The S_N2 Reactivity of 3,3-Disubstituted 1,2-Dioxetanes with Morpholine†

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The reaction of morpholine with the 3-aryl-3-methyldioxetanes **1a–c** (Y = 4-OMe, H, 4-NO_2), the 3-(methoxymethyl)-3-phenyldioxetane (**1d**), and the 3-(halomethyl) 3-phenyldioxetanes **1e,f** (X = Cl, Br) was investigated to determine the S_N2 reactivity of these dioxetanes and the product distribution of the hydroxylamine ether **2** adducts and the dioxetane fragmentation products **3**. It was shown that the overall rectivity and the product distribution are strongly dependent on the substituents of the dioxetanes **1**. Thus, the reactivity of the dioxetanes **1** toward morpholine was demonstrated to correlate with the electron-accepting propensity of the substituents in the 3-position, while the product distribution depends on the electronic features of the primary dipolar adduct, which results from nucleophilic attack at the dioxetane peroxide bond. Electron-donating substituents (Y = 4-OMe) favor proton transfer from the hydroxylammonium site to the alkoxide ion due to the enhanced basicity of the latter, and, therefore, the formation of the hydroxylamine ether **2** is promoted. Additionally, electron-accepting substituents (Y = NO_2) facilitate the Grob fragmentation of the primary dipolar adduct to the dioxetane cleavage products **3**. The unexpected formation of the hydroperoxide **4f** in the reaction of the dioxetane **1f** with morpholine was shown to result from acid-catalyzed ring opening of the dioxetane by morpholinium bromide and subsequent morpholine trapping of the resulting stabilized, bromine-bridged benzylic cation.

Introduction

S_N2 reactivity of 3,3-disubstituted 1,2-dioxetanes with nucleophiles at the sterically less hindered site of the peroxide bond has been shown to be a novel reaction mode for this class of strained peroxides.[1] α-(Halomethyl)-substituted dioxetanes were employed to establish the initial nucleophilic attack by intramolecular halide displacement with the primarily formed alkoxide ion to afford epoxides.[2] Additionally, dioxetane fragmentation products were observed in nearly all reactions of dioxetanes with nucleophiles.[3]

The factors which determine the formation of the addition products at the peroxide bond versus the dioxetane fragmentation products are less well understood. For example, *cis*-3,4-diethoxydioxetane as well as the 3,3-dibenzyl- and 3-methyl-3-phenyldioxetanes gave with triethylamine exclusively the corresponding dioxetane fragmentation products even at low temperatures.[4] In contrast, the reaction of the 3-(bromomethyl)-3-phenyldioxetane with tertiary amines (e.g. Et_3N and DABCO) afforded the labile *N*-alkoxytrialkylammonium epoxides as the only detected adducts.[5]

To rationalize the effect of substitution on the phenyl ring and the methyl group on the overall S_N2 reactivity and the product distribution of adduct and dioxetane fragmentation product formation, we have investigated the reactions of the 3-aryl-3-methyldioxetanes **1a–c** and the 3-(halomethyl)- and 3-(methoxymethyl)-3-phenyldioxetanes **1d–f** with morpholine as a model nucleophile. Herein, we present the detailed results of this study. Of mechanistic significance is our finding that dioxetane **1a** with an electron donor (*p*-OCH_3) forms mainly hydroxylamine ether **2a**, while **1c** with an electron acceptor (*p*-NO_2) undergoes mainly Grob-type fragmentation. Moreover, the novel acid-catalyzed ring opening of the (bromomethyl)-substituted dioxetane **1f** by morpholinum hydrobromide has been discovered, which is unprecedented for such dioxetanes.

Results

The transformations of the dioxetanes **1a–f** with morpholine were carried out at 0 °C in methylene chloride (Scheme 1). In all cases, mixtures of the hydroxylamine ethers **2** and the dioxetane fragmentation products **3** were obtained (Table 1). The quantification of the products **2** and **3** was performed by means of ^1H NMR spectroscopy. The unknown hydroxylamine ethers **2a–d** were isolated by silica gel column chromatography and were fully characterized.

While the three aryl-substituted dioxetanes **1a–c** afforded significant amounts of the dioxetane fragmentation products **3a–c**, the corresponding ω-substituted acetophenones **3d–f** were produced only in negligible amounts in the reactions of the 3-methyl-substituted dioxetanes **1d–f** with morpholine. The reaction times dropped from 14 h for the *p*-methoxy-substituted dioxetane **1a** (entry 1) to 2 h for the *p*-nitro derivative **1c** (entry 3). In the same order, the product ratio of the hydroxylamine ethers **2** and the dioxetane fragmentation products **3** shifted from 70:30 (entry 1) for dioxetane **1a** to 33:67 (entry 3) for derivative **1c**. On the other hand, the 3-methyl-substituted dioxetanes **1d–f** were completely consumed within 3–12 min (entries 4–6) to yield almost exclusively the hydroxylamine ethers **2d–f**.

The hydroxylamine ethers **2** show complex signals for the morpholine ring protons in their ^1H NMR spectra.

† Dedicated to Prof. G. Modena on the occasion of his 70th birthday.
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(1) (a) Adam, W.; Heil, M.; Mosandl, T.; Saha-Möller, C. R. Dioxetanes and α-Peroxy Lactones, Four-Membered Ring Cyclic Peroxides. In *Organic Peroxides*; Ando, W., Ed.; John Wiley & Sons: Chichester, U.K., 1992; pp 221–254. (b) Adam, W.; Treiber, A. *J. Org. Chem.* **1994**, *59*, 840–844. (c) Adam, W.; Harrer, H. M.; Treiber, A. *J. Am. Chem. Soc.* **1994**, *116*, 7581–7587.
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(3) Adam, W.; Epe, B.; Schiffmann, D.; Vargas, F.; Wild, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 429–431.
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(5) Adam, W.; Heil, M. *J. Am. Chem. Soc.* **1992**, *114*, 5591–5598.

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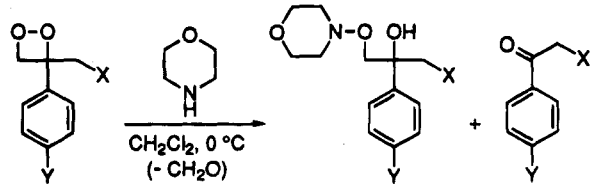
Scheme 1



1 2 3

	a	b	c	d	e	f
x	H	H	H	OMe	Cl	Br
Y	OMe	H	NO_2	H	H	H

Table 1. Product Studies of the Reaction of Dioxetanes 1a–f with Morpholine[a]

				products[d]	
entry	dioxetane	time[b] (min)	mb[c] (%)	addition, **2** (%)[e]	fragmentation, **3** (%)[e]
1	**1b**	840	87	70 (60)	30 (25)
2	**1b**	660	>95	46 (43)	54 (43)
3	**1c**	120	>95	33 (26)	67 (54)
4	**1d**	12	>95	>95 (62)	<5 (1)
5	**1e**	3	>95	>95[f]	<5[f]
6	**1f**	5	>95[b]	>95[f,g]	<5[f]

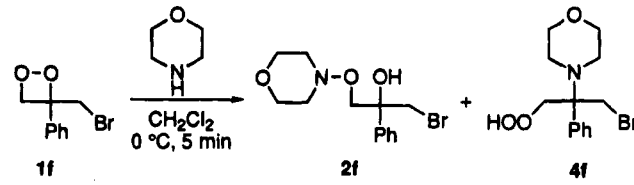
[a] In methylene chloride at 0 °C. [b] Reaction time for >95% conversion for all dioxetanes **1**. [c] Mass balance determined from the ^{1}H NMR spectrum of the crude product mixture. Hexamethyldisiloxane used as internal standard. [d] Product distribution calculated from the characteristic signals in the ^{1}H NMR spectrum of the crude product mixture. Hexamethyldisiloxane used as internal standard, normalized to 100% (error ca. 5% of the stated values). [e] Yields of isolated product in parentheses. [f] Not isolated. [g] About 70:30 mixture of the hydroxylamine ether **2f** (O alkylation) and the hydroperoxide **4f** (C alkylation).

While the free base exhibits two resonances,[6] one at higher field (δ 2.80) for the methylene groups adjacent to the nitrogen and the other at lower field (δ 3.65) for those adjacent to the oxygen atom, these morpholine ring protons are split into six signals in the hydroxylamine ethers **2**. The presence of a stereogenic center, together with hindered inversion of the nitrogen atom through hydrogen bonding with the β-hydroxy group, seems to cause the observed inequivalence. The hydrogen-bridge formation is evidenced by a strong downfield shift to δ 5–6 of the β-hydroxy proton in the hydroxylamine ethers **2**.

A more complex product mixture was observed in the reaction of 3-(bromomethyl)-3-phenyldioxetane (**1f**) with morpholine (entry 6). Although the dioxetane **1f** was completely consumed within 5 min, the positive peroxide test (KI/HOAc) clearly indicated the presence of a new peroxidic product (Scheme 2), to which the structure **4f** was assigned. The situation was further complicated by the fact that the hydroxylamine ether **2f** as well as the new peroxide **4f** decomposed upon attempted low-temperature column chromatography. Apart from small amounts (2%) of ω-bromoacetophenone (**3f**), 9% of *N*-[2-(phenyloxiranyl)propoxy]morpholine (**5f**), 59% of the diol **6f**, 18% of ω-morpholinoacetophenone (**3g**), and 32% of *N*-hydroxymorpholine were also isolated. A control experiment revealed that **3g** was not formed from **3f** by nucleophilic substitution with morpholine under the reaction conditions.

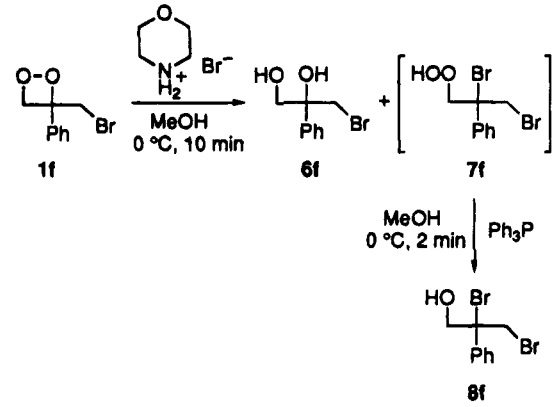
(6) *Spektroskopische Methoden in der organischen Chemie*, 3rd ed.; Hesse, M., Meier, H., Zeeh, B., Eds.; Georg Thieme Verlag: Stuttgart, Germany, 1987; p 175.

Scheme 2



1f 2f 4f

Scheme 3



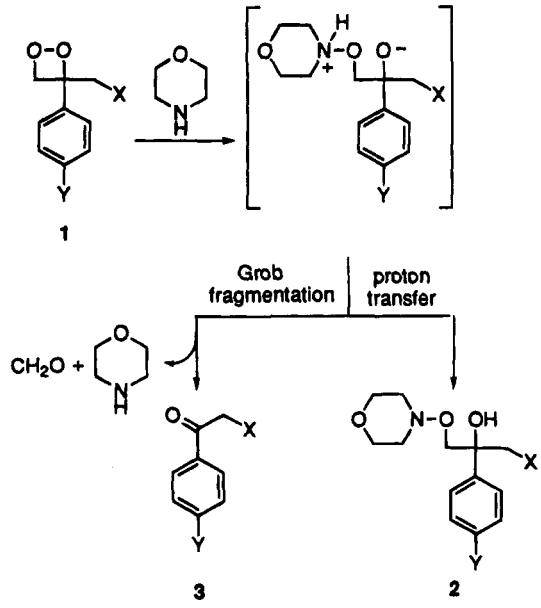
1f 6f 7f 8f

To characterize the new peroxide **4f**, the reaction was repeated in deuteriochloroform and the product formation was directly monitored by means of low-temperature NMR spectroscopy. The ^{1}H NMR spectrum of the crude reaction mixture showed the hydroxylamine ether **2f** to be the main product, as evidenced by the typical signals of the morpholine protons. In the ^{13}C NMR spectrum, the 1-bromo-3-hydroperoxy-2-phenylpropane (**4f**) could also be observed. Its structural assignment is mainly based on the two characteristic resonances at δ 41.1 (t) and 88.5 (t) for the bromomethyl and hydroperoxymethyl groups. Furthermore, the inequivalence of the four morpholine carbon atoms in the ^{13}C NMR spectrum of the hydroperoxide **4f** (δ 53.8, 55.3, 68.1, 68.5) suggests that the morpholine moiety is connected directly to the stereogenic center. In contrast, the resonances of the morpholine carbon atoms in the hydroxylamine ethers **2** appear as two distinct signals.

The formation of the hydroperoxide **4f** in the reaction of dioxetane **1f** with morpholine was temperature dependent. While 29% of hydroperoxide **4f** was observed (iodometry) at a reaction temperature of 20 °C, at 0 °C, the yield dropped to 15%, and at −20 °C, the yield dropped to 8%. At −60 °C, no hydroperoxide **4f** could be detected by means of the peroxide test. Furthermore, a control experiment established that the hydroperoxide **4f** was completely suppressed when the reaction of dioxetane **1f** with morpholine was conducted in the presence of potassium carbonate as base.

When the dioxetane **1f** was allowed to react with 1 equiv of morpholine hydrobromide in methanol at 0 °C, a mixture of the diol **6f** and the hydroperoxide **7f** was obtained (Scheme 3). The structure of hydroperoxide **7f** was again established by means of ^{13}C NMR spectroscopy (δ 37.3 and 87.0 for the bromomethyl and the hydroperoxymethyl groups, respectively). Unfortunately, this new dibromo hydroperoxide was too labile for isolation, even during low-temperature column chromatography. Therefore, the crude reaction mixture was treated with triphenylphosphine and the corresponding dibromo alcohol **8f** was isolated by means of silica gel chromatography in 6% yield, together with 56% bromo diol **6f**.

Scheme 4



In contrast to morpholine hydrobromide, treatment of the dioxetane **1f** with 1 equiv of the hydrobromides of diisopropylamine and triethylamine gave exclusively the diol **6f** as evidenced by TLC as well as by NMR spectroscopy. No peroxide **4f** could be detected in these reactions.

Discussion

The mechanistic rationalization for the formation of the hydroxylamine ethers **2** and the dioxetane fragmentation products **3** is presented in Scheme 4. It has been established for a variety of 3,3-disubstituted dioxetanes[1] that they readily react with nucleophiles by S_N2 attack at the sterically more exposed oxygen atom of the peroxide bond. Subsequent proton transfer from the hydroxylammonium nitrogen atom to the alkoxide ion converts the primary formed zwitterionic intermediate to the stable hydroxylamine ethers **2**.

Two mechanistic options may be considered for the formation of the fragmentation products **3** in the reaction of the dioxetanes **1** with nucleophiles. These are the electron transfer mechanism[7] and the Grob fragmentation.[8] The latter process has been proposed to explain the occurrence of dioxetane fragmentation products in the reaction of 3,3-disubstituted derivatives with nucleophiles.[1b,9]

Several facts speak against electron transfer as the initiation step for the dioxetane fragmentation. The 3-(halomethyl)-substituted dioxetanes **1e,f** have been used to differentiate between S_N2 and electron transfer reactivity in the reactions of 3,3-disubstituted dioxetanes with nucleophiles.[10] Electron transfer from the amine nucleophile to the dioxetanes **1e,f** would generate a radical anion, which is known[11] to fragment into formaldehyde and the ketyl radical anion of the α-halo-substituted ketone. The latter undergo rapid loss of a halide ion, and after uptake of a hydrogen atom from the solvent, the dehalogenated ketones are produced. This mechanistic probe has been applied to exclude electron transfer in the reactions of dioxetanes with NADH derivatives.[10] Also in the present case, the lack of dehalogenated fragmentation products in the reaction of the dioxetanes **1e,f** with morpholine argues against the involvement of electron transfer chemistry.

The product ratios of the hydroxylamine ethers **2** and the dioxetane fragmentation products **3** in the reaction of the three 3-aryl-substituted dioxetanes **1a–c** speak in favor of Grob fragmentation. The latter competes with the formation of adduct **2** and is controlled by the basicity of the alkoxide ion, in which a proton is transferred from the hydroxylammonium ion of the initially formed amine adduct. Since electron-donating substituents on the 3-aryl group enhance the basicity of the alkoxide ion, the *p*-methoxy-substituted dioxetane **1a** should yield a higher fraction of hydroxylamine ether **2** than the *p*-nitro-substituted derivative **1c**, as is observed (entries 1 and 3). Additionally, the formation of the ketone products (the driving force for the Grob fragmentation in the primary zwitterionic intermediate) appears to be more feasible for electron-accepting substituents attached to the carbonyl functionality, as is displayed in the observed product ratios for the reaction of the dioxetanes **1a–c**, in that the fraction of dioxetane fragmentation products **3a–c** increases with the electron-accepting ability of the para substituents (entries 1–3).

The complex product mixture (Scheme 3) for the reaction of the bromomethyl-substituted dioxetane **1f** with morpholine is rationalized mechanistically in Scheme 5. The products, **2f**, **5f**, and **6f** can be reconciled quite straightforwardly. Thus, S_N2 attack and proton transfer afford the adduct **2f** initially. Subsequent dehydrobromination (path A in Scheme 5) leads to epoxide **5f**, while hydrolysis (path B in Scheme 5) generates diol **6f** and *N*-hydroxymorpholine. The instability of the hydroxylamine ethers formed in the reaction of other secondary amines (e.g. diisopropylamine) with dioxetane **1f** has been documented in the literature,[9] but nothing has been reported about the fate of these unstable species. The formation of the hydroperoxide **4f** is a consequence of HBr formation in the **2f** → **5f** step (path A in Scheme 5). The HBr is neutralized in the form of the morpholinium bromide, which is sufficiently acidic (pK_a 8.33[12]) to catalyze ring opening of the dioxetane **1f** to produce the bromine-stabilized hydroperoxy-substituted carbocation (path C in Scheme 5). Nucleophilic attack of the latter by free morpholine affords the hydroperoxide **4f**.

Support for this mechanistic rationalization has recently been provided by the reaction of dioxetane **1f** with 3′,5′-diacetyl-2′-deoxythymidine.[13] The latter is also sufficiently acidic to catalyze ring opening of dioxetane **1f** with formation of the benzylic cation. The exceptional behavior of dioxetane **1f** was explained in terms of the additional stabilization of the benzylic cation derived from formation of a bromonium ion. Bronsted or Lewis acid-catalyzed dioxetane ring opening has already been observed earlier for other systems.[14]

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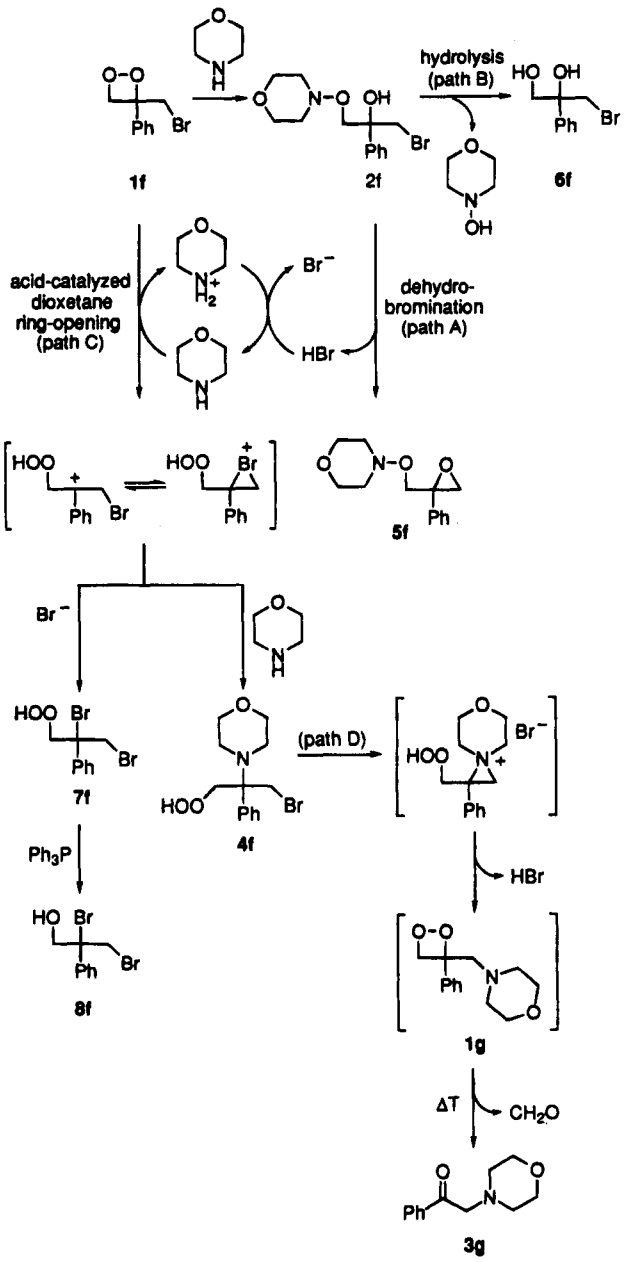
(11) Tanner, D. D.; Chen, J. J.; Chen, L.; Luelo, C. *J. Am. Chem. Soc.* **1991**, *113*, 8074–8081.
(12) *CRC Handbook of Chemistry and Physics*, 67th ed.; Weast, R. C., Ed.; CRC Press, Inc.: Boca Raton, FL, 1986, pp D159–161.
(13) Adam, W.; Treiber, A. *J. Am. Chem. Soc.*, submitted for publication, 1994.
(14) (a) Bartlett, P. D.; Baumstark, A. L.; Landis, M. E. *J. Am. Chem. Soc.* **1977**, *99*, 1890–1892. (b) Adam, W.; Hadjiarapoglou, L.; Mosandl, T.; Saha-Möller, C. R.; Wild, D. *J. Am. Chem. Soc.* **1991**, *113*, 8005–8011.

Scheme 5



More direct evidence constitutes the control experiment with authentic morpholine hydrobromide. Indeed, the latter catalyzes the ring opening of dioxetane **1f** (path C in Scheme 5) to yield the hydroperoxide **7f**, which was characterized in terms of dibromo alcohol **8f** by triphenylphosphine deoxygenation. In contrast, the hydrobromides of diisopropylamine (pK_a = 10.96[12]) and triethylamine (pK_a = 11.01[12]) are not sufficiently acidic to promote such dioxetane ring opening (path C in Scheme 5).

To explain the formation of the ω-morpholinoacetophenone (**3g**) from the hydroperoxide **4f**, we propose as the first step internal S_N2 attack by the morpholino nitrogen atom with bromide ion elimination to generate the spiroammonium ion (path D in Scheme 5). Subsequent nucleophilic attack by the hydroperoxide functionality leads to 3-(morpholinomethyl)-3-phenyldioxetane (**1g**) on cyclization. The latter dioxetane decomposes into formaldehyde and the ω-substituted acetophenone **3g**. The formation of acetophenone **3g** through direct reaction of morpholine with ω-bromoacetophenone (**3f**), the dioxetane **1f** fragmentation product, was ruled out by means of the control experiment that under the reaction conditions morpholine is unreactive toward ω-bromoacetophenone (cf. Results). Unfortunately, dioxetane **1g** was not detected, presumably in view of its labile nature, a characteristic trait of amino-substituted dioxetanes.

In summary, we conclude that the reactivity of the dioxetanes **1** toward morpholine, or for that matter nucleophiles in general, is mainly determined by the electron-accepting propensity of the substituents in the 3-position. The energy of the σ^* orbital (LUMO) of the dioxetane **1** is decreased, and, therefore, the S_N2 reaction mode at the peroxide bond is favored. The product distribution between the hydroxylamine ethers **2** and the dioxetane fragmentation products **3** correlates with the electronic features of the primary dipolar adduct produced in the nucleophilic attack at the peroxide bond. Hydroxylamine ether **2** formation depends on the basicity of the alkoxide ion, which is enhanced by electron-donating substituents in the para position of the 3-aryl-substituted dioxetanes **1a–c**, while Grob fragmentation to the dioxetane cleavage products is enhanced by the increasing electron-accepting ability of the substituents. An unexpected novel pathway constitutes the formation of the hydroperoxide **4f** in the reaction of the dioxetane **1f** with morpholine, which results from acid-catalyzed ring opening of the dioxetane by morpholinium bromide and subsequent morpholine trapping of the stabilized, bromine-bridged benzylic cation.

Experimental Section

General Aspects. Melting points were taken on a Reichert Thermovar Kofler apparatus and are uncorrected. ^1H NMR spectra were taken on a Bruker AC 200 (200 MHz) and a Bruker AC 250 (250 MHz) with $CDCl_3$ as internal standard. ^{13}C NMR spectra were taken on a Bruker AC 200 (50 MHz) and a Bruker AC 250 (63 MHz) with $CDCl_3$ as internal standard. If not otherwise stated, all spectra were recorded at ambient temperature. Infrared spectra were taken on a Perkin-Elmer 1420 ratio-recording infrared spectrophotometer. Combustion analyses were carried out by the Microanalytical Division on the Institute of Inorganic Chemistry, University of Würzburg. Column chromatography was carried out out on silica gel (63–200 μm) from Woelm; the adsorbant/substrate ratio was ca. 100:1. Thin layer chromatography (TLC) was carried out on Polygram SIL G/UV_{254} (40 × 80 mm) from Macherey-Nagel; peroxides were detected by 10% aqueous KI solution and other products by means of a 5% ethanolic solution of molybdophosphoric acid.

Dioxetanes **1** were prepared according to literature methods by base-catalyzed cyclization of the corresponding β-bromo hydroperoxides.

Caution! β-Bromo hydroperoxides and the 1,2-dioxetanes **1** may decompose spontaneously when allowed to warm up over 0 °C. Dioxetane **1b**, especially, must be handled with extreme care since it may vigorously decompose even at low temperatures.

General Procedure for the Reaction of Dioxetanes 1a–f with Morpholine. A solution of 0.270–0.970 mmol of the particular dioxetanes **1** in 10 mL of methylene chloride was cooled to 0 °C, and 1 equiv of morpholine dissolved in 1 mL of methylene chloride was added. The reaction mixture was stirred at 0 °C until the negative peroxide test (KI/HOAc) indicated complete conversion of the dioxetane **1**. The solvent was evaporated at 20 °C/15 Torr, and the crude product mixture was taken up in deuteriochloroform (0.8 mL) and submitted to ^1H NMR spectroscopy for the determination of the product distribution after addition of hexamethyldisiloxane as internal standard. The products were isolated by means of silica gel column chromatography by eluting with mixtures of methylene chloride and ethyl acetate.

Reaction of 3-(4-Methoxyphenyl)-3methyldioxetane (1a) with Morpholine. According to the above general procedure, 143 mg (0.790 mmol) of dioxetane **1a**[15] was allowed to react with 69.1 mg (0.790 mmol) of morpholine for 14 h. Evaporation of the solvent, followed by column chromatography (10:1 methylene chloride/ethyl acetate), afforded as a first fraction 29.6 mg (25%) of 4-methoxyacetophenone (**3a**) and as a second fraction 127 mg (60%) of the hydroxylamine ether **2a** as a colorless solid.

***N*-[2-Hydroxy-2-(4-methoxyphenyl)propoxy]morpholine (2a):** mp 100–101 °C; R_f (10:1 methylene chloride/ethyl acetate) 0.28; IR (CCl_4) ν 3350, 3000, 2950, 2920, 2880, 1620, 1530, 1475, 1395, 1310, 1260, 1190, 1120, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.47 (s, 3 H), 2.50 (td, J_1 = 10.9 Hz, J_2 = 3.5 Hz, 1 H), 2.65 (td, J_1 = 10.9 Hz, J_2 = 3.5 Hz, 1 H), 2.94 (dd, J_1 = 10.7 Hz, J_2 = 1.9 Hz, 1 H), 3.30 (dd, J_1 = 10.6 Hz, J_2 = 1.9 Hz, 1 H), 3.4–3.7 (m, 2 H), 3.80 (s, 3 H) 3.8–4.0 (m, 4 H), 5.50 (s, 1 H), 6.88 (d, J = 8.9 Hz, 2 H), 7.39 (d, J = 8.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.5 (q), 55.4 (q), 55.7 (t), 66.3 (t), 75.9 (s), 77.2 (t), 113.6 (d), 126.6 (d), 138.1 (s), 158.5 (s). Anal. Calcd for $C_{14}H_{21}NO_4$ (267.4): C, 62.89; H, 7.93; N, 5.24. Found: C, 63.03; H, 8.30, N, 5.33.

Reaction of 3-Methyl-3-phenyldioxetane (1b) with Morpholine. According to the above general procedure, 145 mg (0.970 mmol) of dioxetane **1b**[16] was allowed to react with 84.5 mg (0.970 mmol) of morpholine for 11 h. Evaporation of the solvent, followed by silica gel chromatography (6:1 methylene chloride/ethyl acetate), afforded as a first fraction 50.5 mg (43%) of acetophenone (**3b**) and as a second fraction 99.1 mg (42%) of the hydroxylamine ether **2b** as a colorless solid.

***N*-(2-Hydroxy-2-phenylpropoxy)morpholine (2b):** mp 51–52 °C; R_f (6:1 methylene chloride/ethyl acetate) 0.28; IR (CCl_4) ν 3340, 2970, 2860, 1540, 1260, 1215, 1105, 1010 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.49 (s, 3 H), 2.50 (td, J_1 = 10.9 Hz, J_2 = 3.5 Hz, 1 H), 2.64 (td, J_1 = 10.9 Hz, J_2 = 3.5 Hz, 1 H), 2.91 (dd, J_1 = 10.7 Hz, J_2 = 1.9 Hz, 1 H), 3.29 (dd, J_1 = 10.7 Hz, J_2 = 1.9 Hz, 1 H), 3.4–3.7 (m, 2 H), 3.8–4.0 (m, 2 H), AB pattern (δ_A 3.87, δ_B 3.96, J = 12.5 Hz, 2 H), 5.45 (s, 1 H), 7.2–7.6 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.3 (q), 55.5 (t), 66.1 (t), 76.0 (s), 76.8 (t), 125.2 (d), 126.7 (d), 128.1 (d), 145.8 (s). Anal. Calcd for $C_{13}H_{19}NO_3$ (237.3): C, 65.78; H, 8.08; N, 5.90. Found: C, 65.38; H, 8.20; N, 5.90.

Reaction of 3-(4-Nitrophenyl)-3-methoxydioxetane (1c) with Morpholine. According to the above general procedure, 63.0 mg (0.320 mmol) of dioxetane **1c**[15] was allowed to react with 27.9 mg (0.320 mmol) of morpholine for 2 h. Evaporation of the solvent, followed by silica gel column chromatography (6:1 methylene chloride/ethyl acetate), afforded as a first fraction 15.3 mg (0.170 mmol) of 4-nitroacetophenone (**3c**) and as a second fraction 23.5 mg (26%) of the hydroxylamine ether **2c** as a colorless solid.

***N*-[2-Hydroxy-2-(4-nitrophenyl)propoxy]morpholine (2c):** mp 111 °C; R_f (6:1 methylene chloride/ethyl acetate) 0.52; IR (CCl_4) ν 3340, 2970, 2860, 1540, 1260, 1215, 1105, 1010 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.49 (s, 3 H), 2.50 (td, J_1 = 10.9 Hz, J_2 = 3.5 Hz, 1 H), 2.64 (td, J_1 = 10.9 Hz, J_2 = 3.5 Hz, 1 H), 2.91 (dd, J_1 = 10.7 Hz, J_2 = 1.9 Hz, 1 H), 3.29 (dd, J_1 = 10.7 Hz, J_2 = 1.9 Hz, 1 H), 3.4–3.7 (m, 2 H), 3.8–4.0 (m, 2 H), AB pattern (δ_A 3.87, δ_B 3.96, J = 12.5 Hz, 2 H), 5.45 (s, 1 H), 7.65 (d, J = 8.6 Hz, 2 H), 8.20 (d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.3 (q), 55.5 (t), 66.1 (t), 76.0 (s), 76.8 (t), 125.2 (d), 126.7 (d), 142.1 (s), 153.6 (s). Anal. Calcd for $C_{13}H_{18}N_2O_5$ (282.3): C, 55.32; H, 6.43; N, 9.93. Found: C, 55.64; H, 6.59; N, 9.70.

Reaction of 3-(Methoxymethyl)-3-phenyldioxetane (1d) with Morpholine. According to the above general procedure, 100 mg (0.550 mmol) of dioxetane **1d**[12] was allowed to react with 48.3 mg (0.550 mmol) of morpholine for 12 min. Evaporation of the solvent, followed by silica gel column chromatography (10:1 methylene chloride/ethyl acetate), afforded as a first fraction traces of ω-methoxyacetophenone (**3d**). As a second fraction, 91.2 mg (62%) of the hydroxylamine ether **2d** was obtained as a colorless oil.

***N*-(2-Hydroxy-3-methoxy-2-phenylpropoxy)morpholine (2d):** R_f (10:1 methylene chloride/ethyl acetate) 0.20; IR (CCl_4) ν 3240, 2990, 2950, 2870, 1560, 1305, 1260, 1220, 1110, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.52 (td, J_1 = 10.9 Hz, J_2 = 3.4 Hz, 1 H), 2.64 (tdd, J_1 = 10.9 Hz, J_2 = 3.4 Hz, 1 H), 2.88 (dd, J_1 = 10.7 Hz, J_2 = 1.9 Hz, 1 H), 3.26 (dd, J_1 = 10.7 Hz, J_2 = 1.9 Hz, 1 H), 3.4–3.7 (m, 2 H), 3.34 (s, 3 H), AB pattern (δ_A 3.51, δ_B 3.58, J = 9.7 Hz, 2 H), 3.8–4.0 (m, 2 H), AB pattern (δ_A 4.05, δ_B 4.18 J = 12.5 Hz, 2 H), 7.2–7.6 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.3 (t), 55.4 (t), 59.4 (q), 65.9 (t), 67.9 (t), 73.6 (t), 77.1 (s), 78.1 (t), 125.8 (d), 126.9 (d), 127.8 (d), 142.5 (s). Anal. Calcd for $C_{14}H_{21}NO_4$ (267.4): C, 62.91; H, 7.92; N, 5.24. Found: C, 62.70; H, 7.98; N, 5.21.

Reaction of 3-(Chloromethyl)-3-phenyldioxetane (1e) with Morpholine. Fifty milligrams (0.270 mmol) of dioxetane **1e** was dissolved in 0.8 mL of deuteriochloroform, the mixture was transferred to a NMR tube at 0 °C, and 23.7 mg (0.270 mmol) of morpholine was added. After 3 min, the peroxide test (KI/HOAc) showed complete consumption of the dioxetane. ^1H and ^{13}C NMR analysis of the crude reaction mixture showed the hydroxylamine ether **2e** to be the main product (>95%), besides small amounts (<5%) of ω-chloroacetophenone (**3e**). The NMR spectral data of the compounds **2e** and **3e** were in accordance with data reported in the literature.[5]

Reaction of 3-(Bromomethyl)-3-phenyldioxetane (1f) with Morpholine. Dioxetane **1f** (200 mg, 0.873 mmol) was dissolved in 10 mL of methylene chloride at 0 °C, and 76.1 mg (0.873 mmol) of morpholine was added. After 5 min of reaction time, no dioxetane **1f** could be detected by TLC. The reaction mixture was kept at 0 °C for 14 h and was then submitted to silica gel column chromatography (20:1 methylene chloride/methanol). As a first fraction, 6.90 mg (4%) of ω-bromoacetophenone (**3f**) was isolated, followed by 18.4 mg (9%) of *N*-(2-phenyl-2,3-epoxypropoxy)morpholine (**5f**). As a third fraction, a mixture of 119 mg (59%) of the diol **6f** and 32.4 mg (18%) of ω-morpholinoacetophenone (**3g**) was obtained. Finally, 32.4 mg (36%) of *N*-hydroxymorpholine was eluted by using pure methanol. The diol **6f**[15] and the ω-substituted acetophenones **3f** and **3g** are known in the literature and were identified by their ^1H and ^{13}C NMR spectra.

***N*-(2-Phenyl-2,3-epoxypropoxy)morpholine (5f):** R_f (20:1 methylene chloride/methanol) 0.58; IR (CCl_4) ν 3660, 2940, 2900, 2820, 1650, 1585, 1440, 1420, 1250, 1200, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.62 (m, 2 H), 2.80 (d, J = 5.5 Hz, 1 H), 3.0–3.2 (m, 2 H), 3.12 (d, J = 5.5 Hz, 1 H), 3.54 (t, J = 11.3 Hz, 2 H), 3.84 (m, 2 H), AB pattern (δ_A 4.09, δ_B 4.31, J = 11.9 Hz, 2 H), 7.3–7.5 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 53.7 (t), 56.2 (t), 56.2 (t), 58.2 (s), 66.2 (t), 74.4 (), 126.0 (d), 127.7 (d), 128.3 (d), 138.0 (s). A satisfactory elemental analysis of the epoxide **5f** could not be obtained due to its labile nature.

3-Bromo-2-phenylpropane-1,2-diol (6f): R_f (20:1 methylene chloride/methanol) 0.43; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.20 (br s, 1 H), 3.50 (br s, 1 H), AB pattern (δ_A 3.82, δ_B 3.93, J = 10.7 Hz, 2 H), 3.85 (br s, 2 H), 7.30–7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 41.0 (t), 68.2 (t), 75.8 (s), 125.4 (d), 127.9 (d), 128.5 (d), 140.9 (s).

Reaction of 3-(Bromomethyl)-3-phenyldioxetane (1f) with Morpholine (Low-Temperature NMR Experiment). A sample of 50.0 mg (0.220 mmol) of dioxetane **1f** was dissolved in 0.8 mL of deuteriochloroform at 0 °C, and 19.2 mg (0.220 mmol) of morpholine was added. The ^1H NMR spectrum was recorded after 5 min, which showed complete conversion of the dioxetane, but the peroxide test (KI/HOAc) of the reaction mixture was still positive. Low-temperature ^1H and ^{13}C NMR spectroscopy of the crude reaction mixture indicated the formation of two compounds, which were identified as the hydroxylamine ether **2f** and 1-bromo-3-hydroperoxy-2-morpholino-2-phenylpropane (**4f**). Due to their labile nature, neither hydroxylamine ether **2f** nor hydroperoxide **4f** could be isolated by low-temperature column chromatography.

***N*-(3-Bromo-2-hydroxy-2-phenylpropoxy)morpholine (2f):** R_f (20:1 methylene chloride/methanol) 0.36; ^1H NMR ($CDCl_3$, 200 MHz, −20 °C) δ 2.47 (dt, J_1 = 10.9 Hz, J_2 = 3.2

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Hz, 1 H), 2.65 (td, J_1 = 10.9 Hz, J_2 = 3.1 Hz, 1 H), 3.2–4.0 (m, 6 H), AB pattern (δ_A 3.63, δ_B 3.69, J = 10.6 Hz, 2 H), AB pattern (δ_A 4.07, δ_B 4.23, J = 13.1 Hz, 2 H), 7.2–7.6 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz, −20 °C) δ 40.6 (t), 55.2 (t), 65.9 (t), 73.4 (t), 76.8 (s), 125.7 (d), 127.6 (d), 128.3 (d), 141.5 (s).

1-Bromo-3-hydroperoxy-2-morpholino-2-phenylpropane (4f): R_f (20:1 methylene chloride/methanol) 0.62; ^{1}H NMR resonances of the hydroperoxide **4f** completely superimposed by the signals of hydroxylamine ether **2f**; ^{13}C NMR ($CDCl_3$, 50 MHz, −20 °C) δ 41.1 (t), 53.8 (t), 55.3 (t), 68.1 (t), 68.5 (t), 66.7 (s), 88.5 (t), 125.3 (d), 127.9 (d), 128.6 (d), 138.5 (s).

Formation of the Hydroperoxide 4f at Variable Temperature. A sample of 50.0 mg (0.218 mmol) of dioxetane **1f** was dissolved in 1 mL of deuteriochloroform, and the solution was cooled to the appropriate temperature. Then 19.0 mg (0.219 mmol) of morpholine was added, and the reaction was monitored by means of TLC (20:1 methylene chloride/methanol). When the dioxetane **1f** was completely consumed, the solution was brought to 0 °C and the peroxide content was determined iodometrically to be <3% (−60 °C), 8% (−20 °C), 15% (0 °C), and 29% (20 °C).

Reaction of Dioxetane 1f with Morpholine Hydrobromide. A sample of 200 mg (0.873 mmol) of the dioxetane **1f** was dissolved in 10 mL of dry methanol, and the solution was cooled to 0 °C. To the solution was added 147 mg (0.873 mmol) of morpholine hydrobromide, and after 10 min, the dioxetane **1f** was completely consumed. The solvent was evaporated at 0 °C/15 Torr, and the crude product mixture was submitted to low-temperature NMR spectoscopy.

2,3-Dibromo-2-phenylpropyl Hydroperoxide (7f). The ^{1}H NMR resonances of the hydroperoxide **7f** were completely superimposed by those of the diol **6f** and the morpholine hydrobromide; ^{13}C NMR (methanol-d_4, 200 MHz, −20 °C) δ 37.3 (t), 69.1 (s), 87.0 (t), 126.4 (d), 128.1 (d), 128.6 (d), 141.3 (s).

To the above reaction mixture was added 229 mg (0.873 mmol) of triphenylphosphine, and the mixture was stirred at 0 °C for 2 min until the negative peroxide test indicated the complete deoxygenation of the hydroperoxide **7f**. The solvent was removed at 20 °C/15 Torr, and the crude product mixture was submitted to silica gel column chromatography by eluting with methylene chloride. As a first fraction, 15.4 mg (6%) of the dibromo alcohol **8f** was isolated (colorless oil), followed by 103 mg (51%) of the diol **6f** (colorless oil which crystallized upon standing at room temperature).

2,3-Dibromo-2-phenylpropan-1-ol (8f): R_f (methylene chloride) 0.53; IR (CCl_4) ν 3460–3200, 3085, 3050, 1570, 1455, 1260, 1225, 1095, 1085, 1020, 960 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.27 (dd, J_1 = 8.5 Hz, J_2 = 5.4 Hz, 1 H), AB pattern (δ_A 4.23, δ_B 4.40, J = 10.3 Hz, 2 H), AB pattern (δ_A 4.26, dd, J_1 = 12.5 Hz, J_2 = 5.4 Hz, 1 H, δ_B 4.43, dd, J_1 = 12.5 Hz, J_2 = 8.5 Hz, 2 H), 7.3–7.7 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.4 (t), 67.2 (t), 71.9 (s), 127.1 (d), 128.7 (d), 129.0 (d), 138.6 (s). Anal. Calcd for $C_9H_{11}Br_2O$ (294.0): C, 36.77, H, 3.44. Found: C, 37.05; H, 3.61.

Reaction of Dioxetane 1f with Diisopropylamine Hydrobromide. A sample of 50.0 mg (0.218 mmol) of dioxetane **1f** was dissolved in 5 mL of dry methanol, and the solution was cooled to 0 °C. To the mixture was added 39.7 mg (0.218 mmol) of diisopropylamine hydrobromide as a methanol solution (ca. 1 mL). After 10 min of reaction time, no dioxetane **1f** could be detected by TLC and the solvent was evaporated at 20 °C/15 Torr. TLC as well as the ^{1}H and ^{13}C NMR spectra of the crude product mixture showed the diol **6f** to be the only product.

Reaction of Dioxetane 1f with Triethylamine Hydrobromide. By following the above procedure, a sample of 50.0 mg (0.218 mmol) of dioxetane **1f** in 5 mL of dry methanol at 0 °C was treated with 39.7 mg (0.218 mmol) of triethylamine hydrobromide. After 10 min, no dioxetane **1f** could be detected by TLC and the solvent was evaporated at 20 °C/15 Torr. TLC as well as the ^{1}H and ^{13}C NMR spectra of the crude product mixture showed the diol **6f** to be the only product formed.

Reaction of ω-Bromoacetophenone (3f) with Morpholine. A sample of 50.0 mg (0.251 mmol) of ω-bromoacetophenone (**3f**) was dissolved in 0.8 mL of deuteriochloroform. To the cooled (0 °C) solution was added 21.9 mg (0.251 mmol) of morpholine, and the solution was kept for 5 min. ^{1}H NMR spectroscopy as well as TLC was used to demonstrate that, within this reaction time, no ω-morpholinoacetophenone (**3g**) was formed.

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