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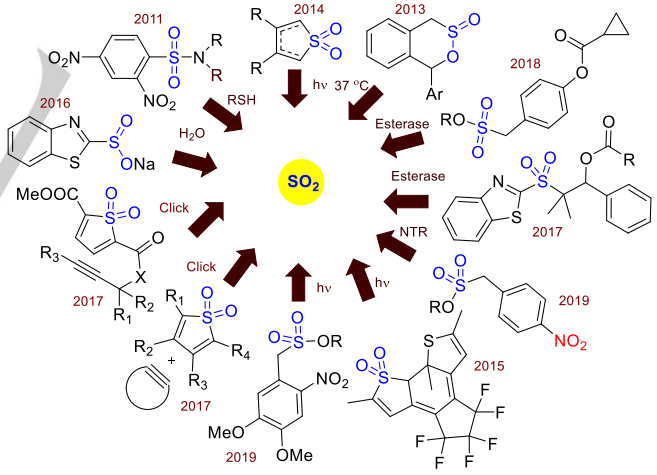
Synthesis and evaluation of cyclic sulfite diesters as sulfur dioxide (SO_2) donors

Satish R. Malwal†, Kundansingh A. Pardeshi, Harinath Chakrapani*

Abstract: Although sulfur dioxide (SO_2) finds widespread use in the food industry as its hydrated form, sulfite, a number of aspects of SO_2 biology remain to be completely understood. Among the tools available for intracellular enhancement of SO_2, most suffer from poor cell permeability and a lack of control over SO_2 release. We report 1,2-cyclic sulfite diesters as a new class of reliable SO_2 donors that dissociate in buffer through a nucleophilic displacement to produce SO_2 with tuneable release profiles. We provide data in support of the suitability of these SO_2 donors to enhance intracellular levels of SO_2 at an efficiency superior to sodium bisulfite, the most commonly used SO_2 donor for cellular studies.

Introduction

Sulfur dioxide (SO_2) is an environmental pollutant that is also produced during metabolism of sulfur containing amino acids[1] as well as hydrogen sulfide (H_2S), which is known to mediate a number of cellular processes.[1d, 2] The known vasodilatory effects of SO_2 in animal models suggest possible signaling roles for this gas as well.[3] SO_2 is also used in the food industry as a preservative and an anti-bacterial agent.[4] At elevated levels SO_2 is known to cause biomacromolecular damage and cell death;[5] these damaging effects are perhaps responsible for the anti-bacterial properties of this gas. However, due to the limited understanding of molecular mechanisms of action of this gas, reliably producing[6] and detecting SO_2 within cells are necessary. While there are numerous probes for SO_2, biological studies have thus far relied on gaseous SO_2 or a complex formulation of inorganic sulfites.[7] Both methods may not be well suited for enhancing SO_2 within cells and offer no temporal control over SO_2 release. Furthermore, they are useful for studying effects of SO_2 as a single dose, which is unsuitable for study of prolonged exposure. Thus, the chemical biology of SO_2 remains largely uncharacterized.[15] Our laboratory has developed several strategies having different triggers for generating SO_2 under physiological conditions using small organic molecules.[8] First, 2,4-dinitrophenylsulfonamides with tunable rates of generation of SO_2 when triggered by biological thiols were reported (Scheme 1). The use of thiol is used as a trigger may complicate biological studies as targets of SO_2 include biologically relevant disulfides and thiols.[8a, 8b, 9] In a second strategy, a series of benzosultines as SO_2 donors with controlled rate of generation of SO_2 under physiological condition, having heat as a trigger was reported (Scheme 1).[8c] Although benzosultines are stable as solids, they are not highly suited for prolonged storage at room temperature as stock solutions. In third strategy, benzosulfones were reported as photochemically activated SO_2 donors by our group and others (Scheme 1).[8d] These compounds might have limitations associated with the inconvenience associated with using a light source in cellular studies and possibly by intensity of light that was required for SO_2 generation.[10] Xian et al. reported sodium benzothiazole sulfonate as water-soluble SO_2 donor, having limitation of prolonged half-life ($t_{1/2}$ = 13 days) at physiological pH 7.4.[11] Recently, SO_2 donors, using esterase[8f, 12], nitroreductase[13], thiol[14]and light[15] as a trigger, and click reaction as a mode of SO_2 donation, have been reported by our, Singh's group and Wang's group (Scheme 1). These strategies rely on the use of cellular enzyme or a bio-orthogonal reaction, which can result in variable generation of sulfur dioxide depending on the availability of the stimulus. Therefore, new self-immolative SO_2 donors which are stable at room temperature and permeate cells to enhance intracellular SO_2 could help better understand cellular responses to this important gaseous molecule.



Scheme 1. Reported strategies for generation of SO_2 under physiological conditions.

1,2-Cyclic sulfite diesters were considered as SO_2 donors (Scheme 2). Upon attack by a nucleophile (such as water), a sulfite monoester would be formed, which could spontaneously decompose to produce SO_2. Modulating substituents "R" or perhaps the pK_a of the leaving group would help tune the rate of substitution by a nucleophile and possibly SO_2 release. Here, we report results of synthesis and evaluation of a series of 1,2-cyclic sulfite diesters as SO_2 donors.

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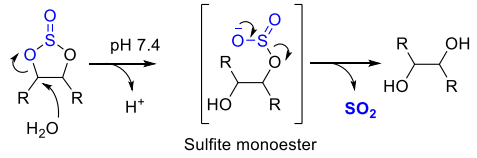


Scheme 2. Sulfite diesters can decompose in pH 7.4 buffer to produce SO_2.

Results and Discussion

1,2-diols used for synthesis of 1,2-cyclic sulfite diesters were either commercially available (**1** and **2**; Figure 1) or prepared by Upjohn dihydroxylation from corresponding olefin by OsO_4 mediated dihydroxylation[16] (diols **3**-**5** and **11**; Figure 1) or by nucleophilic ring opening of 4-substituted styrene oxide by 10% aq. K_2CO_3 solution. The diol **6** and **10** were synthesized from L-tartaric acid, and $NaBH_4$ mediated reduction[17] of (±)-benzoin respectively. The diols **7** and **8**-**9** were prepared by ring opening of corresponding (±)-phenyloxirane and substituted (±)-phenyloxirane, in 10% K_2CO_3 reflux condition respectively. Various 1,2-cyclic sulfite diesters (**12**-**22**) were prepared by the reaction of 1,2-diols with thionyl chloride, triethylamine and imidazole in DCM at 0 °C (Table 1).[18] The *cis*-1,2-diols **3** and **4**, gave an isomeric mixture (depending on sulfoxide orientation) of **14** (1:0.68), **15** (1:0.64) by ^{1}H NMR.[19] The diols **5**, **6** and **11** afforded mixture of diastereomers of **16**, **17** and **18** in the ratios (depending on chirality of sulfoxide), **16** (1:0.95), **17** (~1:1) and **22** (1:0.86) by ^{1}H NMR. The racemic 1,2-diols **7**-**10** afforded mixture of diastereomers for **18**-**21**.

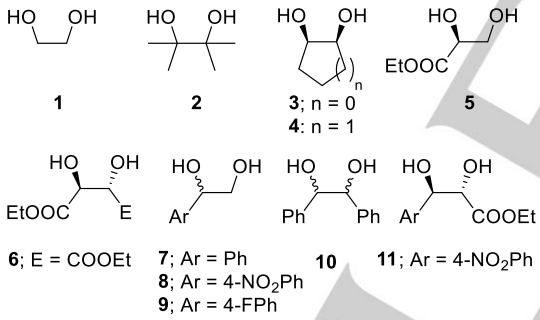
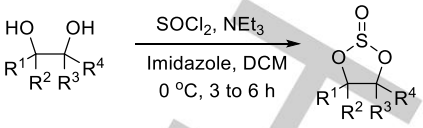


Figure 1. 1,2-diols prepared for synthesis of 1,2-cyclic sulfite diesters.

The aforementioned derivatives **12**-**22** were evaluated for SO_2 release in pH 7.4 phosphate buffer. First, ethylene glycol derivative **12** was incubated at 37 °C in pH 7.4 buffer for 30 min. The reaction was monitored for SO_2 generation by ion chromatography equipped with an ion conductivity detector;[8b] SO_2 was quantified as sulfite, SO_3^{2-}. After 30 min, **12** gave 45% of SO_2 (Table 2, entry 1). The pinacol derivative **13** produced negligible amounts of SO_2 and a 2% yield was recorded (Table 2, entry 2). These results suggest that increasing sterics on the carbon bearing the sulfite functional group reduced the propensity for decomposition of the compound supporting direct displacement at the carbon, which involves formation of a sulfite monoester, which in turn rapidly rearranges to produce SO_2 and an alcohol (Scheme 2)

Table 1. Synthesis of 1,2-cyclic sulfite diesters.



Entry	R^1	R^2	R^3	R^4	Diol	Prod	Yield (%)
1	-H	-H	-H	-H	**1**	**12**	78
2	$-CH_3$	$-CH_3$	$-CH_3$	$-CH_3$	**2**	**13**	96
3	$-(CH_2)_3-$	-H	$-(CH_2)_3-$	-H	**3**	**14**	90
4	$-(CH_2)_4-$	-H	$-(CH_2)_4-$	-H	**4**	**15**	69
5	-COOEt	-H	-H	-H	**5**	**16**	87
6	-COOEt	-H	-COOEt	-H	**6**	**17**	80
7	-Ph	-H	-H	-H	**7**	**18**	93
8	4-NO_2-Ph-	-H	-H	-H	**8**	**19**	81
9	4-F-Ph-	-H	-H	-H	**9**	**20**	75
10	-Ph	-H	-Ph	-H	**10**	**21**	86
11	4-NO_2-Ph-	-H	-COOEt	-H	**11**	**22**	75

In the cases of **12**-**15**, nearly similar pK_a values for the alcohols implies that any difference in SO_2 yields must be due to increased steric hinderance at the carbon bearing the sulfite ester. The diesters **12**, **14** and **15** gave SO_2 yields > 20% after 30 min, whereas pinacol derivative **13** gave 2% of SO_2. These results suggest that when leaving group was similar the important determinant of observed reaction rates was sterics supporting the proposed mechanism (Scheme 2). These results are also consistent with previous reports[20] of 1,2-cyclic sulfite diesters undergoing nucleophilic substitution with various nucleophiles such as chloride, azide and $(CH_3OOC)_2HC^-$ at one of the activated carbon atoms (Scheme 2).[20-21] The hydrolysis of cyclic sulfite esters of normal, or *cis* or *trans* diols under acidic (cat. H_2SO_4/$HClO_4$) or basic (2 eq. NaOH) reflux condition, results in sulfur-oxygen bond fission to give corresponding diol without change in stereo-configuration.[20, 22]

In order to study the electronic effect on decomposition, diesters **16** and **17** were incubated in pH 7.4 buffer and 93% and 98% SO_2, respectively were recorded (Table 2, entry 5 and 6). These compounds contain an electron withdrawing substituent as compared to ethylene glycol diester **12**. The electron withdrawing nature of the ester enhances electrophilicity of the carbon bearing the sulfite functional group contributing to an increased rate of displacement.

Next, decomposition of derivatives with phenyl substituent **18**-**21** was carried out. After 30 min, the phenyl derivative **18** gave 73% of SO_2 (Table 2, entry 7). The 4-NO_2- phenyl derivative **19** on the other hand produced higher amount of SO_2 and a 96% yield was obtained (Table 2, entry 8). Incubation of the 4-F-phenyl derivative **20** (Table 2, entry 9) resulted in a nearly similar SO_2 yield as that of phenyl derivative **18**. The diphenyl derivative **21**

gave 83% SO_2 after 30 min (Table 2, entry 10). These results suggest that electron withdrawing group on phenyl substituent increases the rate of decomposition, again consistent with a nucleophilic displacement mechanism. Hence, it appears that SO_2 generation has little dependence on the nature of the leaving group and the intermediate formed is quite unstable and collapses to produce sulfur dioxide (Scheme 2). Steric and electronic factors around the electrophilic carbon determine yields of sulfur dioxide while the pK_a doesn't appear to affect the outcome of the reaction. The possibility of a concerted process, i.e. nucleophilic displacement along with generation of SO_2 cannot be ruled out. Lastly, consistent with this trend compound **22**, which has a strong electron withdrawing group attached to the core skeleton gave an excellent yield.

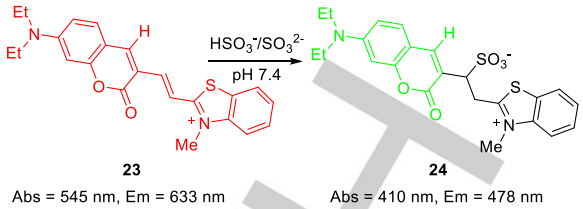
Table 2. Sulfur dioxide yields and calculated pK_as of 1,2-diols.

Entry	Compd	% SO_2 yield after 30 min	pK_a[a]
1	**12**	45	14.40
2	**13**	2	14.23
3	**14**	25	14.25
4	**15**	21	14.27
5	**16**	93	11.91
6	**17**	98	10.64
7	**18**	73	13.83
8	**19**	96	13.48
9	**20**	68	13.73
10	**21**	83	13.70
11	**22**	95	11.53

[a]Values are for the corresponding 1,2-diol (most acidic proton) calculated using ChemBioDraw Ultra 16.0.

A number of SO_2 probes that typically use the distinct nucleophilic properties of sulfite/bisulfite have been developed by various groups.[23]. For example, Sun *et al.* have reported probe **23** for selective detection of SO_2 derivatives HSO_3^-/SO_3^{2-} in pH 7.4 buffer (Scheme 3).[23c] The probe **23** absorbs at 545 nm and upon reaction with HSO_3^-/SO_3^{2-} , a distinct and ratiometric shift to an absorbance at 410 nm (for **24**) was observed (see Supporting Information, Figures S1 and S2). A similar UV profile was observed when **23** was reacted with the SO_2 donor **17** supporting the intermediacy of sulfite (Figure 2a). The probe **23** fluoresces in the red region and upon reaction with SO_3^{2-}/HSO_3^- it forms green fluorescing adduct **24** (Figure 2b). When **23** was treated with sulfite diester **17**, we find a similar shift in emission (Figure 2b). Together, these data independently confirm the ability of **17** to generate SO_2 in pH 7.4 buffer.

The expected product formed during hydrolysis in buffer is the diol (Scheme 2). In order to confirm this, we incubated **19** in pH 7.4 buffer and monitored the decomposition and formation of 1-(4-nitrophenyl)ethane-1,2-diol **8** (Figure 3). We find nearly complete disappearance of **19** during 30 min with the formation of **8** as the exclusive product (Figure 3) and a nearly quantitative yield of SO_2 (Table 2, entry 8). Thus, the decomposition of the sulfite monoester was rapid and SO_2 is likely to be generated as soon as the intermediate is produced (Scheme 2).



Scheme 3. Reaction of probe **23** with sulfites

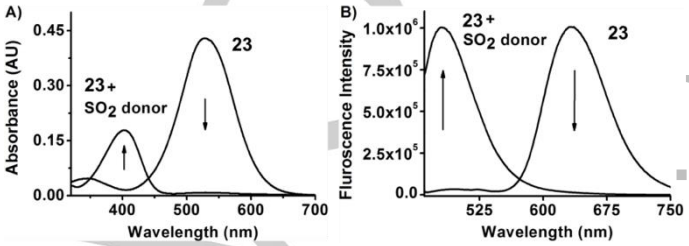


Figure 2. (A) UV-vis spectra of probe (10 μM) in presence of 100 μM of **17** in pH 7.4 1% DMSO/PB. (B) Fluorescence spectra of probe (10 μM) in presence of 100 μM of **17** in pH 7.4 1% DMSO/PB.

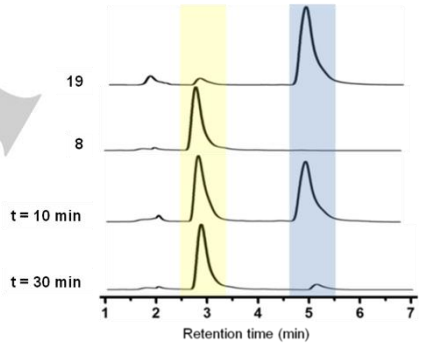


Figure 3. Decomposition of **19** in pH 7.4 1% DMSO/PB was monitored by HPLC, 1:1 ACN/H_2O isocratic gradient, wavelength, λ = 254 nm. During 30 min, nearly complete decomposition of **19** with concomitant formation of **8** was observed.

Having established the suitability of cyclic sulfite esters for molecular biology studies, cell permeability as well as the suitability of these compounds for enhancing intracellular levels of SO_2 was examined. The ratiometric probe **23** has been previously reported to be suitable for detection of intracellular sulfite/bisulfite. When DLD-1 cells treated with **23** (10 μM), we found a distinct fluorescence signal only in the red channel but not in the green channel (Figure 4A-C).[23c]

When cells pre-treated with **23** were exposed to **17** (20 μM), a decrease in fluorescence signal in the red channel with concomitant increase in fluorescence increase in green channel was observed (Figure 4D-F). Under similar conditions, when a similar experiment was conducted with authentic bisulfite, we found a similar profile.[23c] However, an increased concentration of 200 μM was necessary to elicit this response whereas with the donor developed in this study, a significantly lower concentration could achieve enhancement of intracellular SO_2. Above results

suggest the compatibility of cyclic sulfite diesters with cellular nucleophiles. Lastly, a cell viability assay conducted with human cervical cancer cells (HeLa) revealed SO_2 donors **17** and **13** were not significant inhibitors of proliferation at 100 μM (see Supporting Information, Figures S3 and S4). Thus, the SO_2 donor **17** might find convenient use for studying cellular responses to enhanced reactive sulfur species.

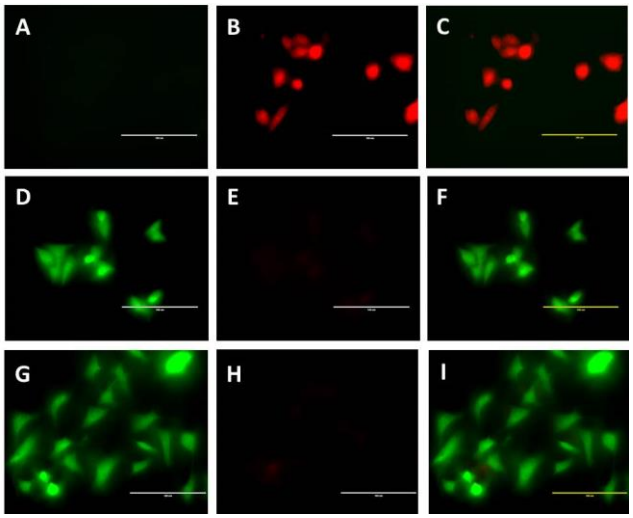


Figure 4. Live cell imaging carried out with DLD-1 cells (A) cells incubated with probe **23** (10 μM) from the green channel; (B) imaging of (A) from the red channel; (C) overlay of (A) and (B); (D) fluorescence imaging of cells incubated with probe **23** (10 μM) for 30 min, and further incubated with **17** (20 μM) for 30 min from the green channel; (E) fluorescence imaging of (D) from the red channel; (F) overlap of (D) and (E); (G) fluorescence imaging of cells incubated with probe **23** (10 μM) for 30 min, and further incubated with $NaHSO_3$ (200 μM) for 30 min from the green channel; (G) imaging of (F) from the red channel; (I) overlay of (G) and (H); Scale bar: 100 μm.

Conclusions

In summary, we report a series of 1,2-cyclic sulfite diesters that: can be easily synthesized; are stable at room temperature; have tunable SO_2 release profiles; and are well suited to study effects of enhanced intracellular levels of SO_2 and duration of exposure to this reactive species. Together, we present superior alternatives to inorganic sulfites, the most commonly used SO_2 donors. These compounds are easy to prepare and store and readily dissociate to produce SO_2. Due to the fundamental importance of redox regulation in cellular growth and survival, perturbation of redox homeostasis has emerged as a possible mechanism for the development of new therapeutics.[24] Thus, reliably generating reactive oxygen,[25] nitrogen[26] and sulfur species[8a, 8b, 8e] may have a range of applications including developing small molecule-based inhibitors of against bacteria such as *Staphylococcus aureus*,[8e, 25e] *Mycobacterium tuberculosis*[8a, 8b, 25a, 25b] as well as cancer.[27]

Acknowledgments

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Keywords: Sulfur dioxide, Cyclic sulphite ester, Reactive sulfur species, sulfite

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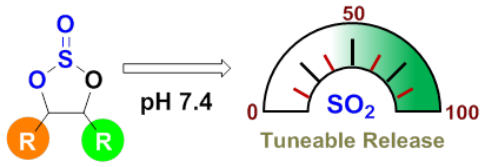

Tunable release of sulfur dioxide achieved by cyclic sulfite esters

Synthesis and evaluation of cyclic sulfite diesters as sulfur dioxide (SO_2) donors*

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