J|A|C|S
COMMUNICATIONS

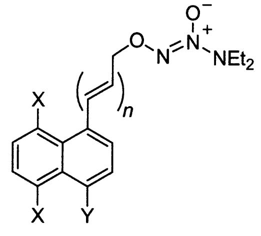
Controlled Photochemical Release of Nitric Oxide from O^2-Naphthylmethyl- and O^2-Naphthylallyl-Substituted Diazeniumdiolates

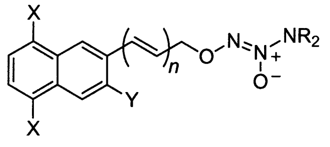
K. Mani Bushan, Hua Xu, Patrick H. Ruane, Raechelle A. D'Sa, Christopher M. Pavlos,
Joseph A. Smith, Tevye C. Celius, and John P. Toscano*

Department of Chemistry, Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218

Received July 31, 2002

Anions such as 1-(*N*,*N*-dialkylamino)diazen-1-ium-1,2-diolates (**1**) are stable as solid salts, but release up to 2 mol of the important bioregulatory molecule nitric oxide (NO) when dissolved in aqueous solution at physiologically relevant conditions.[1] The rate of NO release can be varied by modifying the substituents R, pH, or temperature.[1] To extend the usefulness and applications of diazeniumdiolates as NO donors, we have been developing efficient photosensitive protecting groups for these anions.[2,3] Our previous work has demonstrated that the photochemistry of O^2-alkyl- and O^2-benzyl-substituted diazeniumdiolates can be severely complicated by a reaction that produces potentially carcinogenic nitrosamine and an oxynitrene intermediate[4] (see Scheme 1, Path A). More recently, we have shown that for a series of meta-substituted O^2-benzyl-protected diazeniumdiolates, the desired photorelease of **1** (see Scheme 1, Path B) competes more effectively with this undesired reaction pathway for those derivatives with stronger π-donating meta substituents.[5] Near quantitative release of **1** is obtained with the 3,5-dihydroxybenzyl derivative, but only at pH values above 10. The highest contribution from the photorelease reaction pathway observed at neutral pH is 50%, obtained with the 3,5-bis-dimethylamino derivative. An additional shortcoming of these benzyl derivatives is the complication caused by potential secondary photolysis of photoreleased **1**, which has $\lambda_{\max} =$ ca. 250 nm and tails out to $A = 0$ at approximately 320 nm.[6] Reported herein is an extension of our previous work to O^2-naphthylmethyl- and O^2-naphthylallyl-substituted diazeniumdiolates **2**−**10** that addresses these deficiencies.





2 $n = 0$, X = H, Y = H
3 $n = 0$, X = H, Y = Me
4 $n = 1$, X = H, Y = H
5 $n = 0$, X = OMe, Y = H
6 $n = 1$, X = OMe, Y = H

7 $n = 0$, X = OMe, Y = H, R = Et
8 $n = 0$, X = H, Y = OMe, R = Et
9 $n = 1$, X = H, Y = OMe, R = Et
10 $n = 1$, X = H, Y = OMe,
NR_2 = piperidinyl

Since Pincock and co-workers have examined the photochemistry of a series of 1-naphthylmethyl esters and demonstrated efficient carboxylate photorelease for the 4-methyl derivative as well as for the unsubstituted parent compound,[7] we initially examined 1-naphthylmethyl derivatives **2** and **3**. Unfortunately, these derivatives provide substantial amounts of nitrosamine **11** and very little photorelease of diazeniumdiolate **1** (Table 1).

Scheme 1

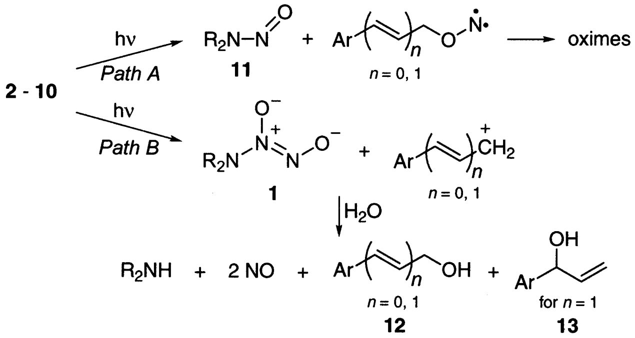


Table 1. Yields of Products[a] Following Photolysis of O^2-Naphthylmethyl- and O^2-Naphthylallyl-Substituted Diazeniumdiolates

reactant	nitrosamine **11**	oximes	aldehyde	alcohol **12**	rearranged alcohol **13**	diazeniumdiolate **1**[b]	quantum yield[c]
2	74	35	42	14	−	1	0.007
3	75	*d*	*d*	*d*	−	1	*d*
4	72	31	4	8	24	25	0.12
5	53	23	0	42	−	40	0.12
6	16	*d*	*d*	26	53	95	0.66
7	53	*d*	*d*	36	−	32	0.055
8	62	35	20	34	−	20	0.025
9	10	16	0	14	52	50	0.15
10	14	3	2	16	46	50	0.10

[a] Average of at least three measurements, estimated error ±5%; based on the percent reactant converted (30−40%). Photolyses (typically for ca. 15 s) were carried out in a Rayonet reactor (300 nm for compounds **2**−**4** and **8**, 350 nm for compounds **5**−**7**, **9**, and **10**) in argon-purged 90−95% aqueous acetonitrile. Secondary photochemistry is negligible under these conditions. [b] Based on percent reactant converted (determined by HPLC analysis), the yield of NO measured, and the observation that diazeniumdiolate **1** (R = Et) gives 1.5 equiv of NO for compounds **2**−**9** and diazeniumdiolate **1** (NR_2 = piperidinyl) gives 1.8 equiv of NO for compound **10**.[8] [c] For reactant photodecomposition, using the azobenzene actinometer;[9] photolysis at 300 nm (Rayonet) for compounds **2**−**4** and **8**, and at 355 nm (Nd:YAG laser) for compounds **5**−**7**, **9**, and **10**. [d] Not determined.

Following the recent report of Rao and co-workers showing that arylallyl acetates undergo efficient ionic photodissociation in polar solvents,[10] we also examined naphthylallyl derivative **4**. Here, we observe approximately 25% photorelease of diazeniumdiolate **1** (Table 1).

Although photolysis of the parent O^2-benzyl-substituted derivative results in negligible release of **1**, we were able to enhance this process significantly with electron-donating meta substitution. This substitution pattern was examined on the basis of the well-established meta effect of electron-donating groups favoring the

---

* To whom correspondence should be addressed. E-mail: jtoscano@jhu.edu.

10.1021/ja027957h CCC: $22.00 © 2002 American Chemical Society

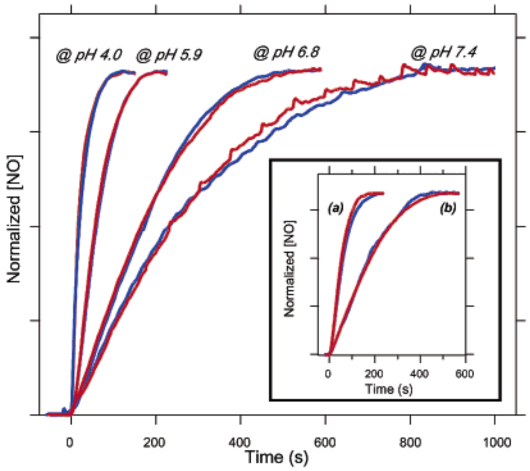


Figure 1. NO release rates observed following photolysis (Xe-arc lamp with a 324-nm long pass filter) of **6** (0.5 μM in 99% aqueous acetonitrile at 25 °C) at varying solution pH's (in blue) compared with the corresponding rates observed for the thermal dissociation of the sodium salt of diazeniumdiolate **1** (R = Et) at the same pH's (in red). The inset shows an analogous comparison for (a) the photolysis of **10** (in blue) with the thermal dissociation of **1** (NR_2 = piperidinyl) (in red) and (b) the photolysis of **9** (in blue) with the thermal dissociation of **1** (R = Et) (in red) at pH 6.8.

formation of ionic products in photochemical reactions of benzylic systems.[7,11] To determine what substitution patterns might enhance the photorelease of **1** in naphthylmethyl and naphthylallyl systems, we examined reported substituent effects on the excited-state acidity of 1- and 2-naphthols.[12] Electron-*withdrawing* substituents in the 5 and 8 positions and in the 3, 5, and 8 positions for 1- and 2-naphthol, respectively, enhance the excited state acidity. We reasoned, therefore, that these positions transmit electronic effects most effectively in the excited states of naphthalene derivatives and that electron-*donating* substituents in these positions would enhance the formation of a naphthylmethyl or naphthylallyl cation, resulting in the desired photorelease of diazeniumdiolate anion **1** (Path B, Scheme 1).

To test this hypothesis, methoxy-substituted compounds **5**−**9** were synthesized and, along with the parent compounds **2** and **4**, were analyzed for products following photolysis. Yields of organic products, quantified by HPLC analysis, are given in Table 1.[13] Quantification of NO released upon photolysis was performed as described previously[5] and was used to derive yields of photoreleased **1** (see also Supporting Information).

The diazeniumdiolate yields presented in Table 1 indicate that the appropriate methoxy group substitution pattern has a significant effect on the efficiency of the photorelease of **1**, for example, **2** (1% release) versus **5** (40% release) and **4** (25% release) versus **6** (95% release). In addition, naphthylallyl derivatives perform better than their naphthylmethyl analogues, for example, **5** (40% release) versus **6** (95% release) and **8** (20% release) versus **9** (50% release). This latter trend may be the result of production of a more stable naphthylallyl cation or may reflect greater transfer of electron density in the excited states of the naphthylallyl systems as suggested by simple Hückel calculations. These calculations, at least qualitatively, reproduce the general trends observed for diazeniumdiolate photorelease from compounds **2**−**9** (Supporting Information).

The most efficient NO-releasing compound of those examined in this study, both in terms of diazeniumdiolate photorelease and quantum yield of photodecomposition, is naphthylallyl derivative **6**. Importantly, this precursor overcomes the shortcomings of the previously studied benzyl derivatives.[5] The high efficiency of diazeniumdiolate photorelease is not pH-dependent and can be initiated by long-wavelength (≥350 nm) light, making this diazeniumdiolate precursor potentially well-suited for a range of biological applications.[14]

Since the rate of NO release from diazeniumdiolate **1** can be controlled by factors such as the substituents R, pH, and temperature, an additional advantageous feature of **6** (and of the other derivatives reported here) is that the flux of NO can be controlled (and varied) by these factors. Figure 1 demonstrates that the NO release rate observed following photolysis of **6** is exactly analogous to that observed for thermal dissociation of the sodium salt of **1** (R = Et) and, moreover, shows the same pH dependence. In addition, the inset of Figure 1 shows that the rate of NO release following photolysis at a particular pH can be varied by simply changing the nature of the released diazeniumdiolate, for example, from a diethylamine derivative (**1** (R = Et)) to a piperidine derivative (**1** (NR_2 = piperidinyl)).

Acknowledgment. We gratefully acknowledge the National Institutes of Health (R01 GM58109) for generous support of this research. J.P.T. also acknowledges a Camille Dreyfus Teacher-Scholar Award and an Alfred P. Sloan Research Fellowship. J.A.S. acknowledges a Jean Dreyfus Boissevain Undergraduate Scholarship. We also thank Professor Jakob Wirz for helpful discussions.

Supporting Information Available: Experimental details concerning the synthesis of **2**−**10** and of authentic products, quantification of photoreleased diazeniumdiolate **1**, and Hückel calculations on the first excited states of **2**−**10** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a recent review of the chemistry of diazeniumdiolate derivatives, see: Hrabie, J. A.; Keefer, L. K. *Chem. Rev.* **2002**, *102*, 1135−1154.
(2) For a previous study involving potential photochemical precursors to diazeniumdiolates **1**, see: Makings, L. R.; Tsien, R. Y. *J. Biol. Chem.* **1994**, *269*, 6282−6285.
(3) For a recent review of NO-donor chemistry, see: Wang, P. G.; Xian, M.; Tang, X.; Wu, X.; Wen, Z.; Cai, T.; Janczuk, A. J. *Chem. Rev.* **2002**, *102*, 1091−1134.
(4) Srinivasan, A.; Kebede, N.; Saavedra, J. E.; Nikolaitchik, A. V.; Brady, D. A.; Yourd, E. Y.; Davies, K. M.; Keefer, L. K.; Toscano, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 5465−5472.
(5) Ruane, P. H.; Bushan, K. M.; Pavlos, C. M.; D'Sa, R. A.; Toscano, J. P. *J. Am. Chem. Soc.* **2002**, *124*, 9806−9811.
(6) A full characterization of the photochemistry of diazeniumdiolates **1** will soon be reported: D'Sa, R. A.; Ruane, P. H.; Kumar, N. A.; Relyea, H. A.; Toscano, J. P. Manuscript in preparation.
(7) (a) Givens, R. S.; Matuszewski, B.; Neywick, C. V. *J. Am. Chem. Soc.* **1974**, *96*, 5547−5552. (b) DeCosta, D. P.; Pincock, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 2180−2190. (c) Pincock, J. A. *Acc. Chem. Res.* **1997**, *30*, 43−49
(8) (a) Maragos, C. M.; Morley, D.; Wink, D. A.; Dunams, T. M.; Saavedra, J. E.; Hoffman, A.; Bove, A. A.; Isaac, L.; Hrabie, J. A.; Keefer, L. K. *J. Med. Chem.* **1991**, *34*, 3242−3247. (b) Ramamurthi, A.; Lewis, R. S. *Chem. Res. Toxicol.* **1997**, *10*, 408−413. (c) Supporting Information.
(9) Frank, R.; Gauglitz, G. *J. Photochem.* **1977**, *7*, 355−357.
(10) Rao, G. V.; Reddy, M. J. R.; Srinivas, K.; Reddy, M. J. R.; Bushan, K. M.; Rao, V. J. *Photochem. Photobiol.* **2002**, *76*, 29−34.
(11) (a) Zimmerman, H. E. *J. Am. Chem. Soc.* **1995**, *117*, 8988−8991. (b) Zimmerman, H. E. *J. Phys. Chem. A* **1998**, *102*, 5616−5621.
(12) (a) Seiler, P.; Wirz, J. *Tetrahedron Lett.* **1971**, 1683−1686. (b) Shizuka, H. *Acc. Chem. Res.* **1985**, *18*, 141−147. (c) Tolbert, L. M.; Solntsev, K. M. *Acc. Chem. Res.* **2002**, *35*, 19−27. (d) Agmon, N.; Rettig, W.; Groth, C. *J. Am. Chem. Soc.* **2002**, *124*, 1089−1096.
(13) The observed aldehydes are not primary products of either Path A or B (Scheme 1). They likely arise from secondary photolysis of primary oxime products as has been observed,[4,5] or via a reaction pathway involving the extrusion of nitrous oxide (N_2O) that has also been observed.[4]
(14) Compound **6** has a UV−vis absorption band centered at 336 nm (ϵ = 9780 M^{-1} cm^{-1}) that tails out to $A = 0$ at approximately 400 nm. It is soluble up to 20 μM in 95% aqueous acetonitrile and is stable at room temperature in pH 2, 7, and 11 solutions for at least 24 h. We are currently developing derivatives of **6** with enhanced water solubility; these results will be reported in due course.

JA027957H