A Chemical (Dark) Source of Singlet Oxygen: Ozone Splitting Promoted by Tin(II) Salts

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Summary. A novel chemical source of singlet oxygen based on the conversion of ozone by tin(II) was developed into a method feasible for preparative purposes. The optimum reagent for this purpose was found to be Sn(II) triflate in ethyl acetate as the solvent.

Keywords. Ozonization; Luminescence detection; SEDEX; Tin(II) triflate.

Introduction

Ozone has found industrial applications as a selective oxidant to cleave double bonds in fine chemicals synthesis [1]. Besides this spectacular aspect, ozone could also be viewed as a source of singlet oxygen. The latter is usually generated by photosensitization of oxygen [2]. This useful oxidation reagent, which has unique properties with respect to chemical selectivity, product distribution, and mildness of reaction conditions, has been also generated by chemical reactions. Thus, oxidation of hydrogen peroxide by sodium hypochlorite [3] or the disproportionation of hydrogen peroxide catalyzed by molybdate ions [4] produce singlet oxygen in quantitative yield. It has been also found that naphthalene endoperoxides generate singlet oxygen in biological media [5]. Additional chemical sources of singlet oxygen (or derivatives with "crypto-singlet oxygen") have been developed involving a formal transfer of one oxygen atom from ozone to a suited substrate. Examples are the phosphite ozonides [6–9], ether hydrotrioxides [10], silyl hydrotrioxide [11], a variety of biomolecules [12], and chlorine dioxide [13].

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By screening inorganic ions by means of a sensitive detector for exothermic processes (SEDEX) and IR luminescence spectroscopy to detect the production of singlet oxygen it has been found recently that tin(II) acetate in acetic acid promoted formation of singlet oxygen from ozone and would thus also constitute a promising candidate to use chemically generated singlet oxygen for preparative purposes [14]. Experiments to develop a reagent for the (dark) chemical formation of singlet oxygen based on tin(II) are described in this report.

Results and Discussion

The finding that tin(II) acetate in acetic acid produced singlet oxygen from ozone [14] formed the starting point of our investigations. Of course, the first question was if tin(II) acetate was already the optimum reagent and acetic acid the solvent of choice. In addition, the mechanistic aspect should also be approached to some extent in order to apply such hypotheses in the process of optimization, as *e.g.* in finding optimum temperatures or dosing rates.

As the most suited method to optimize the reaction conditions, synchronous recording of ozone in- and output and IR luminescence spectroscopy was chosen in a first step. The reference we used was the 100% singlet oxygen yield of ozone/triphenyl phosphite [6, 8]. The area under the luminescence signal was thus normalized to one equivalent of singlet oxygen. As an example, the traces recorded for triphenyl phosphite in acetic acid at room temperature are shown in Fig. 1. Accordingly, after 5.5 minutes one equivalent of ozone was absorbed and concomitantly ozone could then be detected leaving the reaction mixture. The luminescence signal starts after a short delay with a spike returning to a plateau until one equivalent of ozone had been introduced. Then there was a steady growth of the signal peaking after about 1.5 minutes and eventually tailing off to zero. The luminescence trace clearly describes the various reaction steps occurring with different rates. The reaction proceeds first with the formation of the phosphite ozonide, which at room temperature decomposes into singlet oxygen and phosphate (*cf.* Refs. [6, 8]). Based on the total ozone uptake of 1.6 equivalents of ozone the efficiency of singlet oxygen formation (mol $^1O_2$/mol O_3) was observed to amount 62%. For the system triphenylphosphite/ozone the solvent was observed to be of minor importance. Thus efficiencies of 54 and 52% for ethyl acetate and dichloromethane were measured.

Optimizing Tin(II) Reagent and Solvent

For preparative purposes it is important to find a homogeneous system in which a tin(II) compound, ozone, and a substrate susceptible towards singlet oxygen can be dissolved. Homogeneity is mandatory in order to suppress the physical quenching of singlet oxygen. Accordingly, there are several restrictions to the system. Using the method described above it was first of all observed that optimal results for the system tin(II) acetate/acetic acid [14] were obtained only when the ozone concentration of the feed gas was kept at about $20\,g/m^3$. Higher concentrations yielded much lower efficiencies. This makes sense because the different reaction rates and the reactant input are to be sensibly balanced to each other. In the experiments using luminescence the anion was changed from acetate to chloride and then to
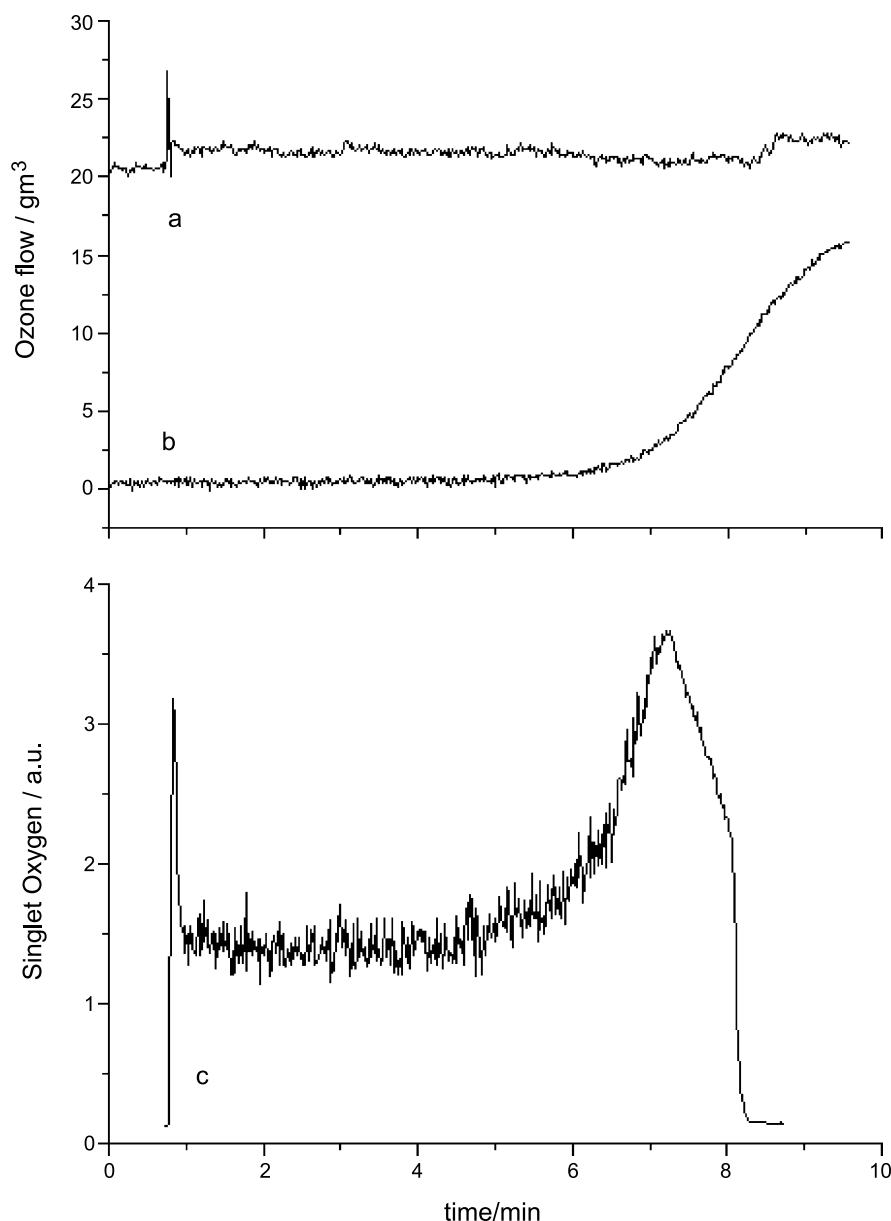
Fig. 1. Reaction of triphenyl phosphite with ozone in acetic acid at 20°C (a...ozone in, b...ozone out, c...luminescence signal at 1270 nm – arbitrary units derived from SEV output)

trifluoromethanesulfonate (triflate) with ethyl acetate as the solvent and efficiencies of 51 (see above), 100, and 56% were obtained. Remarkably, ozonization of tin(II) triflate in ethyl acetate at 20°C in presence of the singlet oxygen scavenger 9,10-dimethylanthracene even enhanced the efficiency of singlet oxygen generation to about 87%. Interestingly enough, tin(II) phthalocyanine/acetic acid/ozone gave virtually no luminescence signal, but a color change of the reaction mixture from blue to green indicating oxidative transformations of the phthalocyanine ring instead of singlet oxygen formation.

With respect to its simplicity of measurement and the preparative aspect of the work batch ozonolysis was then chosen for a broader screening of reaction conditions. In these experiments ozone consumption was taken as an estimate of singlet oxygen production with ozone/triphenylphosphite. The choice of solvents depended mostly on the solubility of the tin(II) salts. Tin(II) chloride dissolved in methanol, *N*-methylpyrrolidone, or *tert*-butyl acetate yielded ozone consumptions of 7, 12, and 11%, which is rather low and certainly not suited for preparative purposes. Tin(II) picolinate in acetic acid and tin(II) tetrafluoroborate in methanol displayed values of 2 and 25%, with the latter also still not convincing with respect to a preparative option. Tin(II) mesylate proved to be more efficient in certain solvents. Thus methanol, methanol/ethyl acetate (1/1) and *N*-methylpyrrolidone gave ozone consumptions of 36, 50, and 29%. Tin(II) triflate in methanol or *N*-methylpyrrolidone gave 38 and 23%. However, in acetonitrile or ethyl acetate quantitative ozone consumption was observed with this tin salt equaling that observed for the standard system ozone/ triphenyl phosphite. From these results it became obvious that protic or complexing solvents strongly retard ozone consumption.

According to these experiments the system ozone/tin(II) triflate in ethyl acetate or acetonitrile as the solvent was a candidate for preparative applications. Tin(II) triflate perfectly fulfils all the requirements of a mediator for the preparative generation of singlet oxygen from ozone. Thus it is soluble in organic solvents, reacts fast and stoichiometrically with ozone, and it produces singlet oxygen in high yields. For the development of a continuous preparative process tin(II) triflate might be even recovered by a subsequent reductive step from its tin(IV) product.

Mechanistic Aspects

To substantiate the idea that a tin triflate ozonide is formed at low temperatures, which then decomposes to oxo-tin(IV) triflate and singlet oxygen in analogy to the phosphite case [6, 8], a solution of tin(II) triflate in ethyl acetate was treated with one equivalent of ozone at −80°C. After removal of residual ozone, the singlet oxygen trap α-terpinene was added and the solution was warmed to −10°C. After work-up the α-terpinene was quantitatively converted to ascaridole thus documenting indeed that a stable ozonide of tin triflate was formed at low temperatures. The complex formed at −80°C is only stable at these low temperatures as corresponding experiments in the temperature range down to −40°C displayed no ascaridole
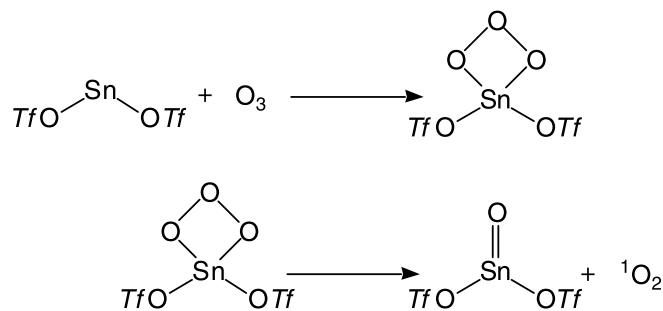
Scheme 1

formation. The formation of such a tin-ozone complex is supported also by the fact that tin(II) is known as a strong *Lewis* acid, which is prone to react with nucleophiles. Thus tin(II) triflate is used as a catalyst for chiral aldol reactions [15]. In analogy to the ozone/triphenylphosphine system [6, 8] we conclude that the tin(II) promoted formation of singlet oxygen from ozone follows the route of Scheme 1.

The Preparative Use of Tin(II) Triflate/Ethyl Acetate

For the preparative use of the ozone/tin(II) triflate/ethyl acetate system advanced above one has to take into account that most substrates for singlet oxygen are also easily attacked by ozone. Thus some measure has to be taken to avoid such reactions of ozone with the substrate. One way is to use the primary reaction of the tin salt with ozone to form an ozonide at low temperatures as shown above. Thus formation of this ozonide at low temperatures, stripping off any surplus ozone and then reacting the complex with the substrate at elevated temperatures solves the problem and can provide high yields of product as exemplified already above with the conversion of α-terpinene to ascaridole.

However, the preparative problems encountered working at low temperatures seemed to advocate also a more continuous process at elevated temperatures in addition to the batch procedure. Accordingly, substrates exemplifying the modes of singlet oxygen reactions, namely cycloaddition followed by cleavage (1,3-diphenylisobenzofuran to 1,2-dibenzoylbenzene), *ene*-reaction (β-pinene to myrtenol hydroperoxide), and [2+4] cycloaddition (α-terpinene to ascaridole) [5], were chosen to react under anhydrous conditions. Thus two equivalents of tin(II) triflate were ozonized in ethyl acetate at $-20°C$ while continuously adding one equivalent of substrate. The excess of tin(II) triflate was necessary to prevent an excess of ozone, which of course, would lead exclusively to ozone derived products. The three substrates were converted to products in more than 95%. In the first case the product (the substrate in this case was tested to be more or less inert against ozone) could be isolated in about 70% yield, whereas in the latter two cases the isolated yields amounted to only 3 and 29% of the desired products myrtenol hydroperoxide and ascaridole. In these latter cases it turned out that the side products originated mainly from the ozonization of the substrates.

For the latter case it should be mentioned that some of the initially formed ascaridole was transformed into *p*-cymene by the tin(II) triflate. This could be proven by blank experiments, *i.e.* ascaridole was reacted with tin(II) triflate in ethyl acetate at room temperature for 30 minutes. After this time the ascaridole was quantitatively converted into *p*-cymene. Interestingly enough, the same result was obtained when ascaridole was added to the tin(II) triflate ozone adduct dissolved in ethyl acetate at $-80°C$ and warming up the reaction mixture to $+3°C$. This might indicate the presence of an equilibrium between the ozonide and its educts at temperatures higher than $-80°C$.

In conclusion it was shown that for a certain substrate tin(II) triflate promoted ozone splitting in ethyl acetate to yield the (dark) singlet oxygen product is viable on a preparative scale either using the low temperature bulk methodology or the semi-continuous dosing procedure. With the latter methodology the experimental parameters (temperature, reagent excess, substrate addition rate) have to be

carefully adjusted in every individual case to reach optimum conditions. Thus the reaction could be either run in form of a batch procedure at low temperatures giving higher yields, or in a semi-continuous way where the yields achieved are strongly dependent on a suitable balance of the reaction parameters.

Experimental

Ozone was generated by means of an OZONE GENERATOR BMT 802X and 803, a BMT Messtechnik Berlin, or a Fischer OZON 503 generator. The flux of oxygen was $0.5\,dm^3\,O_2/min$ at standard pressure. Ozone was monitored by means of the OZONE ANALYZER BMT 963 VENT, BMT Messtechnik Berlin; OSTI, Walnut Creek, CA, using optical absorption. The values given are $g\,ozone/m^3$ ($0°C$, $10^2\,kPa$) and are corrected for pressure and temperature. These monitors were used for all batch ozonolysis, SEDEX, and luminescence experiments.

Batch ozonizations were carried out in a $100\,cm^3$ jacketed vessel equipped with a mechanical stirrer, gas inlet pipe with a frit, a reflux cooler in the off-gas stream, and a Ni/CrNi-thermocouple. $1.0\,g$ of the selected tin(II) compound was dissolved in the given solvent (mixture). This solution was cooled to the specified temperature and ozonized until ozone was detected in the off-gas stream. The ozone uptake was calculated and compared to the amount of the applied tin compound.

The SEDEX apparatus (Systag, System Technik AG, Rüschlikon, CH) consisted of an oven, which provided the continuous monitoring of potentially harmful and exothermic reactions. It allows visual observation of the sample under investigation. After equilibration, the solutions were subjected to ozonization while measuring the temperature inside and outside of the reaction vessel as well as the ozone concentrations being applied to the solution and the one passing out of the vessel.

Tin(II) triflate ($0.5\,g$, $1.2\,mmol$) was dissolved in $50\,cm^3$ of ethyl acetate. This solution was subjected to ozonisation at $-20°C$ using a gas flow of $0.06\,m^3\,O_2/h$ and an ozone concentration of $6\,g\,O_3/m^3$ for 9.5 minutes. Then $0.6\,mmol$ of the substrate dissolved in $15\,cm^3$ of ethyl acetate were added continuously by means of a perfusor pump ($93\,cm^3/h$). The products were analyzed by GC (Hewlett-Packard HP-5MS), HPLC (Nova-Pak $4\,\mu m$ W01961), and ^1H NMR spectra (Bruker DRX 300).

Solutions of $1\,mmol$ salt in $50\,cm^3$ of solvent were prepared resulting in a final concentration of $20\,mmol$ metal ions/dm^3. The sample vessel (glass) was filled with the solution and attached to a fitting head bearing a frit for the incoming ozone, a fitting for the off-gas and an immersion coil for cooling the solution. This apparatus was fixed with a clamp to the optical bench in front of the shutter wheel, which was operated at about $170\,Hz$. To exclude any sources of light the apparatus was covered by a box sealed with black stage tape. The solution was cooled to the desired temperature. In all experiments, the ozone flux was kept at $0.03\,m^3/h$. The ozone generator was operated at 20 to $80\,g\,O_3/m^3$. The concentration of the incoming and outgoing ozone was measured by two ozone monitors and recorded by an AD-USB interface connected to a portable computer. The recording of the ozone concentration and the luminescence detection was started simultaneously at the beginning of ozone introduction.

The luminescence originating from the sample cell was detected by means of a N_2 cooled germanium diode detector (North Coast Scientific Corp., Model EO-817L), connected to a lock-in amplifier from Stanford Research Systems Model SR830 DSP. The detector was powered by a North Coast Scientific Corp. Model Bias Supply Model 823A. The luminescence apparatus was calibrated by ozonizing triphenylphosphite in the corresponding solvents.

References

[1] Bailey PS (1978) Ozonization in Organic Chemistry. Academic Press, New York
[2] Boden RM (1975) Synthesis 783

[3] Foote CS, Wexler S (1964) J Am Chem Soc **86**: 3879
[4] Aubry JM, Cazin B (1988) Inorg Chem **27**: 2013
[5] Pierlot C, Aubry JM, Briviba K, Sies H, di Mascio P (2000) Methods Enzymol **319**: 3
[6] Murray RW, Kaplan ML (1969) J Am Chem Soc **91**: 5358
[7] Falk H, Leimhofer J (1995) Monatsh Chem **126**: 85
[8] Bartlett PD, Mendenhall GD (1970) J Am Chem Soc **92**: 210
[9] Mori A, Abe M, Nojima M (2001) J Org Chem **66**: 3548
[10] Murray RW, Lumma WC, Lin JWP (1970) J Am Chem Soc **92**: 3205
[11] Corey EJ, Mehrotra MM, Khan AU (1986) J Am Chem Soc **108**: 2472
[12] Kanofsky JR, Sima P (1991) J Biol Chem **256**: 9039
[13] Chertova YS, Avzyamova EV (2000) Russ J Phys Chem **74**: 473
[14] Emsenhuber M, Pöchlauer P, Aubry J-M, Nardello V, Falk H (2003) Monatsh Chem **134**: 387
[15] Kobayashi S, Uchiro H, Shiina I, Mukaiyama T (1993) Tetrahedron **49**: 1761