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Generation of Mono- and Bis-dioxiranes from 2,3-Butanedione

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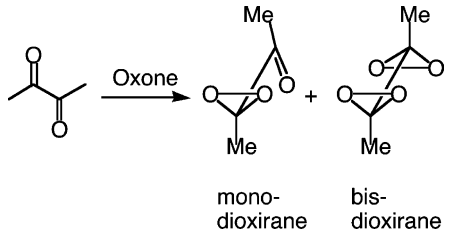
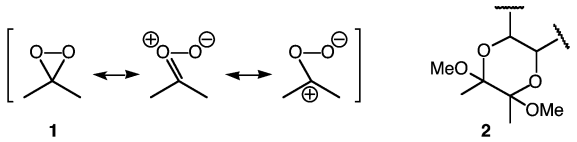


Biacetyl reacts with oxone to give bis-dioxirane [3,3′-dimethyl-3,3′-bidioxirane, **3B**] and mono-dioxirane [1-(3-methyl-dioxiran-3-yl)ethanone, **3A**)]. Bis-dioxirane **3B** is formed when two oxygens are incorporated into biacetyl, while mono-dioxirane **3A** incorporated only one. A greater stability is observed in **3B** compared to **3A**, which is attributed to an α-dioxiranyl (anomeric) effect in the former. In contrast, **3A** suffers from a destabilizing π-electron withdrawing effect from the adjacent carbonyl group.

Dimethyldioxirane (**1**) possesses low strain energy (11 kcal/mol) compared to oxirane (26 kcal/mol) and cyclopropane (27 kcal/mol) based on ab initio calculations.[1] The low strain energy of **1** was rationalized assuming *gem*-dioxa anomeric stabilization (Scheme 1).[1] Vicinal *gem*-dioxa-containing molecules are known. Thus, structures bearing 1,2-bis-acetals would be topologically similar to a hypothetical bis-dioxirane (**3B**, Scheme 2). The comparison of **1** with butane-2,3-bisacetal (**2**), such as the 1,1,2,2-oxygenation generated as a protecting group for 1,2-diols, led us to raise the following question: *Can more than one dioxirane center occupy a molecule?* Despite the intense interest in the synthesis of dioxiranes,[2] in studies gauging dioxirane stability,[3] and in oxone-mediated cleavage of 1,2-dicarbonyl compounds,[4] no studies have yet focused on molecules containing adjacent α-dioxirane groups (1,2-bis-dioxiranes). The juxtaposition of two dioxirane groups would represent a new type of structure in dioxirane chemistry.

SCHEME 1



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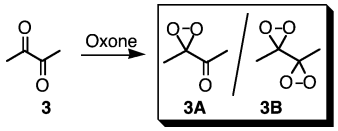
SCHEME 2



3 3A 3B

In the present work, we focus on the synthesis of a molecule containing α-dioxirane groups, **3B**, along with mono-dioxirane **3A**. Rationale is presented to account for the greater stability of **3B** compared to **3A**.

NMR Spectroscopy and Chemical Trapping. The oxidation of biacetyl (1.23 M) in buffered aqueous solution at pH 7 was conducted in the presence of oxone (0.48 M) at −17 °C. Separation of the organic-soluble fraction at −17 °C led to the detection of the mono-dioxirane **3A** and the bis-dioxirane **3B** along with carbon dioxide, acetic acid, and other byproducts (discussed later). The low-temperature separation method permitted an NMR analysis at −17 °C of unstable **3A** and **3B**. Two sets of peaks disappeared as a result of addition of sulfide or on warming the sample to 25 °C according to NMR. An HMBC experiment on **3A** shows a long-range correlation of H2 (1.59 ppm) with the dioxirane carbon (94.5 ppm) and carbonyl carbon (208.0 ppm) (Figure 1). A directly attached methyl carbon of H2 was identified at 24.4 ppm by a HSQC experiment. However, the methyl α to the carbonyl group (2.41 ppm) is obscured by the biacetyl peak. With a HMBC experiment on **3B**, the correlation between H1 (1.41 ppm) and dioxirane carbon (110.5 ppm) was identified, while a HSQC experiment confirmed the directly attached methyl carbon at 21.6 ppm (Figure 2). The measured integral values indicate that the relative ratio of **3A**:**3B** is 5:1. Dioxiranes **3A** and **3B** are stable at −17 °C but cannot be obtained in pure form to enable their complete characterization.

Chemical trapping studies[5] provided strong evidence for the presence of the dioxirane intermediates **3A/3B**. Oxygenation

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(2) A very abbreviated list of the literature includes: (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (b) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (c) Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792. (d) Sartori, G.; Armstrong, A.; Maggi, R.; Mazzacani, A.; Sartorio, R.; Bigi, F.; Dominguez-Fernandez, B. *J. Org. Chem.* **2003**, *68*, 3232. (d) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497. (e) Curci, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* **2006**, *39*, 1. (f) Chan, T.-C.; Chan, W.-Y.; Chan, W.-K.; Vrijmoed, L. L. P.; O'Toole, D. K.; Wong, M.-K.; Che, C.-M. *Environ. Sci. Technol.* **2006**, *40*, 625.

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(5) Sulfides have been used previously to assay dioxirane content: (a) Murray, R. W.; Jeyaraman, R.; Pillay, M. K. *J. Org. Chem.* **1987**, *52*, 746. (b) Gonzalez-Nunez, M. E.; Mello, R.; Royo, J.; Rios, J. V.; Asensio, G. *J. Am. Chem. Soc.* **2002**, *124*, 9154.

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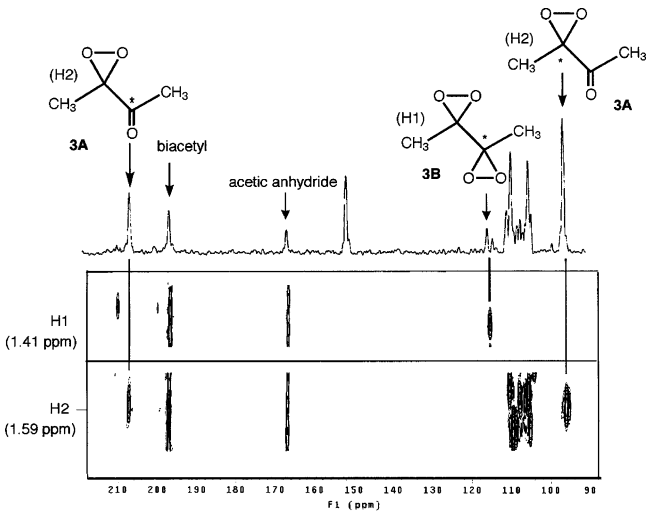


FIGURE 1. HMBC −17 °C spectra [600 MHz, $CDCl_3$:$CHCl_3$ (4:1 ratio)] of **3A** and **3B** taken from the $CHCl_3$ extract of the biacetyl (1.23 M) oxone (0.48 M) buffer mixture. The extra cross-peaks are attributed to solvents and hydrated compounds.

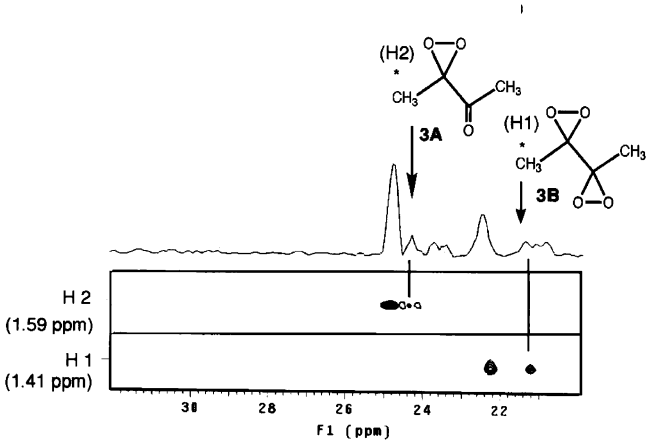
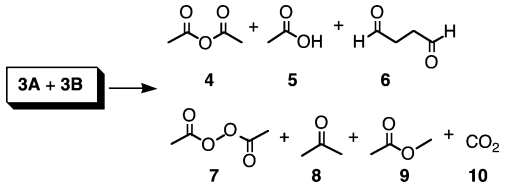


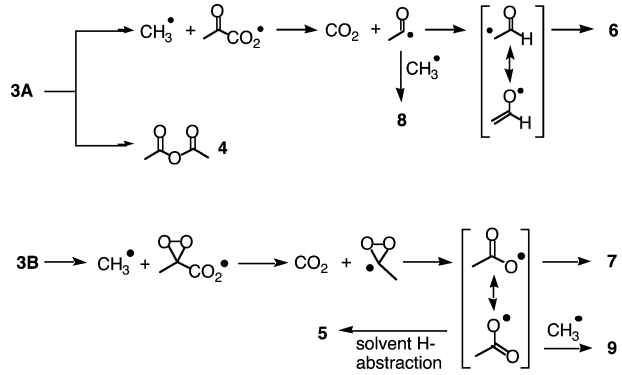
FIGURE 2. HSQC −17 °C spectra [600 MHz, $CDCl_3$:$CHCl_3$ (4:1 ratio)] of **3A** and **3B** taken from the $CHCl_3$ extract of the biacetyl (1.23 M) oxone (0.48 M) buffer mixture. The extra cross-peaks are attributed to solvents and hydrated compounds.

of added Ph_2S or (p-CH_3O−C_6H_4)$_2$S proceeded at −17 °C in the presence of the organic-soluble fraction of the biacetyl−oxone mixture and was monitored by GC/MS and ^{1}H NMR, respectively. (Control reactions demonstrate that oxone was not present in the organic-soluble fraction after the extraction and is not responsible for the sulfide oxidation reaction) The products formed are the corresponding Ph_2SO and (p-CH_3O−C_6H_4)$_2$SO. The concentrations of sulfoxides were determined to be 0.06 M. Combining the data from the sulfide trapping studies, and from NMR detection allowed us to calculate that the −17 °C organic fraction contains 0.05 M **3A** and 0.01 M **3B**. The observation that diacetyl peroxide **7** reacted slowly with Ph_2S and (p-CH_3O−C_6H_4)$_2$S leads us to suggest that the oxygen-transfer chemistry is derived from **3A** and **3B**. A quantitative study of biacetyl with oxone with added olefins also showed the oxygen-transfer chemistry expected of **3A** and **3B**. 2,3-Dimethyl-2-butene and *trans*-stilbene reacted in the presence of the −17 °C $CHCl_3$ fraction. GC/MS analyses of these reactions revealed the formation of the corresponding epoxides,

SCHEME 3



SCHEME 4



2,2,3,3-tetramethyloxirane (41.7% yield) and *trans*-2,3-diphenyloxirane (47.0% yield). These percent yields were determined after 8 h of stirring at −17 °C.

Reaction Products. The biacetyl−oxone reaction is an effective reaction to generate **3A** and **3B**, but the reaction also gives byproducts. Separation of the organic-soluble fraction at −17 °C led to the detection of seven stable byproducts: acetic anhydride (**4**), acetic acid (**5**), succinaldehyde (**6**), diacetyl peroxide (**7**), acetone (**8**), methyl acetate (**9**), and CO_2 (**10**) (Scheme 3). Some compounds exist as hydrates and reside to a greater extent in the aqueous layer, making quantification difficult.[6] The percent conversion of the biacetyl ranged from 30 to 40%. Carbon dioxide, acetic anhydride, and acetic acid are the major components of this reaction in the organic layer, where acetic acid presumably arises from the hydrolysis of acetic anhydride. Evidence for the formation of **4**, **5**, and **7**−**9** was provided by ^{1}H NMR. Carbon dioxide was detected by ^{13}C NMR. The evidence for the existence of monomeric **6** was provided using ^{1}H and ^{13}C NMR, although **6** may also exist as the hydrate or in dimeric or trimeric forms.

The experimental evidence suggests that intermediates **3A/3B** decompose to the final stable products **4**−**10**. We believe that acyloxy and alkyl radicals play a role in the decomposition of **3A** and **3B**, which arises from homolysis of the O−O bond.[7] Dioxirane **3A** can react to give dialdehyde **6**, and **3B** can convert to the stable diacetyl peroxide **7**, by losing CO_2 (Scheme 4). A process involving methyl radical cleavage can give intermediates $CH_3C(=O)CO_2\bullet$ and $CH_3C(O_2)CO_2\bullet$, subsequently yielding $CH_3C\bullet(=O)$ and $CH_3C\bullet(O_2)$, respectively, upon loss of CO_2. There is reason to believe that rearrangements via [$\bullet CH_2CHO \leftrightarrow CH_2{=}CHO\bullet$] precede tail-to-tail dimerization to **6**, and

(6) Hydrated ketones and aldehydes related to this study have been reported: (a) Lin, T. F.; Christian, S. D.; Affsprung, H. E. *J. Phys. Chem.* **1967**, *71*, 968. (b) Lee, Y. J.; Burr, J. G. *Chem. Phys. Lett.* **1976**, *43*, 146. (c) Buschmann, H. J.; Fueldner, H. H.; Knoche, W. *Ber. Bunsen-Ges.* **1980**, *84*, 41. (d) Burkey, T. J.; Fahey, R. C. *J. Am. Chem. Soc.* **1983**, *105*, 868. (e) Segretario, J. P.; Sleszynski, N.; Partch, R. E.; Zuman, P.; Horak, V. *J. Org. Chem.* **1986**, *51*, 5393.

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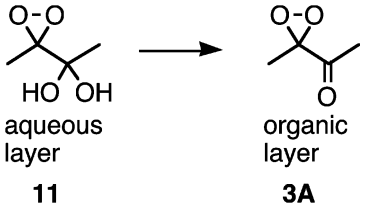
SCHEME 5



CH_3CO_2• precedes dimerization to **7**. Subsequent methyl radical recombination reactions give **8** and **9**, and a H-abstraction process gives **5**. Previous work has been conducted on thermolytic dioxirane fragmentation; electron transfer and radical formations have been suggested.[7,8] The mono-dioxirane **3A** can also produce the stable anhydride **4** by a Baeyer-Villager type rearrangement in an intramolecular process.

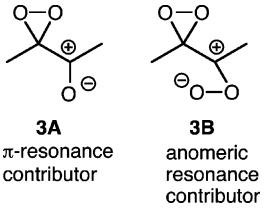
The data suggest that formation of **3B** does not take place efficiently due to a reduced reactivity of the hydrated form of mono-dioxirane with oxone (**11**), which may predominant in the aqueous buffered solution (Scheme 5). Similarly, a previous study reported the equilibrium constant for the monohydration of biacetyl to $CH_3C(OH)_2C(O)CH_3$ to be 2.1.[6c]

The amount of **3A** and **3B** formed is a function of temperature. After heating the −17 °C organic-soluble fraction of the biacetyl−oxone mixture to 25 °C, concentrations of **4**−**10** increased and **3A** and **3B** decreased. Biacetyl serves as the cosolvent and reagent, and the yield of **3A** and **3B** depends on the ratio of biacetyl to oxone used in the reaction. Using an equivalent or excess of oxone to biacetyl (that is, 1:1 and 2:1) resulted in lower concentrations of **3A** and **3B**, but increased concentrations of **4**−**10**. Past a certain point, decomposition of both **3A** and **3B** is facilitated by higher oxone concentrations. Under high oxone-to-biacetyl ratios (5:1 and 10:1) **3A** and **3B** were not observed. The decomposition of **3A** and **3B** and formation of stable products **4**−**10** also takes place rapidly when chloroform, acetonitrile, or buffer is added as a cosolvent with higher added oxone concentrations. It is known that dioxiranes can react with oxone and decompose.

Origin of the Stability of Dioxiranes 3A/3B. The mono-dioxirane **3A** and the bis-dioxirane **3B** differ in their relative stability as revealed by NMR. For example, **3A** decomposes rapidly at 0 °C, while at the same temperature **3B** is stable for 30 min. An explanation on dioxirane stability could follow Bach's lead.[1] The decreased stability of **3A** vs **3B** can be viewed from the greater role of the π-resonance contributor compared to the α-dioxiranyl (anomeric) resonance contributor in terms of α-electron withdrawing capacity (Scheme 6). In contrast to bis-dioxirane **3B**, the mono-dioxirane **3A** will have a weaker O−O bond, as anticipated from a π-electron withdrawing effect from the adjacent carbonyl group. It has been previously shown that substituting one of the methyl groups on **1** with an electron withdrawing CF_3 group increases the electrophilicity of the oxidant.[9]

In conclusion, the data taken together show that the biacetyl−oxone reaction provides the generation of the mono- and bis-dioxiranes, **3A** and **3B**. This result demonstrates that dioxirane

SCHEME 6



units in molecules can be doubled (or even possibly multiplied) to produce new dioxirane structures. A new synthetic utility for **3A** and **3B** has not yet been demonstrated.

Experimental Section

Low-temperature and room-temperature NMR data were acquired on 400 and 600 MHz NMR spectrometers. GC/MS data were also collected. Reagents and solvents [chloroform, chloroform-*d*, 2,3-butanedione, oxone (mono-persulfate triple salt, $2KHSO_5$, $KHSO_4$, and K_2SO_4), sodium phosphate monobasic, sodium phosphate dibasic heptahydrate, sodium sulfite (anhydrous), *m*-chloroperoxybenzoic acid (MCPBA), diphenyl sulfide, diphenyl sulfoxide, 2,3-dimethyl-2-butene, *trans*-stilbene, and triphenyl methane] were obtained commercially and were used as received. The purity of the reagents was checked by ^{1}H NMR and GC/MS prior to use. 2,2,3,3-Tetramethyloxirane and *trans*-2,3-diphenyloxirane were synthesized via MCPBA oxidation of their corresponding alkenes and are known compounds previously described in the literature.[10]

Oxone−biacetyl reactions were conducted with a salted ice bath at −17 °C, where oxone (25 g, 0.0401 mol) in 25 mL of deionized water was added to a solution containing sodium phosphate (pH 7.4, 10 mL), sodium bicarbonate (12 g, 0.14285 mol), chloroform (10 mL), deionized water (10 mL), and 1 g of ice. A −5 °C solution of biacetyl (8 mL, 0.0916 mol) and chloroform (5 mL) was added to the mixture simultaneously with the oxone. Sodium bicarbonate (12.6 g) was used to maintain the pH between 7.4 and 7.8. The reaction mixture was then poured into a beaker cooled to −17 °C containing anhydrous Na_2SO_4: $NaH_2PO_4(H_2O)$:$NaH_2PO_4(7H_2O)$ (4:2:1). The organic layer was separated at low temperature (−17 °C) and dried with magnesium sulfate. Chloroform-*d* was added to a 1 mL sample of the chloroform layer of the reaction mixture, which was then analyzed by low-temperature and room-temperature NMR spectroscopy, and GC/MS. The data used to generate Figures 1 and 2 were collected at −17 °C. Mono-dioxirane [1-(3-methyl-dioxiran-3-yl)ethanone (**3A**)]: ^{1}H NMR ($CDCl_3$, ppm) δ 1.59 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (ppm) δ 208.0, 94.0. Bis-dioxirane [(3,3′-dimethyl-[3,3′]bidioxirane (**3B**)]: ^{1}H NMR ($CDCl_3$, ppm) δ 1.407 (s, 3H); ^{13}C NMR (ppm) 113.7. The data collected for **4**−**10** are consistent with literature values of NMR and/or GC mass spectroscopy.

Concentrations of dioxiranes **3A/3B** were measured by GC/MS with the generation of Ph_2SO from Ph_2S with reference to a calibration curve for Ph_2SO and internal standard, triphenylmethane, and are an average of four runs. Concentrations of dioxirane were also measured by NMR by measuring the generation of (p-CH_3O−$C_6H_4)_2SO$ from (p-CH_3O−$C_6H_4)_2S$ with reference to the internal

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standard triphenylmethane. The concentrations of 2,2,3,3-tetramethyloxirane and *trans*-2,3-diphenyloxirane were determined by GC/MS, where triphenylmethane was used as an internal standard along with prior-determined calibration curves from authentic samples.

Epoxidation and sulfoxidation reactions were conducted as follows: biacetyl (0.008 mol) neat at −5 °C was added to the mixture simultaneously with oxone (24.5 g, 0.04 mol). The organic layer was extracted with $CHCl_3$, washed 3 times with deionized water, dried over anhydrous magnesium sulfate, and added to −10 °C solutions containing either 2,3-dimethyl-2-butene, *trans*-stilbene, diphenyl sulfide, or *p*-methoxyphenyl sulfide (0.001 mol) in 50 mL of acetonitrile. The solutions were stirred for 8 h at −10 °C. Product distributions of the epoxides are the average of four runs. A control experiment demonstrated that oxone was absent in the organic layer, where the solution was examined with added alkenes, which showed that no epoxide was present by GC/MS.

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