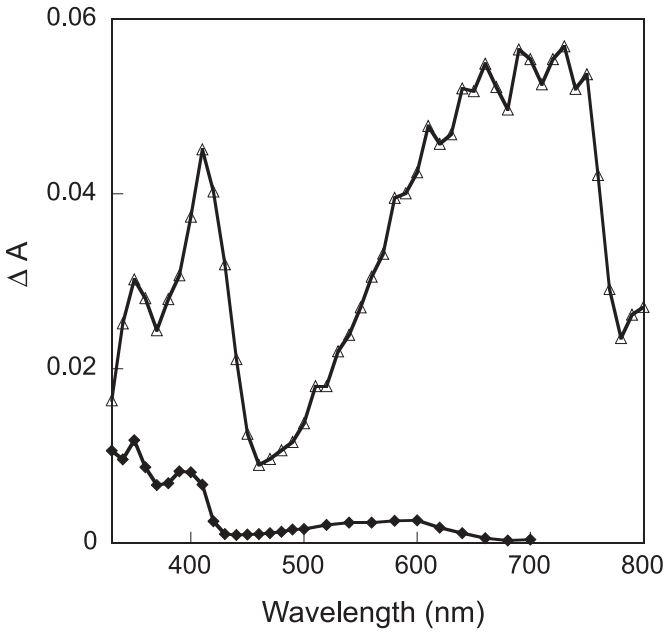


Fig. 8. Transient absorption observed on LFP of **5** in H_2O–CH_3CN (1:1) (triangles) and in neat CH_3CN (diamonds) (λ_{ex} = 308 nm, O_2 purged for both). The decay traces were taken immediately after the laser pulse (~10 ns).



band at 520 nm, a small band at 410 nm, and a strong narrow band at 350 nm. Again, all peaks displayed first-order decay kinetics, each with the same lifetime of 45 ± 2 μs. Product studies showed that **5** does not undergo photosubstitution; therefore, this transient is unlikely to be **28**. Nevertheless, the spectrum closely resembles that assigned to **26a**. Indeed, **5** should be able to form a similar naphthoquinone methide resulting from ESIPT to the 5-position of the naphthol ring. On this basis, we assign this absorption to naphthoquinone methide **33**. The enhanced lifetime of **33** relative to **26a** is probably due to steric shielding of the 5-position by the hydroxyethyl substituent that retards deprotonation at this site. LFP of **5** in neat CH_3CN shows formation of small amounts of the corresponding 1-naphthoxy radical.

Additional support for our assignment of the major transients observed for **1** and **4** as naphthoquinone methides was sought through quenching studies. We have recently shown (23) that ethanolamine can efficiently quench quinone methide intermediates. For **27** (or cation **32**), the expected quenching mechanism is nucleophilic attack at the benzylic position to furnish the ethanolamine adduct, while for quinone methide **26a**, the expected quenching mechanism is base-catalyzed tautomerization. Quenching analyses were first performed for the transients arising from LFP of **4** (Fig. 9). At the smallest ethanolamine concentration used (5.5 mM in H_2O–CH_3CN (1:1)), the short-lived component of the decay (assigned to **32**) was completely quenched, leaving only the longer lived component (assigned to **27**). As carbocations are known to react very rapidly with added nucleophiles, this observation supports our assignment of the short-lived component to **32**. The dynamic quenching of quinone methide **27** with added ethanolamine is plotted in Fig. 9 and a linear correlation was observed, giving a bimolecular quenching rate constant of $1.0 \pm 0.1 \times 10^6$ M^{-1} s^{-1}. A similar quenching analysis was performed for the transient formed on LFP of **1** (assigned to **26a**), and results are presented in Fig. 10. The decay of this transient was also accelerated with added ethanolamine, giving a good linear fit with k_q at $9.0 \pm 1.0 \times 10^5$ M^{-1} s^{-1}.

Fig. 9. Quenching plot showing the increase in the decay rate of **27** at 680 nm with added ethanolamine in H_2O–CH_3CN (1:1). Line is the least-squares fit to the data and gives $k_q = 1.0 \times 10^6$ M^{-1} s^{-1}. Estimated error is ±10%.

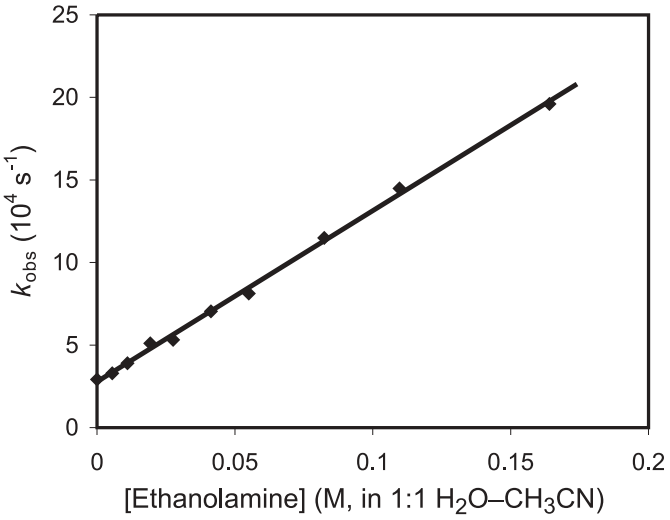
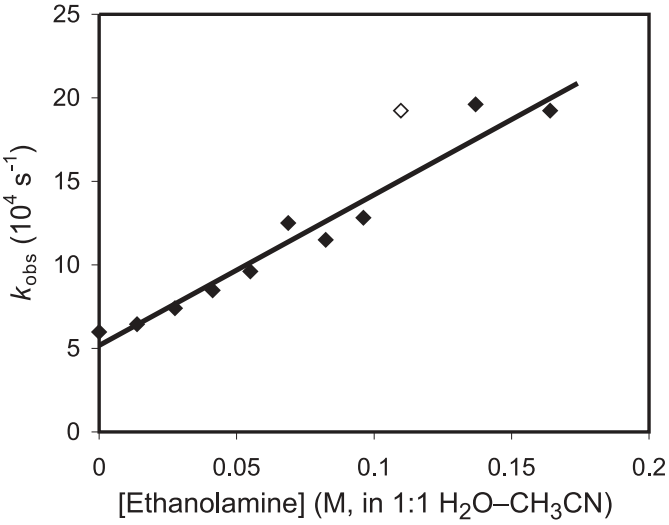


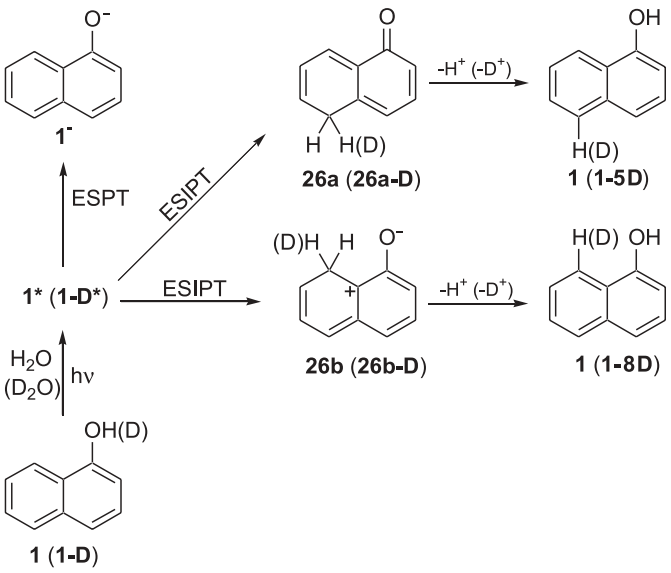
Fig. 10. Quenching plot showing the increase in the decay rate of **26a** at 530 nm with added ethanolamine in H_2O–CH_3CN (1:1). Line is the least-squares fit to the data and gives $k_q = 9.0 \times 10^5$ M^{-1} s^{-1}. Estimated error is ±15%. Outlined point was not included in the least-squares analysis.



Mechanisms of reaction

The deuterium incorporation reaction of **1** on photolysis in D_2O–CH_3CN (1:1) is proposed to occur via a water-mediated ESIPT from the naphthol OH to the aromatic ring carbons at the 5- and 8-positions, to give naphthoquinone methide intermediates **26a** and **26b**, respectively, (Scheme 4). The enhanced acidity of the naphthol OH in the excited state ($pK_a^* = 0.4$) and the enhanced excited-state basicity of the 5- and 8-positions of 1-alkoxy- and 1-hydroxy-substituted naphthalenes suggest that an intramolecular acid–base reaction might be possible. The propensity of **1** to undergo excited-state proton transfer reactions in aqueous conditions is further demonstrated in fluorescence studies, with emission from (**1**$^-$)* observed on photolysis of **1** in aqueous conditions. The protonation of the 5- and 8-positions in the pH range 2.5–9 does not result from electrophilic attack by H_3O^+ (or D_3O^+) since the exchange efficiency is independent of pH (pD) throughout this large pH range. Solvent water alone cannot be acting as the acid, since no exchange was observed for irradiated (basic) solutions of **1**$^-$. Under basic conditions, the naphthalene still has a powerful electron-donating group at the 1-position, and the concentration of water is still very high. It is thus evident that the reaction requires the OH functionality, suggesting that the reaction proceeds through ESIPT from the OH to the ring carbons. The need for water to mediate the proton transfer was clearly borne out by the product studies, with efficient reaction only being observed at fairly high water concentrations. This is because the OH group is too far from the basic sites to allow any direct spatial interaction, so water is needed to "solvate" the proton as it is transferred. We have previously implicated water as mediating ESIPTs between remote sites in other phenols (4). Direct evidence for

Scheme 4.

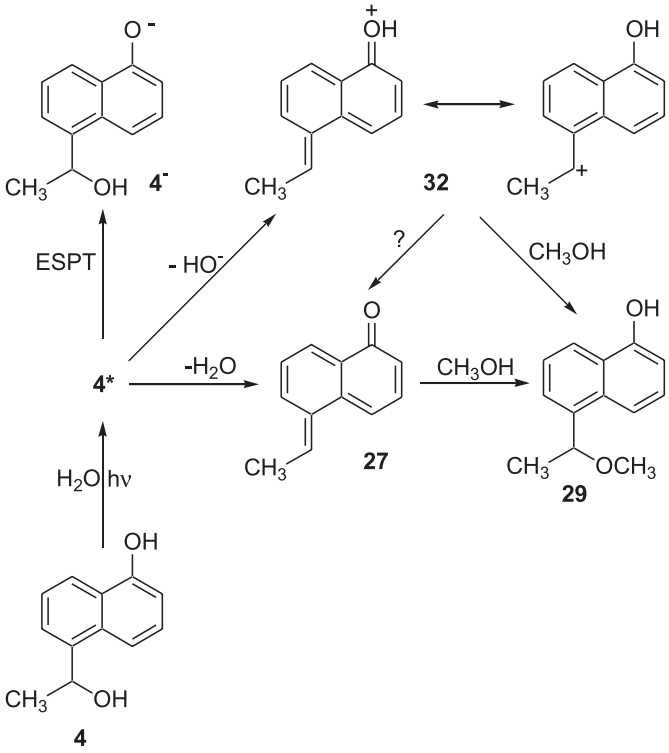


naphthoquinone methide intermediate **26a** that would arise from ESIPT to the 5-position was provided by LFP studies, lending further support to our mechanistic proposal.

An additional consideration of interest in the ESIPT of **1** is the possible presence of other intermediates prior to naphthoquinone methide formation. We recently reported an example of a simple hydroxybiaryl for which ESIPT to two aromatic carbon positions was observed (24). ESIPT to both positions was strongly water dependent, as is the ESIPT of **1** in the present work. Furthermore, the efficiency of exchange of the two positions had almost identical dependencies on water content, which is unlikely if the two routes are wholly independent. To account for this, we suggested that ESIPT first leads to a "proton – π complex", which can rearrange to either of the two possible quinone methides (24). The ESIPT in **1** appears not to occur through this route. Deuterium exchange efficiencies at the 5- and 8-positions appear to have different dependencies on water concentration, with exchange at the 8-position reaching saturation with less water than exchange at the 5-position. This observation favours a mechanistic picture where two separate ESIPTs are occuring that do not share a common intermediate prior to QM formation.

The photosubstitution reaction of **4** is mechanistically related to the ESIPT reaction of **1** in that it relies on excited-state charge transfer from the naphthol OH to the 5-position. The photochemical reactivity of **4** in aqueous solution can be explained as occuring through three different pathways (Scheme 5): (*i*) ESPT of the naphthol proton to solvent water to give $\mathbf{4}^{-}$; (*ii*) dehydroxylation of the benzylic alcohol moiety to give **32**; and (*iii*) photodehydration to form **27**. Evidence for the first pathway comes from the fluorescence studies: emission from $\mathbf{4}^{-*}$ was observed on excitation of **4** at high water concentrations, indicating that an adiabatic ESPT is occuring. As for the second pathway, a short-lived transient observed in LFP studies was assignable to the cation **32** that would result from simple dehydroxylation. Cation **32** might also undergo deprotonation to give **27**. The

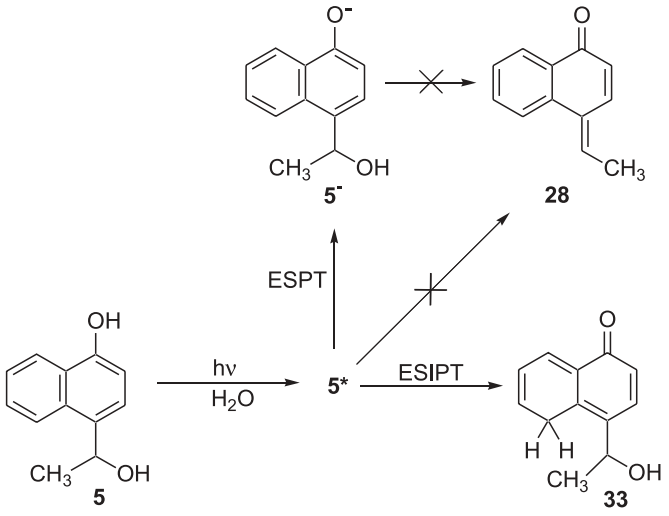
Scheme 5.



third and major pathway involves deprotonation of the naphthol OH concerted with dehydroxylation of the benzylic site to give **27** directly. The formation of the naphthoquinone methide intermediate **27** was inferred from the results of the product studies and the observation of a transient on LFP of **4** that was assignable to **27**. That the reaction to give **27** is concerted was inferred primarily from the fluorescence studies. The enhanced quenching of the fluoresence emission of **4** in aqueous solution by water over 1-naphthol derivatives **1** and **5** shows that an additional deactivation pathway is available for **4** that is not available for **1** or **5**, with this pathway being photodehydration to form **27**. If the ESPT to solvent preceded dehydroxylation of the benzylic alcohol, no enhanced quenching would be observed, since **1**, **4**, and **5** would be expected to have similar ESPT rates. The LFP quenching studies for **4** demonstrated that very small amounts of ethanolamine rapidly quenched the cation. If the cation was a precursor to **27**, the presence of ethanolamine would substantially reduce the amount of **27** that is observed, and that was not the case. Therefore, the only remaining option to explain the reactivity is via a concerted mechanism.

The reactivity of **5** (Scheme 6) is different from that of **4** in that no photosubstitution was observed in the product studies. Photodehydration to form naphthoquinone methide **28** therefore does not occur. The ESIPT in **1** and the photosubstitution reaction of **4** are both interpreted as arising from enhanced localized charge transfer from the naphtholic OH to the 5- and 8- ring positions. The failure of **5** to react through the 4-position confirms that this charge transfer is crucial for photodehydration. A strong transient was observed on LFP of **5** and was assigned to **33**, indicating that **5** reacts though an ESIPT pathway similar to that observed for

Scheme 6.



1. Despite containing a potentially reactive substituent at the 4-position, the chemistry is still dominated by the localized charge transfer to the 5- and 8-positions.

Experimental

General

^{1}H NMR spectra were obtained on Bruker AC300 (300 MHz), AM360 (360 MHz), AVANCE 500 (500 MHz), Varian AM400 (400 MHz), or JEOL FX90Q (90 MHz) instruments in $CDCl_3$ unless otherwise specified. Low-resolution mass spectra were obtained on a Finnigan 3300 (CI) and HR-MS were obtained on a Kratos Concept H (EI) instrument. UV–vis spectra were recorded on a Varian Cary 5 instrument. Acetonitrile (HPLC or spectral grade) used for fluorescence and LFP experiments was dried by distillation from calcium hydride. Organic extracts were dried over anhydrous magnesium sulfate and filtered. pD values were measured for the aqueous portion (prior to mixing with CH_3CN cosolvent) using a Fisher Accumet 915 pH meter and were not corrected for the deuterium isotope effect. Solutions were unbuffered with pD values adjusted with either NaOD (pD > 7) or D_2SO_4 (pD < 7).

Materials

5-(1-Hydroxyethyl)-1-naphthol (4)

A solution of 5-bromo-1-naphthoic acid **11** (12) (4.5 g, 17.9 mmol) and concentrated sulfuric acid (1.35 mL) in methanol (65 mL) was heated at reflux for 8 h, cooled, diluted with diethyl ether and washed with aqueous sodium hydrogen carbonate, water and brine, dried and evaporated under reduced pressure. The residue was crystallized from methanol to give methyl 5-bromo-1-naphthoate **12**. Yield: 3.5 g (74%); mp 66 to 67 °C (lit. (12) mp 66 to 67 °C).

A mixture of **12** (6.0 g, 22.6 mmol), CuBr (0.93 g, 6.5 mmol), ethyl acetate (1.77 mL, 18.1 mmol) and 25% sodium methoxide in methanol (Aldrich; 30.8 mL, 142.6 mmol) was heated under reflux for 3.5 h under nitrogen. The copper salts were filtered and the solid was washed with methanol. The combined filtrate was concentrated to about 5 mL, diluted with water and extracted with dichloromethane. The extracts were washed with brine, dried and evaporated, and crystallized from hexanes to give methyl 5-methoxy-1-naphthoate **13**. Yield 3.43 g (70%); mp 76–76.5 °C (lit. (25) mp 74.5–75.5 °C). This material (7.7 g) was saponified in aqueous methanolic sodium hydroxide to give 5-methoxy-1-naphthoic acid **14**. Yield: 6.1 g (85%); mp 225–227 °C (from ethanol) (lit. (26) mp 227–229 °C).

A solution of **14** (2.02 g, 10 mmol) stirred under nitrogen in anhyd THF (40 mL) was diluted with anhydrous diethyl ether (110 mL) and a 1.5 mol L^{-1} solution of methyl lithium in diethyl ether (16.7 mL, 25 mmol) was added over 20 min at room temperature. The mixture was stirred for 1.5 h and acetone (17 mL) was added. After 5 min, the solution was diluted with 2 mol L^{-1} aqueous hydrochloric acid and extracted with diethyl ether. The organic phase was washed with water, aqueous sodium hydrogen carbonate, water and brine, dried and evaporated under reduced pressure. The residue was crystallized from petroleum ether (bp 60–80 °C) to give 1-acetyl-5-methoxynaphthalene **15**. Yield: 1.56 g (78%), mp 85–87 °C (lit. (27) mp 88 to 89 °C).

Dry *N*-methyl-2-pyrrolidinone (10.5 mL) was added under nitrogen to a mixture of **15** (4.2 g, 21.0 mmol) and anhydrous potassium carbonate (0.145 g, 1.05 mmol) and the mixture was stirred for 5 min at room temperature. Thiophenol (3.23 mL, 31.5 mmol) was added and the mixture was heated at 190 °C for 45 min and cooled. Methanol (105 mL) and triethylamine (4.2 mL) were added, followed by 30% hydrogen peroxide (4.2 mL) in four equal portions over ~5 min. The solution was stirred for 10 min, then concentrated under vacuum to ~10 mL, diluted with 5% aqueous sodium hydroxide and extracted with diethyl ether. The aqueous layer was acidified to pH 2 with 6 mol L^{-1} hydrochloric acid and extracted with diethyl ether and the organic extract was washed with brine, dried and evaporated under reduced pressure. The residue was crystallized from EtOAc–hexanes to give 1-acetyl-5-hydroxynaphthalene **16** as pale yellow crystals. Yield: 2.82 g (72%); mp 173–174.5 °C (lit. (28) mp 172.5–173.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$ – 10% CD_3OD) δ: 2.74 (s, 3H, CH_3), 6.90 (d, J = 7.6 Hz, 1H, Ar-H), 7.40 (m, 1H, Ar-H), 7.47 (m, 1H, Ar-H), 7.92 (d, J = 7.1 Hz, 1H, Ar-H), 8.14 (d, J = 8.6 Hz, 1H, Ar-H), 8.49 (d, J = 8.6 Hz, 1H, Ar-H).

A solution of **16** (1.60 g, 8.60 mmol) in EtOH (59 mL) was stirred at 0 °C and sodium borohydride (0.57 g, 15.1 mmol) was added. After 10 min, the solution was allowed to warm to room temperature and stirred for 1.5 h, then concentrated to ~10 mL. Unreacted borohydride was destroyed by dropwise addition of glacial acetic acid and the solution was diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc–hexanes (3:7)) to give the title alcohol **4** as beige crystals. Yield: 0.89 g (55%); mp 167.5–169 °C (from EtOAc–hexanes). ^{1}H NMR (500 MHz, $CDCl_3$ – 10% CD_3OD) δ: 1.63 (d, J = 6.0 Hz, 3H, Me), 5.62 (q, J = 6.0 Hz, 1H, C*H*OH), 6.85 (d, J = 7.7 Hz, 1H, Ar-H), 7.33 (m, 1H, Ar-H), 7.45 (t, J = 7.7 Hz, 1H, Ar-H), 7.58 (d, J = 8.5 Hz, 1H, Ar-H), 7.68 (d, J = 6.8 Hz, 1H, Ar-H), 8.20 (d, J = 8.6 Hz, 1H, Ar-H). HR-MS calcd. for $C_{12}H_{12}O_2$: 188.0837; observed: 188.0838.

4-(1-Hydroxyethyl)-1-naphthol (5)

1-Acetyl-4-methoxynaphthalene **17** (29) was demethylated as described above for the 5-isomer **15** to give 1-acetyl-4-hydroxynaphthalene **18** as yellow crystals (from aqueous methanol), mp 198–199.5 °C (lit. (30) mp 197 °C).

A solution of **18** (2.0 g, 10.75 mmol) and TBDMS chloride (2.89 g, 19.2 mmol) in anhyd DMF (9.3 mL) was treated with imidazole (2.72 g, 40.0 mmol) and the mixture was stirred at room temperature for 2 h, then diluted with diethyl ether. The diluted solution was washed with 0.1 mol L^{-1} aqueous sodium carbonate and brine, dried and evaporated under reduced pressure to give crude 4-*tert*-butyldimethylsilyloxy-1-acetylnaphthalene **19** as a beige solid. Yield: 2.58 g (80%). This material was used without further purification. Thus, a solution of **19** (3.33 g, 11.1 mmol) in methanol (86 mL) was stirred at 10 °C and treated with sodium borohydride (0.42 g, 11.1 mmol) in three portions. The solution was stirred for 10 min at 10 °C and for 45 min at room temperature, then concentrated to ~30 mL and treated dropwise with glacial acetic acid (1.5 mL). The solution was diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried and evaporated under reduced pressure to give crude 1-(4-*tert*-butyldimethylsilyloxy-1-naphthalenyl)ethanol **20** as a reddish brown viscous gum. Yield: 3.0 g (89%). This material was dissolved in THF (30.5 mL) and treated with 1 mol L^{-1} tetrabutylammonium fluoride in THF (10.93 mL). After 20 min at room temperature the solution was diluted with diethyl ether and washed with water and brine, dried and evaporated under reduced pressure. The residue was flash chromatographed (EtOAc-hexanes (3:7)) to give the title alcohol **5** as a brown solid. Yield: 1.64 g (88%). Crystallization from EtOAc–hexanes was accompanied by some decomposition in the mother liquor but gave the pure alcohol, mp 126–127.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$ – 10% CD_3OD) δ: 1.63 (d, J = 6.5 Hz, 3H, CH_3), 5.57 (q, J = 6.5 Hz, 1H, C*H*OH), 6.83 (d, J = 7.7 Hz, 1H, Ar-H), 7.44–7.47 (m, 2H, Ar-H), 7.49–7.53 (m, 1H, Ar-H), 8.07 (d, J = 8.4 Hz, 1H, Ar-H), 8.27–8.29 (m, 1H, Ar-H). HR-MS calcd. for $C_{12}H_{12}O_2$: 188.0837; observed: 188.0837.

2-(5-Hydroxy-1-naphthalenyl)-2-oxoethyl acetate (9)

A stirred solution of 5-acetoxy-1-naphthoic acid **21** (31) (1.75 g, 7.6 mmol) in dry dichloromethane (30 mL) was treated at room temperature with oxalyl chloride (1.3 mL, 14.9 mmol) and dry DMF (65 μL). After 1 h, the solution was evaporated under reduced pressure and kept overnight under vacuum to leave the crude acid chloride **22**. Yield: 1.95 g (100%). This material (1.89 g, 7.6 mmol) was dissolved in a mixture of anhyd THF and acetonitrile (1:1; 15 mL) and treated with triethylamine (2.11 mL, 15.1 mmol). The solution was cooled in an ice bath and a 2 mol L^{-1} solution of trimethylsilyldiazomethane in hexane (Aldrich; 7.6 mL, 15.2 mmol) was added over 15 min. After 0.5 h, the solution was allowed to warm to room temperature and stirred overnight, then diluted with diethyl ether and washed with sat $NaHCO_3$, water, and brine, dried and evaporated under reduced pressure. The residue was triturated with diethyl ether to give crude diazoketone **23** as a brown solid. Yield: 1.43g (74%). ^{1}H NMR (90 MHz, $CDCl_3$ – 5% CD_3OD) δ: 2.42 (s, 3H, CH_3), 5.66 (s, 1H, CHN_2), 7.23–8.40 (m, 6H, Ar-H).

A solution of **23** (1.43 g, 5.36 mmol) in a mixture of THF and methanol (1:1; 28.6 mL) was treated with concentrated aqueous ammonia (4.77 mL). After 2 h at room temperature, the solution was diluted with ice water and adjusted to pH 8.0 with saturated aqueous oxalic acid. The aqueous layer was extracted with ethyl acetate and the organic extract was washed with water, dried and evaporated under reduced pressure. The residue was flash chromatographed (ethyl acetate – hexanes (3:7)) to give 2-diazo-1-(5-hydroxy-1-naphthalenyl)ethanone **24** as a yellow solid. Yield: 0.56 g (47%). ^{1}H NMR (90 MHz, $CDCl_3$ – 10% CD_3OD) δ: 5.73 (s, 1H, CHN_2), 6.80–8.44 (m, 6H, Ar-H). This material (0.47 g, 2.17 mmol) was added in portions over ~3 min to a stirred mixture of concentrated hydrochloric acid (0.44 mL) and glacial acetic acid (4.4 mL). After 0.5 h, the solution was diluted with water (22 mL) and stirred for 10 min. The precipitated solid was filtered, washed with cold water (3 mL), and dried under vacuum to give crude 1-chloroacetyl-5-hydroxynaphthalene **25** as a yellow powder. Yield: 0.39 g (82%). ^{1}H NMR (90 MHz, $CDCl_3$ – 5% CD_3OD) δ: 4.76 (s, 2H, CH_2Cl), 6.82–8.55 (m, 6H, Ar-H).

A stirred solution of **25** (0.39 g, 1.77 mmol) and glacial acetic acid (0.132 mL, 2.3 mmol) in dry toluene (23 mL) was cooled in ice and treated with DBU (0.344 mL, 2.3 mmol). The solution was stirred in the ice bath for 1 h, then at room temperature overnight. The solution was diluted with water, the aqueous layer was adjusted to pH 2 with 1 mol L^{-1} hydrochloric acid, and the mixture was extracted with diethyl ether. The organic layer was washed with water and brine, dried and evaporated under reduced pressure. The residue was dissolved in ethanol (7 mL), thiourea (0.15 g) was added and the solution was heated at reflux for 0.5 h to remove residual **25**, then concentrated under reduced pressure and partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried and evaporated and the residue was flash chromatographed (ethyl acetate – hexanes (3:7)). The recovered material was crystallized from toluene to give the title compound **9** as yellow plates. Yield: 0.29 g (50%); mp 99.5–101 °C. ^{1}H NMR (400 MHz) δ: 2.25 (s, 3H, CH_3), 5.31 (s, 2H, CH_2), 6.86 (d, J = 7.5 Hz, 1H, Ar-H), 7.39 (dd, J = 7.8 and 8.4 Hz, Ar-H), 7.48 (dd, J = 7.4 and 8.3 Hz, Ar-H), 7.83 (d, J = 7.0 Hz, Ar-H), 8.14 (d, J = 8.6 Hz, Ar-H), 8.44 (d, J = 8.4 Hz, Ar-H). Anal. calcd. for $C_{14}H_{12}O_4$: C 68.85, H 4.95; found: C 68.57, H 4.89.

2-(3-Hydroxyphenyl)-2-oxoethyl acetate (10)

A stirred solution of 3-hydroxyphenacyl bromide (32) (4.0 g, 18.6 mmol) and glacial acetic acid (2.45 mL, 42.8 mmol) in acetonitrile (63 mL) was cooled in an ice bath and treated dropwise with triethylamine (5.44 mL, 39.1 mmol). The solution was allowed to warm to room temperature and stirred for 2 h, then diluted with brine and extracted with diethyl ether. The extract was washed with 1 mol L^{-1} aq. HCl and brine, dried and evaporated under reduced pressure to give a brown gum (3.3 g) that was dissolved in boiling water, decolorized with charcoal, and extracted with diethyl ether. The extract was dried and evaporated and the residue was crystallized from ethyl acetate –

hexanes to give the title compound **10**. Yield: 0.9 g (25%); mp 94 °C. ^{1}H NMR (400 MHz, $CDCl_3$ – 10% CD_3OD) δ: 2.21 (s, 3H, CH_3), 5.30 (s, 2H, CH_2), 6.94–7.46 (m, 4H, Ar-H). Anal. calcd. for $C_{10}H_{10}O_4$: C 61.85, H 5.19; found: C 61.56, H 5.16.

Product studies

Preparative photolyses for **1**, **2**, **4**, and **5** were carried out with samples (10–20 mg) dissolved in the appropriate solvent (40–100 mL) and transferred to a quartz tube. The solution was irradiated in a RPR-100 photochemical reactor fitted with 254 or 300 nm lamps with continuous cooling (by a cold finger) and purging by a stream of argon for approximately 10 min before and continuously during irradiation (via a long stainless steel needle). Photolysis times ranged from 3 to 30 min, depending on the conversion desired, the efficiency of the reaction, and the size of the sample. After photolysis, aqueous samples were worked up by extraction with CH_2Cl_2 after addition of aq. NaCl. Direct evaporation of the organic solvent was used when samples were irradiated in wholly organic solvents. Typical experiments are described below. Analytical scale photolyses were employed for **9** and **10**, using NMR tubes, as described below.

Photolysis of 1

Photolysis of **1** (20 mg) in 1:1 D_2O–CH_3CN (v/v) (40 mL) with eight lamps (300 nm) for 20 min followed by standard workup gave starting material with deuterium incorporation at the 5-position (55%) and 8-position (19%) with no side products, as determined by 500 MHz ^{1}H NMR. MS analysis of the same sample indicated that it consisted of 37% non-deuterated, 52% monodeuterated, and 11% dideuterated substrate, giving the equivalent overall deuterium incorporation as measured by NMR.

Photolysis of 2

Photolysis of **2** (20 mg) in 1:1 D_2O–CH_3CN (v/v) (40 mL) with 16 lamps (300 nm) for 1 h followed by standard workup gave only starting material with no deuterium incorporation at any position, as determined by 500 MHz ^{1}H NMR. MS analysis of the same sample also indicated that no additional deuterium was incorporated in the sample following photolysis.

Photolysis of 4

Photolysis of **4** (50 mg) in 1:1 H_2O–CH_3OH (v/v) (100 mL) with four lamps (300 nm) for 1 min followed by standard workup gave methyl ether **29** in 48% conversion. Photolysis product **29** was chromatographically isolated on silica gel (10% EtOAc in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.58 (d, 3H, CH_3), 3.30 (br s, 3H, OCH_3), 5.04 (q, 1H, ArC-H), 5.80 (br s, 1H, OH), 6.82 (d, 1H, Ar-H), 7.33 (t, 1H, Ar-H), 7.48 (t, 1H, Ar-H), 7.59 (d, 1H, Ar-H), 7.70 (d, 1H, Ar-H) 8.16 (d, 1H, Ar-H). HR-MS calcd. for $C_{13}H_{14}O_2$: 202.0994; observed: 202.0993.

Photolysis of 5

Photolysis of **5** (20 mg) in 1:1 H_2O–CH_3OH (v/v) (100 mL) containing $NaHCO_3$ (25 mg) with 16 lamps (300 nm) for 3 min followed by standard workup cleanly regenerated starting material with no reaction observable by 300 MHz ^{1}H NMR. A small amount of thermal decomposition was observed when $NaHCO_3$ was not added to the solution.

Photolysis of 9 and 10

In a typical procedure, 2–5 mg of substrate was dissolved in ~2 mL of D_2O–CD_3CN (1:1). The solution was transferred to an NMR tube and deoxygenated by purging with argon for 10 min. The tube was then placed in the middle of the Rayonet reactor (16 × 300 nm lamps) and irradiated for up to 30 min. ^{1}H NMR spectra were taken before and after photolysis without workup. Both **9** and **10** were found to be photochemically inert for up to 30 min photolysis. Under these conditions, **6** would have resulted in quantitative conversion to **8** in about 10 min of photolysis.

Quantum yields

The quantum yield for total deuterium incorporation in **1** has been previously reported (8) to be $\Phi_{H\text{-}D}$ = 0.11 in 99% D_2O, pD 3. Our results demonstrate that the exchange efficiency is the same at pD 7 and pD 3, and that the exchange efficiency appears to plateau around 1:1 H_2O–CH_3CN. Given these data, it is reasonable to assume that $\Phi_{H\text{-}D}$ in neutral 1:1 D_2O–CH_3CN solution should be approximately equal to 0.11 as previously measured. The quantum yield for the photosubstitution reaction of **4** was measured relative to the photomethanolysis reaction of *o*-hydroxybenzhydrol in H_2O–CH_3OH (1:1) (Φ = 0.46) (5). Preparative scale photoreactions (10^{-3} mol L^{-1}, 50 mL H_2O–CH_3OH (1:1), Ar purged, 2 × 254 nm lamps, 1–3 min) were performed for **4** and the reference compound, and the extent of reaction was measured by 300 MHz ^{1}H NMR. The reported value of Φ = 0.84 ± 0.04 is the average of three such runs.

Fluorescence measurements

Steady-state fluorescence measurements were conducted on a Photon Technology International A-1010 (PTI) QuantaMaster luminescence spectrometer. All solutions (absorbance ≈ 0.1 at λ_{ex} 300 nm) were purged with argon prior to excitation. Fluorescence lifetimes were measured on a PTI LS-1 instrument using time-correlated single-photon-counting techniques (10 000 counts, λ_{ex} 300 nm, λ_{em} 350 nm).

Laser flash photolysis (LFP)

A Spectra-Physics excimer laser (308 nm, ~10 ns, <30 mJ/pulse) was used for excitation and signals were digitized with a Tektronix TDS 520 recorder. Samples of OD ~ 0.3 at 308 nm were prepared and irradiated in quartz cells. Static cells were used for the kinetic studies of samples, otherwise flow cells were used for all other studies. Samples in flow cells were continuously purged with a stream of N_2 or O_2. Samples in static cells were purged with N_2 or O_2 then sealed prior to photolysis.

Acknowledgments

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for continued support of this research, and for a post-graduate scholarship to one us

(ML). We thank Ms. Kai Zhang and Dr. Darryl W. Brousmiche for some initial experiments.

References

1. P. Wan, B. Barker, L. Diao, M. Fischer, Y. Shi, and C. Yang. Can. J. Chem. **71**, 465 (1996).
2. P. Wan, D.W. Brousmiche, C.Z. Chen, J. Cole, M. Lukeman, and M. Xu. Pure Appl. Chem. **73**, 529 (2001).
3. R.W. Van de Water and T.R.R. Pettus. Tetrahedron, **58**, 5367 (2002).
4. M. Fischer and P. Wan. J. Am. Chem. Soc. **121**, 4555 (1999).
5. L. Diao, C. Yang, and P. Wan. J. Am. Chem. Soc. **117**, 5369 (1995).
6. Y. Shi and P. Wan. J. Chem. Soc. Chem. Commun. 273 (1997).
7. P. Seiler and J. Wirz. Helv. Chim. Acta, **55**, 2693 (1972).
8. S.P. Webb, L.A. Philips, S.W. Yeh, L.M. Tolbert, and J.H. Clark. J. Phys. Chem. **90**, 5154 (1986).
9. (*a*) M. Lukeman and P. Wan. J. Chem. Soc. Chem. Commun. 1004 (2001); (*b*) M. Lukeman and P. Wan. J. Am. Chem. Soc. **124**, 9458 (2002).
10. (*a*) R.S. Givens, A. Jung, C.-H. Park, J. Weber, and W. Bartlett. J. Am. Chem. Soc. **119**, 8369 (1997); (*b*) R.S. Givens, P.S. Athey, B. Matuszewski, L.W. Kueper III, J.-y. Xue, and T. Fister. J. Am. Chem. Soc. **115**, 6001 (1993); (*c*) P.G. Conrad II, R.S. Givens, B. Hellrung, C.S. Rajesh, M. Ramseier, and J. Wirz. J. Am. Chem. Soc. **122**, 9346 (2000).
11. K. Zhang, J.E.T. Corrie, V.R.N. Munasinghe, and P. Wan. J. Am. Chem. Soc. **121**, 5625 (1999).
12. W.F. Short and H. Wang. J. Chem. Soc. 991 (1950).
13. S. Lee, S.P. Frescas, and D.E. Nichols. Synth. Commun. **25**, 2275 (1995).
14. M.K. Nayak and A.K. Chakraborti. Tetrahedron Lett. **38**, 8749 (1997).
15. J.B. Birks. Photophysics of aromatic molecules. Wiley-Interscience, New York. 1983. p. 123.
16. (*a*) H. Shizuka and S. Tobita. J. Am. Chem. Soc. **104**, 6919 (1982); (*b*) H. Shizuka. Acc. Chem. Res. **17**, 141 (1985).
17. R. Pollard, S. Wu, G. Zhang, and P. Wan. J. Org. Chem. **58**, 2605 (1993).
18. P. Wan and G. Zhang. Res. Chem. Intermed. **19**, 119 (1993).
19. (*a*) R.A. McClelland. Tetrahedron, **52**, 6823 (1996); (*b*) N. Mathivanan, F. Cozens, R.A. McClelland, and S. Steenken. J. Am. Chem. Soc. **114**, 2198 (1992).
20. D.N. Kevill and S.W. Anderson. J. Org. Chem. **56**, 1845 (1991).
21. Y. Chiang, A.J. Kresge, B. Hellrung, P. Schünemann, and J. Wirz. Helv. Chim. Acta, **80**, 1106 (1997).
22. H. Shizuka, H. Hagiwara, and M. Fukushima. J. Am. Chem. Soc. **107**, 7816 (1985).
23. D.W. Brousmiche and P. Wan. J. Photochem. Photobiol. A, **149**, 71 (2002).
24. M. Lukeman and P. Wan. J. Am. Chem. Soc. **125**, 1164 (2003).
25. H.J.E. Lowenthal and L. Gottlieb. J. Org. Chem. **57**, 2631 (1992).
26. A.I. Myers and K. Higashiyama. J. Org. Chem. **52**, 4592 (1987).
27. M. Sawada, T. Fujii, Y. Tairaka, and Y. Yukawa. Bull. Chem. Soc. Jpn. **48**, 3356 (1975).
28. T. Bisanz and M. Bukowska. Rocz. Chem. **48**, 777 (1974).
29. N.P. Buu-Hoi and P. Cagniant. Rec. Trav. Chim. Pays–Bas, **64**, 214 (1945).
30. W.H. Hunter, R.M. Quinton, P.H. Sherman, C.R. Worthing, and R.J. Boscott. J. Med. Chem. **7**, 167 (1964).
31. J. Cason. J. Am. Chem. Soc. **63**, 828 (1941).
32. S.J. Pasaribu and L.R. Williams. Aust. J. Chem. **26**, 1327 (1973).