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Sulfonium ylides derived from 2-hydroxy-benzoquinones: crystal and molecular structure and their one-step conversion into Mannich bases by amine *N*-oxides

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Abstract—Reaction of 2-hydroxy-*para*-benzoquinones with DMSO/Ac_2O produced dimethylsulfonium ylides, of which crystal structures as well as solid and liquid state NMR spectra were recorded. The ylides react with tertiary methylamine *N*-oxides in a one-pot, multi-step process to 3-methylamino-substituted benzoquinones. The mechanism starts with a deoxygenative deprotonation of the amine *N*-oxides, followed by a formal electrophilic displacement of DMSO by the resulting carbonium–iminium ion.

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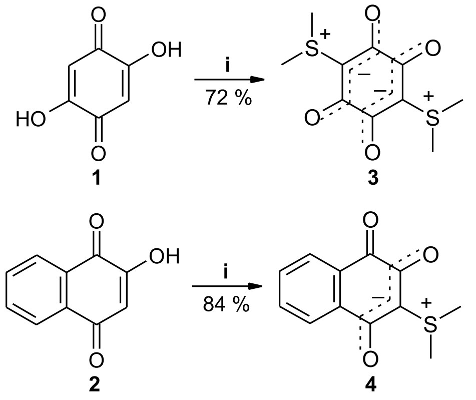
1. Introduction

In our studies on chromophore formation in the Lyocell process—a modern, environmentally benign technology for the production of cellulosic fibers without chemical cellulose derivatization—we treated a multi-component chromophore mixture with acetic anhydride for acetylation purposes. A small amount of a yellow precipitate resulted, the formation of which initially remained non-reproducible for the individual chromophore components, no matter which acetylation procedure was used. Only when we repeated the acetylation in the presence of small amounts of DMSO—following the idea that the original material might have contained residual DMSO-d_6 from NMR experiments—the precipitation reoccurred. By treatment with excess DMSO in acetic anhydride as the solvent yellow, high-melting precipitates were obtained from 2,5-dihydroxybenzoquinone (**1**) and 2-hydroxynaphthoquinone (**2**), which turned out to be the bis(dimethylsulfonium ylide) **3** and dimethylsulfonium ylide **4**, respectively (Scheme 1). A literature study quickly revealed that this reaction had already been reported,[1] albeit without comprehensive analytical characterization of the products and contradictory physical data. Treatment of **3** in glacial acetic acid had even be described to yield recrystallized **3**,[2] even though the product represents the bis(acetic acid) adduct. These inconsistencies prompted us to address the crystal and molecular structure of these ylides in more detail. Furthermore, studies of their behavior under Lyocell conditions, that is, in a melt of *N*-methylmorpholine-*N*-oxide monohydrate (NMMO) at temperatures of about 100 °C, lead to the finding of a hitherto unreported reaction, which we wish to communicate in this study in addition.



i = DMSO (10 eq.), Ac_2O, 100°C (1 h) to r.t. (3 h)

Scheme 1. Formation of sulfonium ylides by treatment of 2-hydroxy-benzoquinones with DMSO/acetic anhydride.

2. Results and discussion

Compound **3** is extremely insoluble in all non-polar and polar aprotic organic solvents tested. It even precipitates

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Keywords: Sulfonium ylides; Amine *N*-oxides; Crystal structure; Benzoquinones.

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from hot DMSO if the formation reaction was carried out in this solvent. Being insoluble in organic amines and moderately soluble in hot acetic or formic acid, it has a very high solubility in water. Bisylide **3** can be recrystallized from concentrated aqueous solutions in large (side length up to 3 mm), yellow prisms, such as those used for obtaining the crystal structure in Figure 1. Crystallization from hot organic acids provides the bis(acid) adducts, such as the bis(acetic acid) adduct (**3** $*$ 2HOAc) and the bis(formic acid) adduct (**3** $*$ 2HCOOH). By analogy, treatment with HCl in organic media provides the microcrystalline bis(hydrochloride), treatment with nitric acid the bis(hydronitrate), while treatment with sulfuric acid failed to give the stoichiometric mono(sulfuric acid) adduct. The insolubility of **3** in organic media is evidently due to its high polarity: the molecule carries two positive and two negative charges located along a relatively small six-membered ring. However, it should be noted that despite the high charge concentration, the overall dipolar moment is zero. The high polarity of the molecule was also reflected in its high melting point, being above 300 °C. The acid adducts melt considerably lower at about 180 °C.

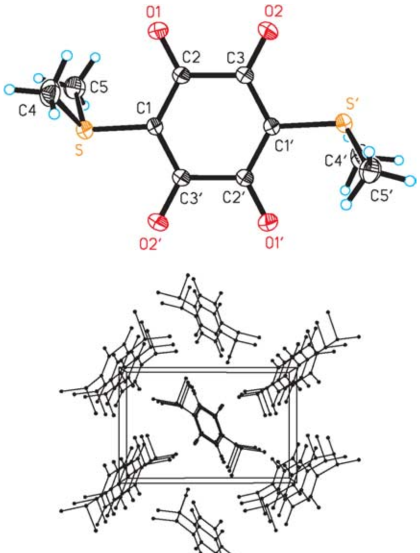


Figure 1. Crystal structure (40% thermal ellipsoid plot) of bis(dimethylsulfonium ylide) **3** and view of the crystal packing down the *a*-axis. The molecule is C_i-symmetric (close to C_{2h}); primed atoms are symmetry equivalents of unprimed ones.

The crystal structure of bisylide **3** is shown in Figure 1. Molecule **3** is highly symmetric. The C–O bond lengths are nearly identical, with 1.231 Å ranging between those of typical double and single bonds. The C1–C2 bond (1.421 Å) having partial double bond character is significantly shorter than the C2–C3 bond, which is a 'proper' single bond (1.549 Å). These values reflect the resonance stabilization of the molecule as shown in Scheme 1. The tight crystal packing with significant C–O dipole–dipole interactions and non-classical C–H···O/C–H···S hydrogen bonds for all methyl H atoms (C5···O=3.060–3.474 Å, C1···S=3.769 Å) agrees with the observed high melting point.

The solid state ^{13}C NMR spectrum of **3** shows two carbonyl resonances and two methyl resonances (Fig. 2). The signal splitting reflects the influence of packing effects in the crystal, which render C2/C3 as well as C4/C5 magnetically inequivalent in solid state. This inequivalence is lost in liquid state, and the solution state spectrum gives three resonances, with the four methyls and four carbonyl carbons, respectively, being magnetically equivalent.

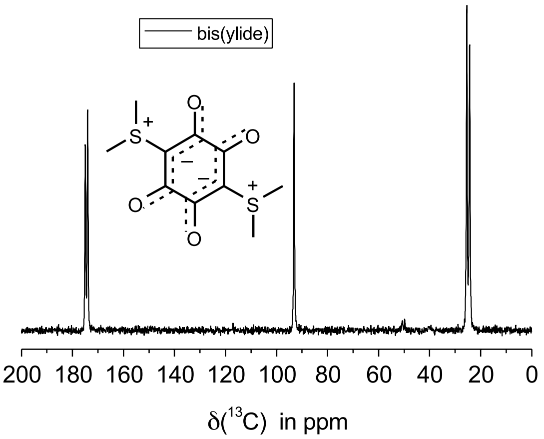


Figure 2. CPMAS ^{13}C NMR spectrum of bisylide **3**.

Similar structural features as described for the bisylide **3** were found for the monoylide **4**, its crystal structure being shown in Figure 3. Apart from the two methyl groups, the whole molecule lies within one plane. The bonds C1–O1 (1.244 Å) and C3–O2 (1.231) are longer than the C4–O3 double bond (1.213 Å). C1–C2 (1.427 Å) and C2–C3 (1.414 Å) are partial double bonds and thus shorter than the single bond C3–C4 (1.541 Å). This corresponds to the charge distribution which results from the participation of different resonance structures as shown in Scheme 1.

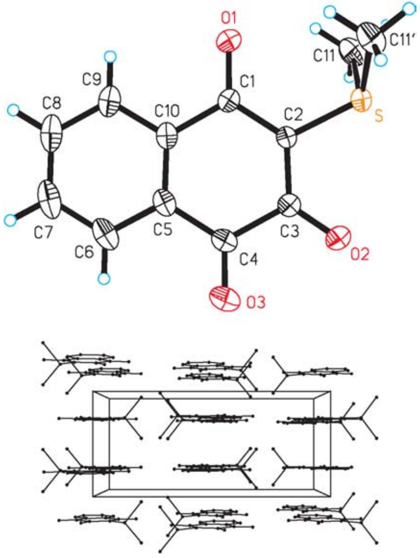
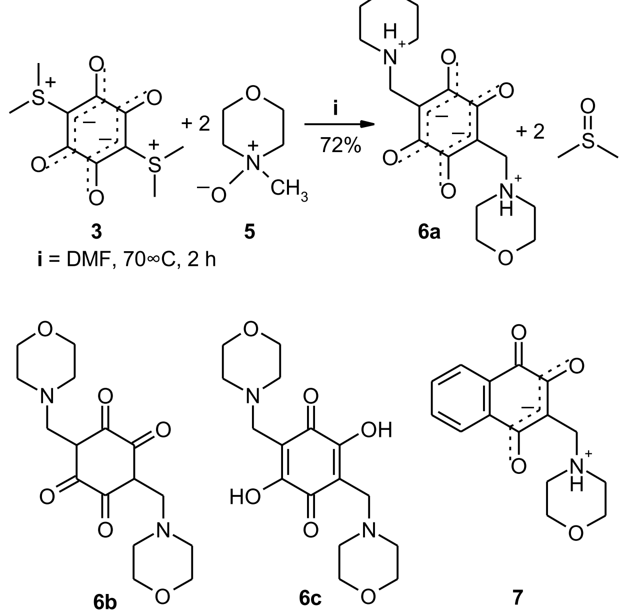


Figure 3. Crystal structure (40% thermal ellipsoid plot) of dimethylsulfonium ylide **4** and view of the crystal packing down the a-axis showing π-stacked layers of molecules. The molecule is C_s-symmetric; C11 and C11′ are symmetry equivalents.

Prompted by the ready formation of bis(hydrochlorides) and bis(carboxylic acid) adducts with **3**, we tried to obtain crystal adducts with NMMO (**5**), which possesses a betaine structure, thus offering a separated positive and negative charge—similar to dissociated acids. Unfortunately co-crystallization did not succeed so far. Attempts to dissolve **3** in a melt of NMMO resulted in a spontaneous, uncontrollable reaction, the high exothermicity of which caused a complete charring of the mixture. While this reaction between the pure reactants at elevated temperatures was evidently useless for synthetic purposes, the reaction can be conducted safely in DMF at 50 °C. Reaction of equimolar amounts of **3** and NMMO under these conditions produced DMSO and bisbetaine **6a**, the intramolecular double salt of Mannich base **6b** or the corresponding benzoquinone **6c**, see Scheme 2.



Scheme 2. Reaction of dimethylsulfonium ylides with tertiary amine *N*-oxides.

Compound **6a** precipitated as red powder, moderately soluble in water and readily soluble in dilute mineral acids. It sublimated under decomposition at about 265 °C. These physical characteristics as well as the solution ^{13}C NMR data—four equivalent oxygen-bound carbonyls and down-field shifted *N*-methylene groups—favor the bis-betaine structure over the neutral Mannich base. This structure was also confirmed by X-ray analysis, which in addition showed **6a** to crystallize as tetrahydrate in large, orange prisms. Each hydrate water is donor of a regular and a bifurcated hydrogen bond (Fig. 4). In an analogous reaction, betain **7** was obtained from naphtho-ylide **4** in 87% yield. Preliminary experiments indicated that the reaction proceeded equally well with other tertiary amine *N*-oxides, such as *N*,*N*-dimethylbenzylamine *N*-oxide and *N*,*N*-dimethyl-dodecylamine *N*-oxide.[3] An authentic sample of **6a** was prepared by double morpholinomethylation of 2,5-dihydroxybenzoquinone.[4]

The reaction in Scheme 2 can be regarded as a superposition of substitution and redox reaction, it formally achieves displacement of a dimethylsulfonium group by a methyl-aminium group with concomitant oxygen transfer from the nitrogen in the amine *N*-oxide to the sulfur in the dimethylsulfonium group, which becomes the rather uncommon leaving group DMSO. The first step of the reaction mechanism is likely to be a nucleophilic attack of the negatively charged oxygen at the sulfur atom. Similar to degradation reactions in tertiary amine *N*-oxides starting with *O*-alkylation[5] or *O*-acylation[6], this process will induce a deoxygenation with simultaneous removal of a proton from the *N*-methyl group, giving a *N*-(methylene)morpholinium ion.[7] Neutral DMSO is released, and the resulting carbanion recombines with this carbonium–iminium ion (Scheme 3). If the reaction between sulfonium ylide and *N*-methylmorpholine *N*-oxide was carried out in the presence of *N*,*N*-dimethyl(methylene)ammonium iodide (Eschenmoser's salt), two products—either with dimethyl-ammonium or morpholinium moiety—were found. The obvious competition between the two carbonium–iminium ions supports the above mechanistic proposal.

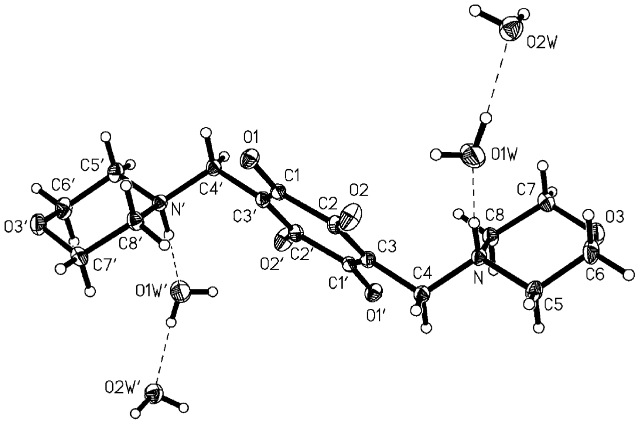
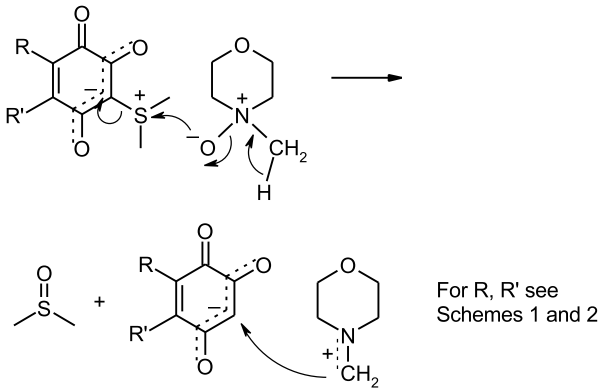


Figure 4. Crystal structure (20% thermal ellipsoid plot) of tetrahydrate of bisbetain **6a**.



Scheme 3. Proposed mechanism of the reaction of dimethylsulfonium ylides with tertiary amine *N*-oxides.

3. Experimental

3.1. General

All chemicals were commercially available. Thin layer chromatography (TLC) was performed on silica gel 60 plates (5×10 cm, 0.25 mm) with fluorescence detection under UV light at 254 nm. Melting points, determined on a Kofler-type micro hot stage with a Reichert-Biovar microscope, are uncorrected.

X-ray data collection was performed with a Bruker AXS Smart APEX CCD diffractometer and graphite monochromatized Mo K_α radiation; corrections for absorption with the program SADABS, structure solution with direct methods, structure refinement on F^2 (Bruker AXS, 2001: programs SMART, version 5.626; SAINT, version 6.36A; SADABS version 2.05; XPREP, version 6.12; SHELXTL, version 6.10. Bruker AXS Inc., Madison, WI, USA).

CCDC-232906 and 232907 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033.

Crystal data for bis(sulfonium ylide) **3**. $C_{10}H_{12}O_4S_2$, M=260.32, monoclinic, space group $P2_1/c$, a=6.0629(4), b=7.7367(5), c=11.9325(7) Å, β=91.087(1)°, V=559.62(6) Å^3, Z=2, D_{calcd}=1.545 g/cm^3, T=300(2) K, μ=0.470 mm^{-1}, F(000)=272, yellow prism (0.70×0.35×0.35 mm), total/unique reflections 4181/1605, R_{int}=0.019. Final refinement: data/restraints/parameters 1605/0/78, GOF=1.08, R_1=0.027, wR_2=0.073 (all data).

Crystal data for sulfonium ylide **4**. $C_{12}H_{10}O_3S$, M=234.26, orthorhombic, space group $Pnma$, a=9.5360(12), b=9.5360(12), c=15.924(2) Å, V=1072.4(2) Å^3, Z=4, D_{calcd}=1. 451 g/cm^3, T=297(2) K, μ=0.289 mm^{-1}, F(000)=488, yellow prism (0.58×0.16×0.14 mm), total/unique reflections 7764/1611, R_{int}=0.025. Final refinement: data/restraints/parameters 1611/0/95, GOF=1.05, R_1=0.058, wR_2=0.143 (all data).

The solid state NMR measurements were recorded on a Bruker DMX Avance 400 spectrometer, using a double channel 4 mm CPMAS. The ^{13}C CPMAS spectra were acquired at a radio frequency of 100.62. MHz. The spinning frequency was 12500 Hz and was stabilized to ±2 Hz. 222 scans have been acquired using a repetition time of 6 s, a CP-time of 5 ms (50% ramp on proton channel) and TPPM decoupling[8] with a phase shift of 10° during the acquisition time.

Spectra in solution were recorded with a Bruker Avance DPX instrument operating at 300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C using tetramethylsilane as internal standard. Homo- and heteronuclear 2D NMR spectroscopy was performed with Bruker standard software. Chemical shifts are given in ppm, coupling constants in Hz. ^{13}C peaks were assigned by means of APT, HMQC and HMBC spectra.

Bis(sulfonium ylide) **3**. 2,5-Dihydroxybenzoquinone (1.40 g, 10 mmol) was suspended in a mixture of acetic anhydride (20 mL) and DMSO (5 mL) and heated under stirring to 100 °C for 1 h. A yellow solid precipitated, which was collected by filtration after additional stirring for 3 h at rt. The solid was thoroughly washed with ethyl acetate and dried in vacuo to provide **3** (1.87 g, 72%), mp (H_2O) >300 °C. Crystals for X-ray diffraction were obtained by slow evaporation of a concentrated aqueous solution,. ^{1}H NMR (D_2O): δ 3.08 (s, 12H, Me). ^{13}C NMR (D_2O): δ 25.4 (Me), 94.4 (C–S), 177.0 (C–O). Anal. Calcd for $C_{10}H_{12}O_4S_2$ (260.33): C 46.14, H 4.65, S 24.63. Found: C 45.82, H 4.41. Recrystallization from glacial acetic acid provided the bis(acetic acid) adduct as yellow needles, mp 182–184 °C. ^{1}H NMR (D_2O): δ 2.22 (s, 6H, Me in Ac), 3.20 (s, 12H, Me). ^{13}C NMR (D_2O): δ 21.4 (Me in Ac), 25.8 (Me), 94.8 (C–S), 177.2 (C–O), 177.5 (C–O in Ac). Anal. Calcd for $C_{14}H_{20}O_8S_2$ (380.44): C 44.20, H 5.30, S 16.86. Found: C 44.08, H 5.40. Recrystallization from formic acid provided the bis(formic acid) adduct as yellow needles, mp 188–191 °C. ^{1}H NMR (D_2O): δ 3.22 (s, 12H, Me), 8.25 (s, 2H, HCO). ^{13}C NMR (D_2O): δ 25.6 (Me), 94.9 (C–S), 177.4 (C–O), 179.3 (HCO). Anal. Calcd for $C_{12}H_{16}O_8S_2$ (352.38): C 40.90, H 4.58, S 18.20. Found: C 41.19, H 4.82.

Sulfonium ylide **4**. Using 2-hydroxynaphthoquinone (**2**) (1.74 g, 10 mmol) instead of **1**, compound **4** was obtained according to the above procedure (1.97 g, 84%), mp 263–265 °C. Crystals for X-ray diffraction were obtained by slow cooling of a concentrated solution in water/methanol (v/v=2:1). ^{1}H NMR (DCOOD): δ 3.30 (s, 6H, Me), 7.82 (t, 1H, ^{Ar}H), 7.92 (t, 1H, ^{Ar}H), 8.11 (t, 2H, ^{Ar}H). ^{13}C NMR (DCOOD): δ 25.7 (Me), 98.5 (C–S), 127.5 (CH), 128.3 (CH), 131.3, 134.1, 134.3 (CH), 136.5 (CH), 172.2, 181.6, 182.4. Anal. Calcd for $C_{12}H_{10}O_3S$ (234.28): C 61.52, H 4.30, S 13.69. Found: C 61.09, H 4.20.

Mannich bisbetaine **6**. Bisylide **3** (0.52 g, 2 mmol) was suspended in DMF (50 mL) and heated to 70 °C. A solution of NMMO monohydrate (**5**, 0.57 g, 4.2 mmol) in DMF (10 mL) was added dropwise during 1 min. After complete addition, the red mixture became clear almost immediately, and a few minutes later a brick-red solid started to precipitate. The mixture was stirred for additional two hours and cooled to rt. The precipitate was isolated by filtration, washed thoroughly with ethyl acetate and dried in vacuo to give **6a** (0.49 g, 72%), mp 265 °C (decomp.). ^{1}H NMR (D_2O): δ 3.20 (t, 8H, N–CH_2–CH$_2$), 3.87 (m, 8H, O–CH_2), 3.95 (s, 4H, N–CH_2–C). ^{13}C NMR (D_2O): δ 51.8 (N–CH$_2$–CH$_2$), 52.2 (N–CH$_2$–C), 64.5 (O–CH$_2$), 103.6 (C), 180.1 (C–O). Anal. Calcd for the monohydrate $C_{16}H_{24}N_2O_7$ (356.38): C 53.93, H 6.79, N 7.86. Found: C 54.50, H 6.25, N 7.42.

Mannich betaine **7**. Employing naphtho-ylide **4** (0.47 g, 2 mmol) instead of **3**, compound **7** was obtained according to the above procedure in 87% yield, mp 192–196 °C. ^{1}H NMR (D_2O): δ 3.16 (t, 4H, N–CH_2–CH$_2$), 3.80 (t, 4H, O–CH_2), 3.92 (s, 2H, N–CH_2–C), 7.81 (t, 1H, ^{Ar}H), 7.90 (t, 1H, ^{Ar}H), 8.10 (t, 2H, ^{Ar}H). ^{13}C NMR (D_2O): δ 51.4 (N–CH$_2$–CH$_2$), 52.4 (N–CH$_2$–C), 64.3 (O–CH$_2$), 101.9, 127.0 (CH), 128.8 (CH), 131.1, 134.5 (CH), 134.6, 136.7 (CH), 177.8, 182.0, 183.1. Anal. Calcd for $C_{15}H_{15}NO_4$ (273.29): C 65.93, H 5.53, N 5.13. Found: C 66.08, H 5.71, N 4.97.

Acknowledgements

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