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Original Scientific Article

Investigations into the Mechanism of Solvolysis of 3-aryloxybenzisothiazoles†

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Abstract. The solvolysis of selected 3-aryloxybenzisothiazoles (6a–c; Figure 1) in alcohols has been theoretically investigated. The geometries of ethers 6a–c were fully optimized at the DFT(O3LYP) level, with the 6-31++G(d,p) and 6-311++G(3df,3pd) basis sets. Calculations including solvation effects were performed with the 6-31++G(d,p) basis set. Overall, theoretical values for bond lengths and angles around the central ether linkage in ethers 6a–c are very close, for the isolated molecule and in methanol, and are also very close to those obtained by X-ray crystallography, revealing that the nature of the substituent on the aryl system has a negligible effect on geometric parameters around the ether linkage. The same applies to charge distributions, predicted using the NPA approach. However, measured rate constants for the solvolysis of the same compounds in alcohols show that the rate is affected by the electron-withdrawing/-donating characteristics of the substituent on the aryl ring and by the polarity of solvent. Two general pathways were considered for the solvolysis of ethers 6: associative (addition-elimination) or dissociative (fragmentation-recombination) mechanisms. Molecular orbital calculations by means of polarized continuum model (PCM) reaction field predicted that solvolysis of ethers 6 prefers an addition-elimination mechanism.

Calculations show also that a dissociative mechanism for the solvolysis of ethers 6a–c is energetically much more demanding than its addition-elimination counterpart and is therefore a highly improbable pathway for the solvolysis. In addition, it was found that the putative cation intermediate formed during a dissociative process should easily convert into its 2-cyanobenzenesulfone cation isomer, via cleavage of the S–N bond.

Keywords: saccharins, saccharyl ethers, solvolysis, mechanistic investigations, structural and solvent effects

INTRODUCTION

Benzisothiazoles, also known as saccharins, are heterocyclic compounds with many relevant applications. The parent compound, saccharin (1,2-benzisothiazol-3(2*H*)-one1,1-dioxide),[1] is a commonly known substance and the oldest artificial sweetener.[2] Moreover, saccharin and its anion, saccharinate, act as ligands in coordination chemistry[3,4] and have recently been considered for the formulation of amide-based ionic liquids.[5–8] Some saccharyl derivatives show biological activity, such as herbicidal,[9,10] antimicrobial and antifungal,[11–14] potential in enzymatic inhibition[15] or *anti*-HIV-1 activity.[16]

Benzisothiazoles are also relevant in organic and bioorganic synthesis. Saccharin is a cheap and versatile starting material for the preparation of related heterocyclic derivatives and a key building block of industrially developed biologically active compounds.[17–19] Addi-

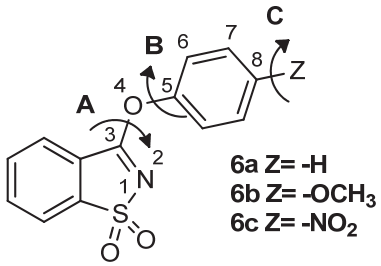

Figure 1. Structure of aryloxysaccharins **6** investigated**.** The atom numbering adopted is shown. Arrows A, B, C relate to conformationally relevant degrees of freedom. **A** represents the dihedral angle defined as $N_2C_3–O_4C_5$ and **B** represents the dihedral angle defined as $C_3O_4–C_5C_6$. Dihedral **C** is not considered for phenoxysaccharin **6a** (X=H); for 4-methoxyphenoxysaccharin **6b**, **C** represents the dihedral angle defined as $C_7C_8–O_9C_{10}$ and for 4-nitrophoenoxysaccharin **6c**, **C** represents the dihedral angle defined as $C_7C_8–N_9O_{10}$.

† Dedicated to Dr. Mirjana Eckert-Maksić on the occasion of her 70th birthday.
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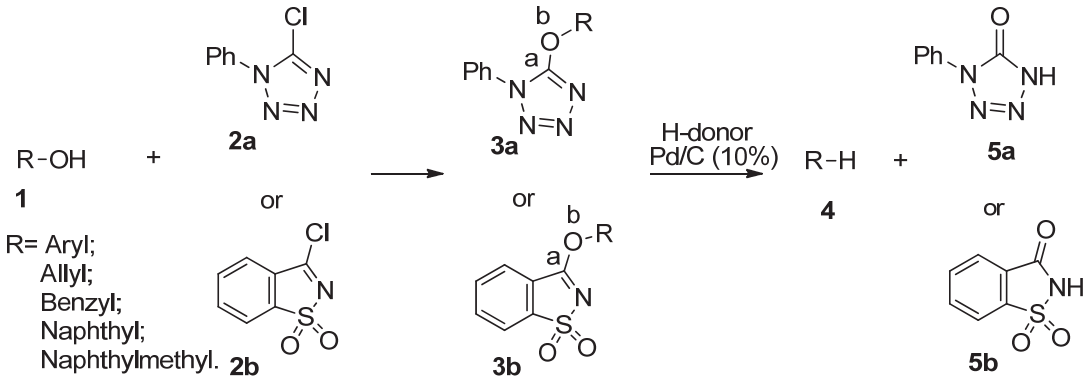
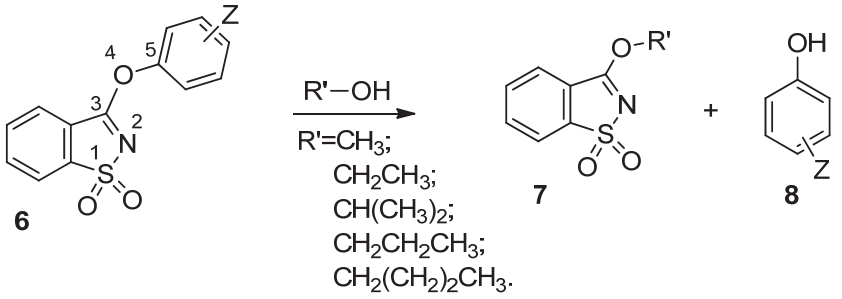


Scheme 1.

tionally, benzisothiazoles are structurally very challenging and belong to a group of heterocycles that play a major role in the design of synthetic methods. Due the strong electron-withdrawing properties of the heterocycles, the halides 5-chloro-1-phenyl tetrazole[20] and 3-chloro-1,2-benzisothiazole 1,1-dioxide (**2a**,**b**; Scheme 1) have been explored as derivatising agents for alcohols, prior to reductive cleavage of the C−O bond catalysed by transition metals.[21–25] Reduction of the C−OH bond in the alcohol is achieved after etherification of the hydroxyl group (**3a,b**; Scheme 1). Derivatization weakens the C−O bond of the original alcohol, so that addition during catalytic transfer hydrogenolysis occurs selectively across this longer bond. This methodology makes use of hydrogen donors, thus avoiding the use of molecular hydrogen, and presents a practical and selective synthetic alternative to other methods.[26–28] The side products, tetrazolone[29] **5a** or saccharin[1] **5b**, are water-soluble and the catalyst is easily filtered off and may be re-used.

Ground state structural features are often used for predicting and interpreting the outcome of reactions.[30,31] The effect of the heterocyclic part on the C−O bond strength in aryl,[32] naphthyl,[32] allyl,[33,34] benzyl[24,35] and naphthylmethyl ethers[25] has been assessed through structural analysis obtained by X-ray crystallography. Reported crystal structures for aryloxy- and naphthoxy-tetrazoles and benzisothiazoles[32] reveal that the central ether linkage (**3**; Scheme 1) is much shorter on the saccharyl or tetrazolyl ether side (C−O *b* around 132 pm) than on the aryl or naphthyl side (O−C *a* around 143 pm), with C−O−C bond angles around 117º. As may be deduced from crystallographic analysis, in these heteroaromatic ethers the ether oxygen appears to show an sp^2 hybridization[32] and is strongly conjugated with the saccharyl or tetrazolyl ring system but not with that of phenyl or naphthyl substituents. The X-ray analyses also show that the plane of the naphthyl or aryl ring is at right angles to that of the saccharyl system. If O conjugates with the carbon atom of the heteroaromatic system through an sp^2 hybrid, then it cannot also conjugate with the aromatic carbon. Indeed, in these molecules the O−C*a* bond is much closer in strength to an aliphatic C−O bond than in the original phenols or naphthols. This change in structure upon derivatization, instrumental for success in transfer *ipso*-replacement reactions,[32] can be ascribed to the saccharyl and the tetrazolyl systems which, together with oxygen, act as excellent leaving groups.

In view of the structural features described, it appeared important to assess the stability of saccharyl ethers in solution, especially when the solvent can act as a nucleophile. For nucleophilic attack on the same aryl ethers, the carbon atom of the C−O−C moiety that lies in the heteroaromatic system (C_3, Scheme 2) is expected



Scheme 2.

to be more susceptible than the other C-atom in the ether linkage (C_5, Scheme 2), because it is more positively charged. In previous work[35] 3-(4-nitrophenoxy) 1,2-benzisothiazole1,1-dioxide and 3-(4-methoxyphenoxy) 1,2-benzisothiazole 1,1-dioxide (**6**, Z = 4-NO_2 and 4-CH_3O, respectively) were refluxed with ethanol. The aryl saccharyl ether bearing the electron-withdrawing nitro group was readily converted into ethyl saccharyl ether **7**, but the ether with the electron-donating methoxy group was found to be unreactive towards solvolysis, even when refluxed for extended periods of time. It may be argued that, for the 4-nitrophenoxy derivative, the ether bond is labile because it suffers the influence of the electron withdrawing 4-nitrophenyl and of the electron deficient heteroaromatic saccharyl ring. Similar behaviour was observed for 2,6-dinitrophenyltriflate[36] and 2,6-dinitrophenyltosylate.[37] Likewise, for 3-(4-methoxyphenoxy) 1,2-benzisothiazole 1,1-dioxide, the electron-donating 4-methoxyphenyl would offset partly the electron-withdrawing effect of the saccharyl ring. It could be hypothesized that the charge density at C_3 would be higher in this ether than in 3-(4-nitrophenoxy) 1,2-benzisothiazole 1,1-dioxide, making the nucleophilic substitution much more difficult for the former than for the latter.

The preliminary results described by Johnstone[35] prompted us to further investigate the mechanism of solvolysis of aryloxybenzisothiazoles **6**. Kinetic studies were conducted for a library of ethers **6** in different alcohols (Scheme 2).[36] Results of these studies have consistently shown that the rate of solvolysis is highly dependent on the substitution pattern and nature of the substituent on the aryl ring. Electron-withdrawing groups Z were found to increase the rate while electron-donating groups were found to decrease it. The rate of solvolysis was also found to increase substantially with increasing dielectric constant of the solvent.[36]

Considering that bond lengths are related to reactivity and electronegativity,[30,31] differences in the relative ether bond lengths for ethers **6** (R = 4-NO_2 and R = 4-CH_3O) could also be hypothesized. However, analysis of reported bond lengths and angles for these ethers, obtained by X-ray crystallography, shows that the ether bond lengths C_3−O_4 and O_4−C_5 are 133.5 and 141.7, and 133.1 and 142.4 pm respectively, revealing no significant difference with the electronic nature of the substituent on the aryl ring, in the crystal.[35] Thus, the opposite electronic effects of nitro and methoxy substituents have no opposed effect on the C_3−O_4−C_5 bond lengths, and the explanation for different chemical behaviour in solvolysis of these ethers cannot be found in ground-state electronic features in the crystal. However, electronic features for the same compounds in solution or in the gas-phase can vary substantially from those observed in solid state and the changes may translate in different reactivity.

We now describe results of a theoretical study on the solvolysis of ethers **6** in alcohols, aimed at complementing our data from kinetic studies and Linear Free Energy Relationship analysis. An addition/elimination mechanism is proposed.

EXPERIMENTAL

All the calculations were performed with the Gaussian 09 program package. Functionals and basis sets were applied as defined in Gaussian.[38] The quantum chemical calculations were performed at the DFT level of theory using either the valence double-ζ polarized 6-31++G(d,p) or the extended valence triple-ζ polarized 6-311++G(3df,3pd) basis set[39–43] and the O3LYP[44] functional. Inclusion of both diffuse and polarization functions in the basis set has been shown to be required for the accurate description of the structure of this type of molecules, as reflected, for example, in the modelling of their infrared spectra.[1,45–47] This requirement results essentially from the presence in the molecules of hypervalent S atoms, as indicated by the strong improvement of the calculated vibrational data for the >SO_2 stretching and bending modes (compared to other vibrations) upon inclusion in the basis set of diffusion and polarization functions.[47,48] The use of the DFT/B3LYP or O3LYP method with the 6-311++G(3df,3dp) basis set was found to be appropriate to attain reliable results at moderate computational effort.[1,45–49]

In the present study, geometries were optimized using the Direct Inversion in the Iterative Subspace (DIIS) method.[50] Vibrational frequencies were calculated at the same level of theory and the nature of the stationary points on the potential energy surface (PES) resulting from optimization was determined by inspection of the corresponding calculated Hessian matrix. Absence of imaginary frequencies indicated that they correspond to true minima. This also enabled the determination of thermodynamic quantities such as zero-point-corrected vibrational energy and free energy at 298.15 K. The charge distribution has been analyzed using the Natural Population Analysis (NPA) performed at the optimized geometries obtained at the DFT/O3LYP level.[51] Solvation effects were included through the use of the polarizable continuum model (PCM), using the integral formalism variant (IEFPCM), as implemented in Gaussian 09, and the internal parameters defined for the used solvents.[52,53] Geometry optimization calculations with solvation effects included were done at the O3LYP/6-31++G(d,p) level, using the optimized gas-phase geometries obtained at this level as starting geometries.

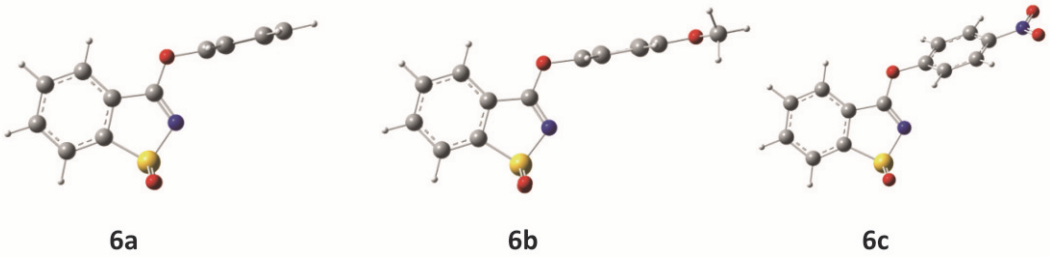


Figure 2. DFT(O3LYP)/6-311++G(3df,3pd) optimized structures of the global minima of monomeric aryloxysaccharins **6a–c**. Optimized geometries are provided in Table S3 (Supporting Information).

RESULTS AND DISCUSSION

The solvolysis of ethers **6** in alcohols was investigated theoretically. Because X-ray data are available for ethers **6** (Z = NO_2, OCH_3),[35] these were chosen for our study, allowing for results of the calculations to be compared with those obtained for the condensed state.

Molecular Geometry and Charge Density Analysis of the Studied Aryl Saccharyl Ethers

The ethers investigated (**6**;Z = H, NO_2, OCH_3) have two (Z = H) and three (Z = NO_2, OCH_3) intramolecular rotational degrees of freedom, represented by arrows in Figure 1, that may result in different conformers. These are related with: (i) the relative orientation of the saccharyl and aryl rings (dihedral angles **A** and **B**; for dihedral **A**, only the *zusammen* (Z) orientation was considered, since conformations where the aryl ring is directed to the phenyl group of the saccharin moiety are expected to correspond to structures of high energy, due to hindrance); (ii) the relative orientation of the substituent and the aryl ring (dihedral angle **C**).

The O3LYP/6-311++G(3df,3pd) fully optimized geometries of the global minimum of the studied molecules are presented in Figure 2. In all these structures, the C−O−C ether linkage was found to stay nearly in the plane of the saccharyl moiety. For the unsubstituted phenoxysaccharin (**6a**; Z = H), the potential energy profile for internal rotation around the dihedral angle **B** calculated at the O3LYP/6-31++G(d,p) level revealed that in the global minimum conformation the **B** dihedral is −92º, i.e., the phenyl substituent is nearly perpendicular to the plane of the heterocycle. In case of the two phenyl-substituted compounds (**6b** and **6c**), the calculations also predicted the phenyl and saccharyl planes as being nearly perpendicular to each other, while the phenyl substituents (4-OCH_3 and 4-NO_2) stay approximately aligned with the plane of the aromatic ring. For 4-methoxyphenoxysaccharin (**6b**; Z = 4-OCH_3), the potential energy surface has its global minimum for the conformation where dihedral **B** is −95º and dihedral **C** is −179º. For 4-nitrophenoxysaccharin (**6c**; Z = 4-NO_2), the global minimum conformation was predicted to correspond to the structure where dihedral **B** is 119º and dihedral **C** is −180º.

Table 1 shows selected bond lengths and angles around the central ether linkage and dihedral angles for aryloxysaccharins **6** investigated, obtained from calculations with the 6-311++G(3df,3pd) and 6-31++G(d,p) basis sets. Structure calculations were also performed in methanol, at the O3LYP/6-31++G(d,p)level, using a Polarizable Continuum Model (PCM). The corresponding parameters determined by X-ray crystallography, available for 4-methoxyphenylsaccharin **6b** and 4-nitrophenylsaccharin **6c**, are also included in the Table 1. For both aryloxysaccharins **6b** and **6c**, the calculated lengths for O_4−C_5 *(a)* and C_3−O_4 *(b)* bonds are around 140 pm and 133 pm, respectively, similar to those observed in the crystalline state (*ca.* 142 and 133 pm). Calculated values for the C−O−C angle are close to 120º, also similar to those obtained in the crystals, and are indicative of a significant degree of sp^2 character on oxygen. The values obtained theoretically for the geometric parameters of the central ether linkage in the 3 studied molecules are also very similar for the isolated molecule (for both basis sets) and in methanol (see Table 1). Overall, the results reveal that the electronic nature of the substituent on the aryl system has very little or no effect on geometric parameters of the ether linkage, even in methanol. Nevertheless, the calculations show that for the nitro-substituted phenoxysaccharin **6c** the relative orientation of the aryl ring to the saccharyl system changes somewhat in methanol, with the dihedral angle **B** varying from around 120º (as found theoretically for the isolated molecule and in the crystalline phase) to about 95º, a value more similar to those calculated for the isolated molecule or observed in the crystalline phase in compounds **6a** and **6b**. Thus, for the most polar ether, the polar solvent induces a significant change in the relative orientation of the two rings, while keeping the structure of the C−O−C linkage practically unaltered.

The charge distribution for aryloxysaccharins **6a−c,** has been analyzed using the Natural Population Analysis (NPA). Atomic charges for sulfur S_1, nitrogen

Table 1. Relevant geometric parameters for phenoxysaccharin (**6a**), 4-methoxyphenoxysaccharin (**6b**) and 4-nitrophenoxysaccharin (**6c**), calculated at the DFT O3LYP 6-31++G(d,p) and 6-311++G(3df,3pd) levels of theory. For comparative purposes, selected structural data obtained from X-ray crystallography are included[a]

Molecule	Dihedral angle / º			Bond length / pm		Angle / º	Basis
	A	B	C	***b***	***a***		
				$C_{(3)}-O_{(4)}$	$O_{(4)}-C_{(5)}$	$C_{(3)}O_{(4)}C_{(5)}$	
6a	0.00	−92.28	-	133.7	140.9	119.4	631++G(d,p)
	0.00	−92.20	-	133.0	140.5	119.5	6311++G(3df,3pd)
	0.00	−92.39	-	132.7	141.2	119.8	methanol
6b	−0.27	−95.10	−179.33	133.6	141.0	119.3	631++G(d,p)
	−0.26	−94.96	−179.27	132.9	140.6	119.4	6311++G(3df,3pd)
	−3.2	−93.7	−177.4	133.1	142.4	116.8	X-ray
	−0.58	−93.24	−179.81	132.7	141.3	119.8	Methanol
6c	−3.72	118.60	−179.99	134.3	139.7	120.4	631++G(d,p)
	−4.21	120.80	−179.97	133.6	139.3	120.8	6311++G(3df,3pd)
	−9.4	119.8	−177.1	133.5	141.7	118.7	X-ray
	−0.02	94.78	−179.83	133.3	140.0	119.9	methanol

[(a)] For definition of the geometric parameters see Figure 1.

N_2, carbons C_3, C_5 and oxygen O_4, and the dipole moments for the molecules, are included in Table 2 (see Figure 1 for atom numbering). The most electronegative natural charges are accumulated on the nitrogen N_2 from the saccharin moiety (−0.7*e*) and on the oxygen O_4 from the ether bridge (−0.4*e*). As expected, the most electropositive atom is carbon C_3, suffering from the electron-withdrawing effect of both the saccharyl ring and the ether oxygen. Comparing relative charges in those atoms for compounds **6a**, **6b** and **6c**, we can see that the electronic nature of the substituent has little or no effect on charge at carbon C_3. However, as expected, substituent effects are significant on carbon C_5 of the aryl ring. The electron donating 4-methoxyphenyl group on **6b** raises the charge density in carbon C_5, compared to the unsubstituted ether **6a,** while the electron withdrawing 4-nitrophenyl group in **6c** lowers the charge density of the same carbon C_5.

In order to gather more information regarding the effect of solvent in the solvolysis mechanisms for each compound, quantum chemical calculations were performed for the compound in methanol, using the PCM method, at the DFT(O3LYP)/6-31++G(d,p) level of theory. The atomic charges calculated in methanol follow the trends observed for the isolated molecules, but a higher dipole moment is predicted, induced by the polar solvent (Table 2). The relative energies obtained in methanol are presented in Table 3. The values of ΔHº, relative to the heat of dissolution, are relatively constant for all three compounds. The average value is 50.58 kJ

Table 2. NPA partial charges on selected atoms of phenoxysaccharin (**6a**), 4-methoxyphenoxysaccharin (**6b**) and 4-nitrophenoxysaccharin(**6c**), and resulting dipole moment ($|\mu|$), as calculated at the DFT(O3LYP)/6-31++G(d,p) level of theory, in vacuum, and in methanol (using the PCM approach)[a]

Molecule	NPA Charges (*q*)					$\|\mu\|$	
	S_1	N_2	C_3	O_4	C_5		
6a	2.410	−0.713	0.589	−0.487	0.273	6.13	vacuum
6b	2.239	−0.709	0.589	−0.485	0.244	6.09	
6c	2.238	−0.765	0.584	−0.486	0.307	8.79	
6a	2.247	−0.757	0.617	−0.472	0.263	8.85	methanol
6b	2.247	−0.759	0.628	−0.470	0.233	8.84	
6c	2.247	−0.749	0.614	−0.472	0.307	12.13	

[a] See Figure 1 for schematic drawings and atom numbering. Atomic charges (*q*) are in units of electron; Dipole moment $|\mu|$ in Debye.

Table 3. Relative energies for aryloxysaccharins **6a−c** in methanol, calculated with a Polarizable Continuum Model (PCM) using the integral formalism variant (IEFPCM), at the DFT (O3LYP)/6-31++G(d,p) level of theory

Molecule	Relative energy / kJ mol^{-1}			
	ΔE_{el}	ΔE_{ZPVE}	ΔH^o	ΔG^o
6a	−45.06	−45.21	−45.38	−42.79
6b	−49.61	−49.98	−50.09	−48.35
6c	−55.86	−56.63	−56.58	−56.72

All relative energies are calculated with respect to the corresponding structure calculated as *in vacuo*. ΔE_{el}, ΔE_{ZPVE}, ΔH^o, ΔG^o state for the relative electronic, zero-point-corrected, enthalpy (at 298.15 K) and Gibbs free energy (at 298.15 K), respectively. The absolute values calculated as *in vacuo* at the DFT (O3LYP)/6-31++G(d,p) level are: **6a** (E_{el} =−1179.09846759, E_{ZPVE} = −1178.902984, E_{H298} = −1178.888803, E_{G298}= −1178.946860 hartree); **6b** (E_{el} = −1293.60410999; E_{ZPVE} = −1293.376320, E_{H298} = −1293.358627, E_{G298}= −1293.404248 hartree) and **6c** (E_{el} = −1383.54979714; E_{ZPVE} = −1383.351869, E_{H298} = −1383.334171, E_{G298}= −1383.399654 hartree).

mol^{-1}, with a standard deviation of 5.60 kJ mol^{-1}. In general, the trends observed in the thermodynamic data for the compounds in methanol are very similar to those calculated for the gas-phase even though, in reactions involving protic solvents, hydrogen bonds are expected to play an important role in thermodynamic parameters and mechanisms involved, but akin in all three molecules investigated.

Effect of solvents with different dielectic constant

The geometry of phenoxysaccharin **6a** was optimized in 5 different alcohols. Table 4 presents the effects of solvent polarity on the energy of **6a** in the ground state. As it can be seen in Table 4, the energy of compound **6a** in alcohols decreases consistently as the dielectric constant of the solvent increases. This stabilizing effect of the solvent polarity is in fact expected to be even stronger for compound **6c**, due the higher relative polarity of this compound. Results from kinetic studies have shown that the rate of solvolysis for these ethers increases consistently with increasing the dielectric constant of the solvent.[36]

Mechanism of Solvolysis

Two general mechanistic pathways for the solvolysis of aryloxybenzisothiazoles **6** were considered, paths a (i), and b (ii), involving associative or dissociative mechanisms. The two possibilities are schematically represented in Figure 3, using a diagram adapted from the More O'Ferrall-Jencks representation.[54,55]

(i) Path *a* represents an addition-elimination mechanism. Nucleophilic attack by the alcohol leads to a zwitterionic tetrahedral intermediate that may develop to a neutral intermediate through proton exchange mediated by solvent, followed by elimination of the aryloxy ion. In a tetrahedral intermediate, phenoxides are known to be better leaving groups than alkoxides. Also, the initially formed tetrahedral zwitterionic intermediate would be more stabilized in a solvent of higher dielectric constant, in keeping with results obtained for relative rates observed in different alcohols.[36]

(ii) Path *b* represents a dissociation-recombination mechanism. If the reaction occurred through a dissociative mechanism cleavage of the C_3−O_4 bond would be expected in the rate-determining step, leading to iminium and aryloxy ions. As discussed, structural data from solid-state analysis and from quantum chemical calculations for the aryloxybenzisothiazoles **6a−c** indicate that bond C_3−O_4 is very strong. Structural data ob-

Table 4. Relative energies of phenoxysaccharin **6a** in alcohols, calculated with a Polarizable Continuum Model (PCM) using the integral formalism variant (IEFPCM), at the DFT (O3LYP)/6-31++G(d,p) level of theory

Solvent	ε	Relative energy/ kJmol^{-1}			
		ΔE_{el}	ΔE_{ZPVE}	ΔH^o	ΔG^o
Methanol	32.613	0.00	0.00	0.00	0.00
Ethanol	24.852	0.78	0.79	0.79	0.80
1-Propanol	20.524	1.46	1.49	1.48	1.50
2-Propanol	19.264	1.64	1.79	1.74	2.09
1-Buthanol	17.332	2.17	2.21	2.20	2.22

All relative energies are calculated with respect to phenoxysaccharin **6a,** in methanol. ΔE_{el}, ΔE_{ZPVE}, ΔH^o, ΔG^o state for the relative electronic, zero-point-corrected, enthalpy (at 298.15 K) and Gibbs free energy (at 298.15 K), respectively. The absolute values calculated for **6a** in methanol at the DFT (O3LYP)/6-31++G(d,p) level are E_{el} = −1179.11562919, E_{ZPVE} = −1178.920205, E_H = −1178.905142, E_{G298}= −1178.963158 hartree). ε is the dielectric constant of the solvents used in the PCM calculation.

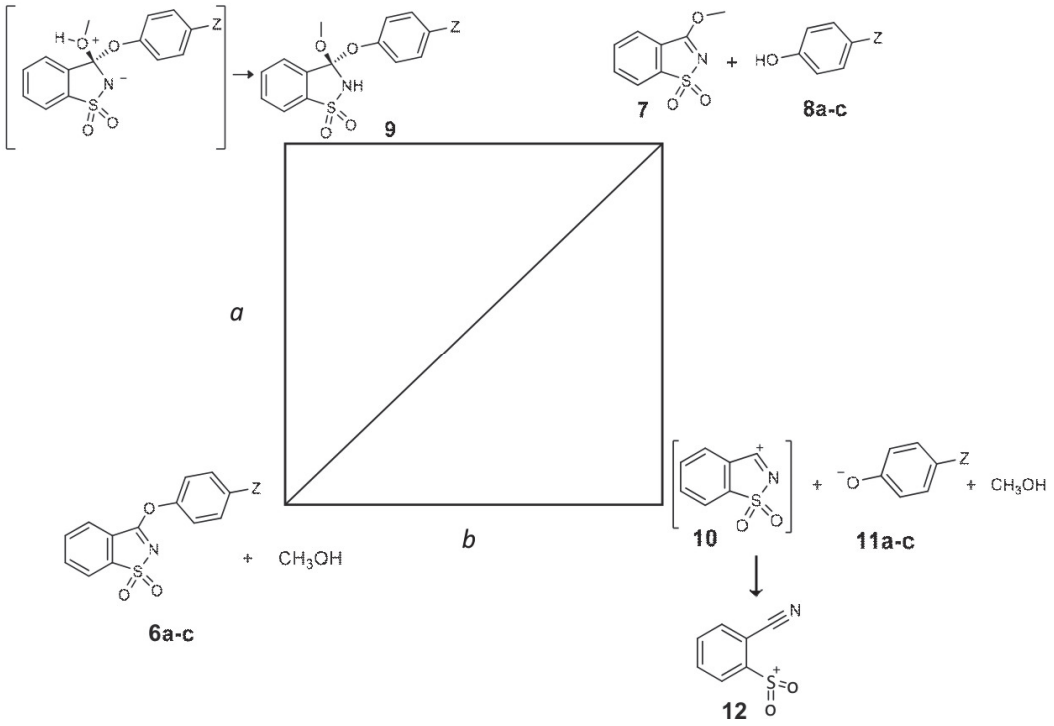


Figure 3. Schematic representation of a *More O'Ferrall-Jencks*-type diagram for the solvolysis of aryloxybenzisothiazoles **6a–c**.

tained through O3LYP/6-31++G(d,p) molecular orbital calculations (Tables 1 and 2) show a C_3–O_4 bond length of around 133 pm and an electronic density at the heteroaromatic carbon C_3 of about (0.59*e*). Cleavage of this bond is expected to require a very high energy of activation and would also be thermochemically disfavored, since it would lead to the formation of a formal positive charge on a carbon that already exhibits a high partially positive charge in the original ether.

To obtain information regarding the energy profiles for both pathways, the energies of the major species involved were calculated. For simplicity and atom economy, we considered methanol as the nucleophile. For pathway *a*, calculations were carried out for ethers **6a–c**. For pathway *b*, only compound **6a** was considered. Results obtained are presented in Figures 4 and 5. As described below, the performed molecular orbital calculations by means of polarized continuum model reaction field predicted that the solvolysis prefers an addition-elimination mechanism.

As proposed in Figure 3 pathway *a* proceeds through a zwitterionic (ZW) structure that may develop to a neutral intermediate. Both the performed calculations in vacuo and in methanol showed that the ZW intermediate is unstable, with no minimum found for this species in the calculated PES, while the neutral intermediate, which results from nucleophilic addition and proton transfer, was found to be a minimum (in solution, the protic solvent molecules participate in the

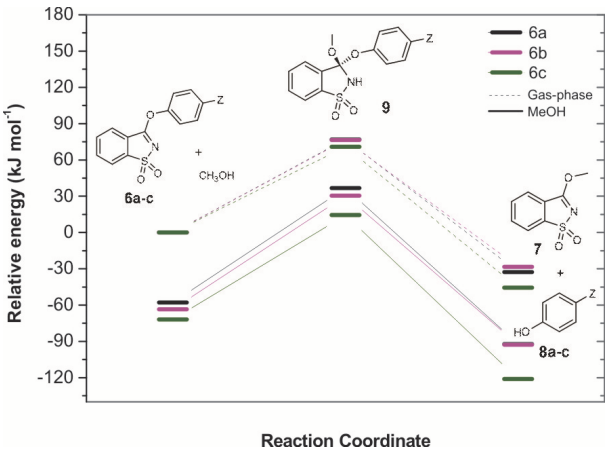


Figure 4. Energy diagram with structures corresponding to the most stable stationary points for solvolysis of aryloxysaccharins **6a–c**, with the formation of methoxysaccharin **7**, considering an addition-elimination mechanism, in gas phase and in methanol, calculated at the DFT(O3LYP)/6-31++G(d,p) level of theory. The relative energies (ΔE_{G298}) are presented in Table 5. In all calculations, the relative zero level of energy was chosen to be the energy of each aryoxysaccharin **6a–c** plus the nucleophile (methanol) in gas phase. Solvent stabilization effects were evaluated by using the PCM approach with the Integral Formalism variant (IEFPCM).

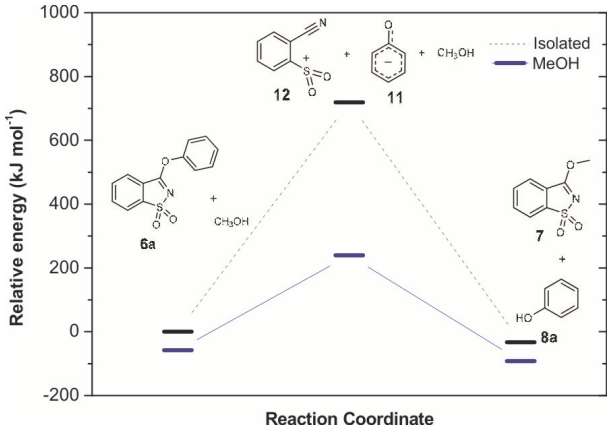


Figure 5. Relative energies of the structures corresponding to the most stable stationary points for the dissociative-associative mechanism of the aryloxysaccharine **6a**, with the formation of methoxysaccharin **7** and phenol **8a**, in vacuum and in methanol, calculated at the DFT(O3LYP)/6-31++G(d,p) level of theory. Solvent stabilization effects were evaluated by using the PCM approach with the Integral Formalism Variant (IEFPCM).

proton exchange). A realistic solute cavity shape and size with explicit consideration of a large number of specific solvent molecules must be used to accurately evaluate the solvent role in the stabilization of the zwitterionic intermediate.[56–60] This type of calculations for the present systems is, however, beyond pratical limitations. Thus, in the following discussion, we explored mechanism *a* considering the neutral intermediate.

In order to examine the effect of substituent on ground state energies of reagents, products and the intermediate formed upon addition of nucleophile, calculations on the gas-phase and in methanol were performed on the different systems under study. Table 5 presents the relative energies of species corresponding to the most stable stationary points for the addition-elimination mechanism (pathway *a*) and the dissociative-associative mechanism (pathway *b*) of the aryloxysaccharins **6a−c**, with the formation of methoxysaccharin **7**, in gas-phase and in methanol, calculated at the DFT(O3LYP)/6-31++G(d,p) level of theory. For a schematic representation, Figure 4 presents a diagram of the relative energies of species corresponding to the most stable stationary points for the addition-elimination mechanism, pathway *a*.

Aryloxysaccharins **6a−c** and the nucleophile methanol, in gas-phase or methanol, were chosen to be the relative zero level of energy. The relative energies of the structures corresponding to the most stable stationary points for the addition-elimination mechanism (pathway *a*) show that the energy for the neutral intermediates from the 3 ethers in the gas phase, is very close, ranging from 71 kJ mol^{-1} in **6c** to 77 kJ mol^{-1} in **6a**. Thus, the nature of the substituent has a negligible effect on the relative energy of said intermediates, in the gas phase. However, substituent effects appear to be more pronounced for the products, where calculated energies vary from −46 kJ mol^{-1}, for products resulting from **6c**, to −28 kJ mol^{-1}, for products resulting from **6b**. Thus, the products from the nitro derivative **6c** are calculated to be more stable (by 18 kJ mol^{-1}) than those from the methoxy derivative **6b** (Table 5).

As shown in Table 5, relative energies in methanol are consistently smaller than in the gas-phase, by ca. 60 kJmol^{-1}, for reagents and products, and by ca. 45 kJ mol^{-1} for the neutral intermediates (see also Figure 4). Additionally, data presented in Table 5 shows that the effect of solvent polarity is more pronounced on the

Table 5. Relative energies (ΔG^{o}; kJ mol^{-1}) of the structures corresponding to the most stable stationary points for the addition-elimination mechanism (pathway *a*) and the dissociative-associative mechanism (pathway *b*) of the aryloxysaccharins **6a–c**, with the formation of methoxysaccharin **7**, in gas-phase and in methanol as solvent, calculated at the DFT (O3LYP)/6-31++G(d,p) level of theory[a]

	Compound	Reagents	Intermediates (pathway *a)*	Intermediates (pathway *b*)	Products
Gas-Phase	6a	0.00	77.07	719.10	−32.62
	6b	0.00	76.36	-	−28.33
	6c	0.00	70.95	-	−45.62
MeOH	6a	0.00 (−57.87)	94.59 (36.72)	297.18 (239.31)	−34.31 (−92.18)
	6b	0.00 (−63.43)	93.91 (30.48)	-	−29.25 (−92.68)
	6c	0.00 (−71.80)	86.28 (14.48)	-	−49.30 (−121.10)

[a] Schematic representation of reagents, intermediates and products for each pathway mechanism are presented in a More O'Ferral-Jencks-type diagram shown in Figure 3. For the dissociative-associative mechanism only compound **6a** was considered. The relative zero level of energy was chosen to be the energy of each aryloxysaccharin **6a–c** plus the nucleophile (methanol) in gas-phase or methanol respectively. Values in parenthesis correspond to the relative energy in methanol calculated with respect to the corresponding aryloxysaccharin **6a-c** plus the nucleophile in the gas-phase. Solvent stabilization effects were evaluated by using the PCM approach with the Integral Formalism variant (IEFPCM).

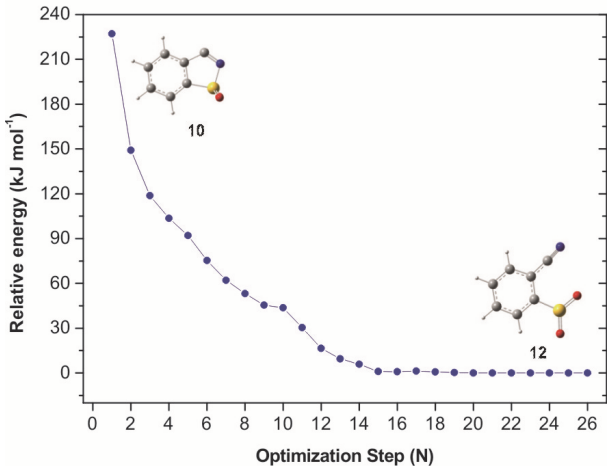


Figure 6. Potential energy profile showing the convergence in energy during optimization of the putative saccharyliminium **10** (formed from cleavage of the C−O bond of **6a**, leading to aryloxy group and a putative saccharylcation), that rearranges to 2-cyanobenzene sulfone **12**, through a cleavage of the S−N bond. Calculations performed at the DFT(O3LYP)/6-311++G(3df,3pd) level.

reactants than on corresponding intermediates. Regarding substituent effects in methanol, the relative energy of intermediates ranges from 86 kJ mol^{-1}, for **6c**, to 95 kJ mol^{-1}, for **6a**, showing a stabilizing effect of the nitro substituent corresponding to about 9 kJ mol^{-1}. The relative energy of products from ethers **6a**−c in methanol ranges from −49 kJ mol^{-1}, for **6c**, to −29 kJ mol^{-1}, for **6b**, showing that the products from the nitro derivative **6c** are calculated to be more stable (by 20 kJ mol^{-1}) than those from the methoxy derivative **6b**. Thus, the substituents induce similar effects on the energy of intermediates and products, in the gas phase and in methanol.

For pathway *b*, only compound **6a** was considered for the theoretical investigation. It is established that the energetic demand of the two processes is determined by the reaction barrier for each process.[61,62] Many efforts were made to determine reaction barriers. Theoretical calculations of the TS were found to be a true challenge. Unfortunately, the calculated activation barriers in vacuum were too high, and no convergence was achieved. However, considering the large energy difference of the intermediates in pathways *a,* and *b*, it appears reasonable to assume that the energy barriers in processes *a* and *b* must indeed be quite different, with the energy barrier associated to process *b* being much larger (see Figures 4 and 5 and Table 5 for values). The energies calculated for the intermediates associated to pathway *b*, in gas-phase and in methanol, are 642.03 kJ mol^{-1} and 202.59 kJ mol^{-1}, respectively, much higher than those associated to pathway *a*, thus making pathway *b* a highly improbable route for the solvolysis. Also, the calculations showed that the putative saccharyl iminium cation **10** formed from the dissociative process leads to a product resulting from cleavage of the S−N bond, the 2-cyanobenzene sulfone cation **12** (see Figure 6), in a barrierless process. A similar ring-opening reaction has been predicted for deprotonated isosaccharin.[1] Isosaccharin is formed from saccharin, through light-induced isomerisation.[1]

CONCLUSION

The solvolysis of aryloxybenzisothiazoles **6a−c** (Figure 3) has been theoretically investigated in different alcohols. The geometries of the investigated ethers were fully optimized at the DFT(O3LYP) level of theory, with the 6-31++G(d,p) and 6-311++G(3df,3pd) basis sets. Calculations including solvation effects were performed with the 6-31++G(d,p) basis set. Overall, values obtained theoretically for the central ether linkage in all studied aryloxysacharins are very close, for the isolated molecule, in both basis sets, and in methanol. Furthermore, theoretical values are also very close to those obtained by X-ray crystallography, revealing that the electronic nature of the substituent on the aryl system has very little or no effect on geometric parameters of the ether linkage. The charge distributions predicted using the NPA approach for the studied compounds also show that the electronic nature of the substituent has little or no effect on the charge of the carbon atom of the C−O−C moiety that lies in the heteroaromatic system. However, measured rate constants for the solvolysis of compounds **6a−c** in methanol, at 40ºC, are 3.84 x 10^{-4} s^{-1} for ether **6a**, 0.91 x 10^{-4} s^{-1} for ether **6b** and 19.9 x 10^{-4} s^{-1} for ether **6c**,[36] showing that the rate of solvolysis is affected by the electron-withdrawing/-donating characteristics of the substituent on the aryl ring. Thus, an explanation for observed differences in rate constants for compounds 6a−c cannot be rationalized by geometric parameters of the ether linkage or by charge distributions in the ground state of reactants.

Two general mechanistic pathways for the solvolysis of aryloxybenzisothiazoles were considered, involving associative or dissociative mechanisms. Molecular orbital calculations by means of polarized continuum model (PCM) reaction field predicted that solvolysis through the addition-elimination mechanism is preferred. We propose a mechanism whereby initial addition of nucleophile to carbon C_3 of the saccharyl system leads to an unstable zwitterionic structure that develops to a neutral intermediate. Comparing the corresponding relative energies for the intermediates and products from the studied compounds, we concluded that the electron donating methoxy substituent induces a minor change in the relative energies, while the electron with-

drawing nitro substituent has a more significant stabilizing effect on both intermediates and products.

Calculations show also that a dissociative-associative mechanism for the solvolysis of the studied aryloxysaccharins is energetically much more demanding than its addition-elimination counterpart, making the dissociative-associative pathway a highly improbable route for the solvolysis. In addition, it was found that the putative cation intermediate formed during the dissociative process should easily convert into its 2-cyanobenzene sulfone cation isomer, *via* cleavage of the S−N bond.

Supplementary Materials. – Supporting informations to the paper are enclosed to the electronic version of the article. These data can be found on the website of *Croatica Chemica Acta* (http://public.carnet.hr/ccacaa).

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Supporting Information

Investigations into the mechanism of solvolysisof 3-aryloxybenzisothiazoles.

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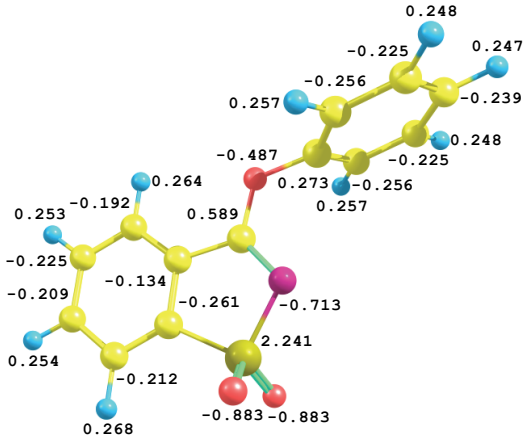
Index

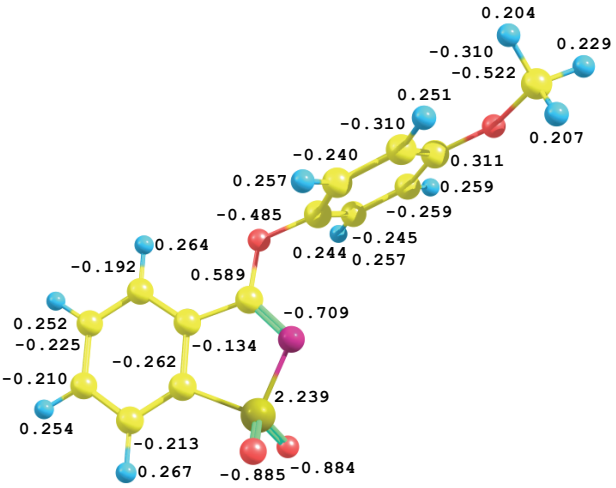
Table S1. Structure of the aryloxysaccharins investigated, optimized at the O3LYP/6-31++G(d,p) level of theory, with Cartesian coordinates and NPA charges.* 2

Table S2. Structure of the 2-cyanobenzene sulfone cation, optimized at the O3LYP/6-31++G(d,p) level of theory, with Cartesian coordinates and NPA charges.* 4

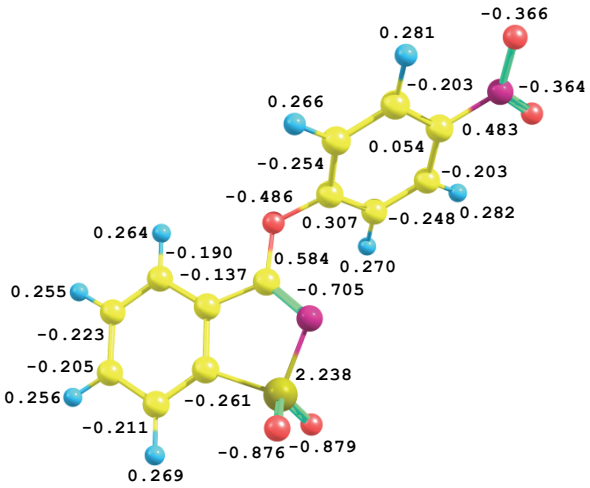
Table S3. Calculated Cartesian coordinates (Å) for each of the considered structures 5

Table S1. Structure of the aryloxysaccharins investigated, optimized at the O3LYP/6-31++G(d,p) level of theory, with Cartesian coordinates and NPA charges.*





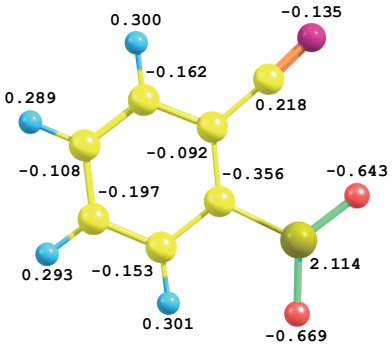
6a					**6b**				
Atom	**X**	**Y**	**Z**	**NPA**	**Atom**	**X**	**Y**	**Z**	**NPA**
C	2.31741200	0.12375800	0.00000000	-0.26118	C	-3.03499000	0.19760500	-0.04183700	0.26154
C	1.36618100	-0.89427100	0.00000000	-0.13427	C	-2.13574800	-0.86648800	-0.05192500	0.13392
C	1.76249000	-2.23162900	-0.00000200	-0.19195	C	-2.59814800	-2.18096800	-0.11720100	0.19214
C	3.13371400	-2.50930300	-0.00000200	-0.22482	C	-3.98073600	-2.38829100	-0.17183100	0.22528
C	4.07859800	-1.47518100	-0.00000100	-0.20914	C	-4.87263700	-1.30818300	-0.16128300	0.20978
C	3.67958000	-0.13168900	0.00000000	-0.21250	C	-4.40734400	0.01218300	-0.09514500	0.21287
S	1.42653000	1.69328700	0.00000200	2.24071	S	-2.06812800	1.71833700	0.05229400	2.23892
N	-0.12524000	0.98107400	0.00000100	-0.71330	N	-0.55538700	0.93010900	0.07503600	-0.70851
C	0.00903100	-0.30125000	0.00000000	0.58925	C	-0.75117000	-0.34350700	0.01707400	0.58937
H	1.02730000	-3.02946500	-0.00000300	0.26389	H	-1.90396800	-3.01471400	-0.12448500	0.26382
H	3.47083700	-3.54160100	-0.00000300	0.25288	H	-4.36839200	-3.40144200	-0.22264800	0.25249
H	5.13770500	-1.71647600	-0.00000100	0.25393	H	-5.94184500	-1.49500300	-0.20419100	0.25353
H	4.40749700	0.67317700	0.00000000	0.26769	H	-5.09397500	0.85252300	-0.08597500	0.26734
O	1.62806400	2.39295000	1.26675800	-0.88251	O	-2.19024800	2.47721600	-1.19078200	-0.88492
O	1.62806400	2.39295100	-1.26675500	-0.88251	O	-2.28179100	2.37751300	1.33875600	-0.88398
O	-1.01209000	-1.16394200	0.00000000	-0.48712	O	0.22454100	-1.25584500	0.01364600	-0.48462
C	-2.33282300	-0.67298900	0.00000000	0.27335	C	1.56750900	-0.83148000	0.08235500	0.24395
C	-2.97891000	-0.48461700	-1.21780200	-0.25620	C	2.19772400	-0.78468300	1.32460200	-0.24458
C	-2.97891300	-0.48462700	1.21780000	-0.25620	C	2.26118200	-0.56185000	-1.08821100	-0.24006
C	-4.31608500	-0.08094100	-1.21005700	-0.22458	C	3.54515400	-0.45019900	1.38985700	-0.25943
H	-2.44358200	-0.64523100	-2.14778900	0.25713	H	1.63762300	-1.00315400	2.22792900	0.25723
C	-4.31608800	-0.08095100	1.21005600	-0.22458	C	3.61669600	-0.22346400	-1.02529500	-0.30985
H	-2.44358700	-0.64524900	2.14778900	0.25713	H	1.75285800	-0.60700800	-2.04580200	0.25654
C	-4.98524800	0.12121100	0.00000000	-0.23914	C	4.26464000	-0.16497300	0.21675800	0.31077
H	-4.83251400	0.07441500	-2.15283500	0.24837	H	4.05987300	-0.40228500	2.34373500	0.25875
H	-4.83252000	0.07439600	2.15283500	0.24837	H	4.14411300	-0.00998900	-1.94660900	0.25065
H	-6.02488200	0.43512200	0.00000000	0.24728	O	5.57653000	0.15024400	0.39703600	-0.52245
					C	6.37202500	0.46593900	-0.73428300	-0.31030
					H	5.98925300	1.34754600	-1.26328100	0.20699
					H	7.36591400	0.68670900	-0.34197000	0.22949
					H	6.43911800	-0.38021100	-1.42970600	0.20440



6c

Atom	X	Y	Z	NPA
C	3.27923500	0.17133500	-0.01848300	-0.26056
C	2.35891900	-0.86981200	0.09220300	-0.13708
C	2.79551700	-2.18299600	0.26892600	-0.19015
C	4.17416100	-2.41291300	0.32838900	-0.22268
C	5.08689300	-1.35654600	0.21458400	-0.20527
C	4.64781900	-0.03722500	0.03778000	-0.21083
S	2.34667400	1.70098000	-0.23075700	2.23827
N	0.81305400	0.94086300	-0.17524900	-0.70484
C	0.98850300	-0.32310500	-0.00809100	0.58415
H	2.08621100	-2.99920600	0.35669000	0.26398
H	4.54228500	-3.42532400	0.46459100	0.25484
H	6.15249000	-1.56103800	0.26364200	0.25595
H	5.35120700	0.78438900	-0.05037100	0.26943
O	2.48801700	2.55211300	0.94755500	-0.87899
O	2.55414300	2.24632000	-1.56864700	-0.87612
O	-0.01236400	-1.21476800	0.07413400	-0.48581
C	-1.34277900	-0.78891700	0.05625000	0.30683
C	-1.86516900	-0.02768300	1.10234100	-0.24787
C	-2.13976200	-1.24585800	-0.99186000	-0.25378
C	-3.22004100	0.29081000	1.09126400	-0.20251
H	-1.22523000	0.31735800	1.90584900	0.26961
C	-3.49630200	-0.93013800	-1.00213900	-0.20290
H	-1.69920400	-1.83919200	-1.78574900	0.26557
C	-4.01856500	-0.16485700	0.04059400	0.05412
H	-3.65985600	0.88190100	1.88506600	0.28247
H	-4.14386100	-1.26712400	-1.80211400	0.28137
N	-5.45682100	0.16819400	0.03536000	0.48303
O	-6.13409900	-0.25196900	-0.89897700	-0.36617
O	-5.88757600	0.84287900	0.96633300	-0.36405

Table S2. Structure of the 2-cyanobenzene sulfone cation, optimized at the O3LYP/6-31++G(d,p) level of theory, with Cartesian coordinates and NPA charges.*



12				
Atom	**X**	**Y**	**Z**	**NPA**
C	-0.10807900	-0.40527500	0.00002500	-0.35553
C	-0.78344700	0.85889800	-0.00003800	-0.09173
C	-2.18326200	0.82286800	-0.00007200	-0.16239
C	-2.87411500	-0.39431900	-0.00003700	-0.10790
C	-2.19051200	-1.61818000	0.00004200	-0.19731
C	-0.80355800	-1.63741500	0.00006500	-0.15338
S	1.61652500	-0.51086300	-0.00001500	2.11423
N	0.32638200	3.20109700	0.00014800	-0.13451
C	-0.13641600	2.12941700	-0.00003600	0.21841
H	-2.72494200	1.76299400	-0.00012000	0.29975
H	-3.96033500	-0.38317100	-0.00007100	0.28904
H	-2.73686300	-2.55587400	0.00008000	0.29297
H	-0.26297600	-2.57732900	0.00012600	0.30068
O	2.14696400	-1.85305500	0.00001600	-0.66917
O	2.35458300	0.72599800	-0.00007900	-0.64317

*The charge distribution has been analyzed using the Natural Population Analysis (NPA), see: Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.***1985**, *83*, 735.
Color codes: light yellow – C, blue – H, red – O, pink – N, dark yellow – S;
Chemcraft software (http://www.chemcraftprog.com) was used to produce structures shown in Table S1 and Table S2.

Table S3. Calculated Cartesian coordinates (Å) for each of the considered structures

	O3LYP/6-31++G(d,p)				O3LYP/6-311++G(3df,3pd)		
6a							
Atom	**X**	**Y**	**Z**	**Atom**	**X**	**Y**	**Z**
C	2.31741200	0.12375800	0.00000000	C	2.30429600	0.13780700	-0.00000300
C	1.36618100	-0.89427100	0.00000000	C	1.37026900	-0.88949300	-0.00000100
C	1.76249000	-2.23162900	-0.00000200	C	1.77902300	-2.21653200	-0.00000200
C	3.13371400	-2.50930300	-0.00000200	C	3.14690100	-2.47916200	-0.00000400
C	4.07859800	-1.47518100	-0.00000100	C	4.07535800	-1.43880400	-0.00000600
C	3.67958000	-0.13168900	0.00000000	C	3.66345700	-0.10590600	-0.00000500
S	1.42653000	1.69328700	0.00000200	S	1.40168500	1.67783300	0.00000400
N	-0.12524000	0.98107400	0.00000100	N	-0.11151000	0.96912100	0.00000500
C	0.00903100	-0.30125000	0.00000000	C	0.01247100	-0.30774700	0.00000300
H	1.02730000	-3.02946500	-0.00000300	H	1.05516000	-3.02092300	-0.00000100
H	3.47083700	-3.54160100	-0.00000300	H	3.49459100	-3.50492700	-0.00000400
H	5.13770500	-1.71647600	-0.00000100	H	5.13428400	-1.66807800	-0.00000700
H	4.40749700	0.67317700	0.00000000	H	4.38190400	0.70346400	-0.00000700
O	1.62806400	2.39295000	1.26675800	O	1.59673000	2.37008900	1.24012900
O	1.62806400	2.39295100	-1.26675500	O	1.59672200	2.37009900	-1.24011700
O	-1.01209000	-1.16394200	0.00000000	O	-1.00434300	-1.16482300	0.00000300
C	-2.33282300	-0.67298900	0.00000000	C	-2.32154400	-0.67600800	0.00000100
C	-2.97891000	-0.48461700	-1.21780200	C	-2.96529300	-0.48671300	-1.21194400
C	-2.97891300	-0.48462700	1.21780000	C	-2.96530300	-0.48673000	1.21194300
C	-4.31608500	-0.08094100	-1.21005700	C	-4.29649900	-0.08520600	-1.20389100
H	-2.44358200	-0.64523100	-2.14778900	H	-2.43165500	-0.64665700	-2.13977000
C	-4.31608800	-0.08095100	1.21005600	C	-4.29651000	-0.08522300	1.20388400
H	-2.44358700	-0.64524900	2.14778900	H	-2.43167500	-0.64668700	2.13977200
C	-4.98524800	0.12121100	0.00000000	C	-4.96323000	0.11663200	-0.00000500
H	-4.83251400	0.07441500	-2.15283500	H	-4.81112100	0.07018200	-2.14441600
H	-4.83252000	0.07439600	2.15283500	H	-4.81114000	0.07015100	2.14440600
H	-6.02488200	0.43512200	0.00000000	H	-5.99998400	0.42988600	-0.00000800
6b							
Atom	**X**	**Y**	**Z**	**Atom**	**X**	**Y**	**Z**
C	-3.03499000	0.19760500	-0.04183700	C	-3.01793100	0.21085400	-0.04124300
C	-2.13574800	-0.86648800	-0.05192500	C	-2.13655100	-0.86179200	-0.05186200
C	-2.59814800	-2.18096800	-0.11720100	C	-2.61130600	-2.16521900	-0.11770800
C	-3.98073600	-2.38829100	-0.17183100	C	-3.98981000	-2.35723800	-0.17276600
C	-4.87263700	-1.30818300	-0.16128300	C	-4.86468400	-1.27147800	-0.16208000
C	-4.40734400	0.01218300	-0.09514500	C	-4.38665700	0.03748600	-0.09539000
S	-2.06812800	1.71833700	0.05229400	S	-2.04098500	1.70146700	0.05294200
N	-0.55538700	0.93010900	0.07503600	N	-0.56651700	0.91857500	0.07451200
C	-0.75117000	-0.34350700	0.01707400	C	-0.75173600	-0.35014800	0.01687300
H	-1.90396800	-3.01471400	-0.12448500	H	-1.92898900	-3.00512700	-0.12525900
H	-4.36839200	-3.40144200	-0.22264800	H	-4.38793200	-3.36322300	-0.22411100
H	-5.94184500	-1.49500300	-0.20419100	H	-5.93312400	-1.44601700	-0.20553600
H	-5.09397500	0.85252300	-0.08597500	H	-5.06336400	0.88203800	-0.08618400
O	-2.19024800	2.47721600	-1.19078200	O	-2.15783700	2.45228500	-1.16317600
O	-2.28179100	2.37751300	1.33875600	O	-2.24774000	2.35338300	1.31305500
O	0.22454100	-1.25584500	0.01364600	O	0.21977500	-1.25673300	0.01383600
C	1.56750900	-0.83148000	0.08235500	C	1.55936800	-0.83435000	0.08279100
C	2.19772400	-0.78468300	1.32460200	C	2.18698300	-0.78486000	1.31927400
C	2.26118200	-0.56185000	-1.08821100	C	2.25112800	-0.56473600	-1.08141500
C	3.54515400	-0.45019900	1.38985700	C	3.52806300	-0.45054700	1.38447700
H	1.63762300	-1.00315400	2.22792900	H	1.62832900	-1.00191000	2.22054000
C	3.61669600	-0.22346400	-1.02529500	C	3.60045800	-0.22716700	-1.01796500
H	1.75285800	-0.60700800	-2.04580200	H	1.74496100	-0.61014200	-2.03702000
C	4.26464000	-0.16497300	0.21675800	C	4.24715500	-0.16664300	0.21783000
H	4.05987300	-0.40228500	2.34373500	H	4.03932600	-0.40151700	2.33716000
H	4.14411300	-0.00998900	-1.94660900	H	4.12709100	-0.01412200	-1.93648000

O	5.57653000	0.15024400	0.39703600	O	5.55384200	0.14938800	0.39415800
C	6.37202500	0.46593900	-0.73428300	C	6.34322200	0.46423100	-0.73562500
H	5.98925300	1.34754600	-1.26328100	H	5.95824800	1.34133600	-1.26470600
H	7.36591400	0.68670900	-0.34197000	H	7.33664800	0.68778700	-0.35160300
H	6.43911800	-0.38021100	-1.42970600	H	6.40964900	-0.37954100	-1.42958300

6c

Atom	X	Y	Z	Atom	X	Y	Z
C	3.27923500	0.17133500	-0.01848300	C	3.26555200	0.17895400	-0.01944500
C	2.35891900	-0.86981200	0.09220300	C	2.35686000	-0.86551300	0.09419100
C	2.79551700	-2.18299600	0.26892600	C	2.79821400	-2.16941600	0.27838200
C	4.17416100	-2.41291300	0.32838900	C	4.17164800	-2.39108900	0.34367600
C	5.08689300	-1.35654600	0.21458400	C	5.07365000	-1.33412500	0.22788700
C	4.64781900	-0.03722500	0.03778000	C	4.62946400	-0.02437600	0.04349600
S	2.34667400	1.70098000	-0.23075700	S	2.33052500	1.68237100	-0.23912700
N	0.81305400	0.94086300	-0.17524900	N	0.83142700	0.93511400	-0.18747400
C	0.98850300	-0.32310500	-0.00809100	C	0.98909300	-0.32374500	-0.01334700
H	2.08621100	-2.99920600	0.35669000	H	2.09576700	-2.98766900	0.36783900
H	4.54228500	-3.42532400	0.46459100	H	4.54439900	-3.39786200	0.48622300
H	6.15249000	-1.56103800	0.26364200	H	6.13746400	-1.53182700	0.28184500
H	5.35120700	0.78438900	-0.05037100	H	5.32772800	0.79753800	-0.04603300
O	2.48801700	2.55211300	0.94755500	O	2.46544400	2.52694200	0.91073700
O	2.55414300	2.24632000	-1.56864700	O	2.54056800	2.21740300	-1.55096600
O	-0.01236400	-1.21476800	0.07413400	O	-0.01155600	-1.20544000	0.06819700
C	-1.34277900	-0.78891700	0.05625000	C	-1.33827400	-0.78220600	0.05201900
C	-1.86516900	-0.02768300	1.10234100	C	-1.84954600	0.01200800	1.07088600
C	-2.13976200	-1.24585800	-0.99186000	C	-2.14412200	-1.27493600	-0.96493100
C	-3.22004100	0.29081000	1.09126400	C	-3.19924800	0.32629000	1.06317300
H	-1.22523000	0.31735800	1.90584900	H	-1.20418100	0.38490700	1.85351600
C	-3.49630200	-0.93013800	-1.00213900	C	-3.49491300	-0.96145200	-0.97218300
H	-1.69920400	-1.83919200	-1.78574900	H	-1.71309000	-1.89519200	-1.73949300
C	-4.01856500	-0.16485700	0.04059400	C	-4.00495700	-0.16387500	0.04299100
H	-3.65985600	0.88190100	1.88506600	H	-3.63091600	0.94236200	1.83816700
H	-4.14386100	-1.26712400	-1.80211400	H	-4.14941400	-1.32598900	-1.75006700
N	-5.45682100	0.16819400	0.03536000	N	-5.44456200	0.16828200	0.04121600
O	-6.13409900	-0.25196900	-0.89897700	O	-6.12440200	-0.28276800	-0.86385700
O	-5.88757600	0.84287900	0.96633300	O	-5.86064600	0.87047700	0.94552400

12

Atom	X	Y	Z	Atom	X	Y	Z
C	-0.10807900	-0.40527500	0.00002500	C	0.09996700	-0.40266700	0.00000200
C	-0.78344700	0.85889800	-0.00003800	C	0.77215400	0.85816900	0.00000200
C	-2.18326200	0.82286800	-0.00007200	C	2.16490800	0.82469800	0.00000700
C	-2.87411500	-0.39431900	-0.00003700	C	2.85491400	-0.38661800	0.00000300
C	-2.19051200	-1.61818000	0.00004200	C	2.17789100	-1.60736200	-0.00000500
C	-0.80355800	-1.63741500	0.00006500	C	0.79797400	-1.62877300	-0.00000400
S	1.61652500	-0.51086300	-0.00001500	S	-1.59965500	-0.51265900	0.00000300
N	0.32638200	3.20109700	0.00014800	N	-0.33673000	3.18420100	-0.00001100
C	-0.13641600	2.12941700	-0.00003600	C	0.12503200	2.12280400	-0.00000400
H	-2.72494200	1.76299400	-0.00012000	H	2.70467700	1.76262600	0.00001200
H	-3.96033500	-0.38317100	-0.00007100	H	3.93841900	-0.37270000	0.00000800
H	-2.73686300	-2.55587400	0.00008000	H	2.72585900	-2.54076700	-0.00000800
H	-0.26297600	-2.57732900	0.00012600	H	0.25772200	-2.56506800	-0.00000500
O	2.14696400	-1.85305500	0.00001600	O	-2.12290500	-1.82814700	-0.00000700
O	2.35458300	0.72599800	-0.00007900	O	-2.33111000	0.69658900	0.00000900

O3LYP/6-31++G(d,p)

7 **8a**

Atom	X	Y	Z	Atom	X	Y	Z

C	0.57586800	0.87288300	0.00000000
C	0.82170200	-0.49836800	0.00000000
C	2.12863900	-0.98260200	0.00000000
C	3.17238700	-0.05004200	0.00000000
C	2.90999900	1.32628400	0.00000000
C	1.59449600	1.81152100	0.00000000
S	-1.21814900	1.10316900	0.00000000
N	-1.57342300	-0.57449000	0.00000000
C	-0.46378900	-1.23703900	0.00000000
H	2.32485900	-2.04930900	0.00000000
H	4.20075300	-0.39752400	0.00000000
H	3.73730500	2.02933700	0.00000000
H	1.38505100	2.87592000	0.00000000
O	-1.65978700	1.68616200	1.26793700
O	-1.65978700	1.68616200	-1.26793700
O	-0.40100900	-2.56293300	0.00000000
C	-1.65978700	-3.27580200	0.00000000
H	-2.23371500	-3.01676100	-0.89226400
H	-1.38863400	-4.33031300	0.00000000
H	-2.23371500	-3.01676100	0.89226400

C	0.01946100	-1.85960900	0.00000000
C	-1.19140000	-1.16347400	0.00000000
C	-1.20794300	0.23363300	0.00000000
C	0.00000000	0.94322300	0.00000000
C	1.21844600	0.25321000	0.00000000
C	1.21997700	-1.14164400	0.00000000
H	0.02803100	-2.94526700	0.00000000
H	-2.13307700	-1.70586700	0.00000000
H	-2.15557100	0.76844900	0.00000000
H	2.14516900	0.81800500	0.00000000
H	2.16935300	-1.67048800	0.00000000
O	0.05438400	2.30950700	0.00000000
H	-0.84022100	2.66707800	0.00000000

8b

Atom	X	Y	Z
C	-0.93120800	0.27536400	-0.00001300
C	-0.05348400	1.36872000	-0.00000100
C	1.32462700	1.17017200	0.00000600
C	1.85304600	-0.12790600	0.00000300
C	0.98233600	-1.21793700	-0.00000900
C	-0.40226800	-1.02217600	-0.00001700
O	-2.26468800	0.58483900	-0.00002600
H	-0.46636100	2.37247600	0.00000200
H	1.98839500	2.03251300	0.00001500
H	1.39235600	-2.22292300	-0.00001100
H	-1.04811900	-1.89202900	-0.00002800
O	3.20037600	-0.38638800	0.00001100
H	3.68503600	0.44566100	0.00001900
C	-3.20859800	-0.46929300	0.00003000
H	-3.11732400	-1.09790900	-0.89568100
H	-3.11726200	-1.09786700	0.89576400
H	-4.18893500	0.01080500	0.00005200

8c

Atom	X	Y	Z
	-0.69457700	0.00071800	0.00000000
	-0.00371500	-1.21270200	0.00001300
	1.38675400	-1.20533100	0.00001500
	2.08272100	0.01418000	0.00000000
	1.37685000	1.22783900	-0.00001600
	-0.01106600	1.22135700	-0.00001300
	-0.55566000	-2.14474500	0.00002200
	1.93060800	-2.14684400	0.00003000
	1.93031300	2.16071300	-0.00003000
	-0.57142900	2.14836200	-0.00002200
	3.43720500	0.08743600	0.00000000
	3.81745400	-0.79858600	0.00000400
	-2.16047900	-0.00648100	0.00000000
	-2.73920000	1.07922400	0.00003700
	-2.72922200	-1.09789700	-0.00003700

9a

Atom	X	Y	Z
C	-2.18871300	0.34245300	-0.25319600
C	-1.41371500	-0.80862100	-0.24635800
C	-1.92880700	-1.98738900	-0.78377400
C	-3.21963200	-1.97334600	-1.31810200
C	-3.98865900	-0.80128600	-1.31435400
C	-3.47815200	0.38193500	-0.77673000
S	-1.29303400	1.70800900	0.46074600
N	-0.03915400	0.67780300	0.99343500
C	-0.01983000	-0.62945300	0.34621400
H	-1.33163700	-2.89346900	-0.78649200
H	-3.63337700	-2.88355800	-1.74257000
H	-4.99104500	-0.81127800	-1.73220100
H	-4.06298100	1.29594600	-0.76353700
O	-0.80477000	2.63559700	-0.56657300
O	-1.99920500	2.25776900	1.61737600
O	0.87614600	-0.72944700	-0.74504300
C	2.20851400	-0.36786700	-0.56813000
C	3.12618700	-1.25303500	0.00792900
C	2.62749200	0.86657200	-1.07587100

9b

Atom	X	Y	Z
C	-2.75139900	0.53930200	-0.27222900
C	-2.12505200	-0.69796000	-0.32468900
C	-2.75919400	-1.76233300	-0.96440100
C	-4.01484500	-1.54869800	-1.53867500
C	-4.63293100	-0.29220100	-1.47340900
C	-4.00335100	0.77692600	-0.83302200
S	-1.72601800	1.72774600	0.57202800
N	-0.62514600	0.51793700	1.05884300
C	-0.74525500	-0.73703000	0.32397600
H	-2.27879000	-2.73413600	-1.01378300
H	-4.51951000	-2.36782300	-2.04290600
H	-5.61061300	-0.14675600	-1.92344400
H	-4.47140900	1.75409600	-0.77195600
O	-1.09183400	2.66360400	-0.36452600
O	-2.40647200	2.27310600	1.74625500
O	0.17688000	-0.88316000	-0.73861800
C	1.52950500	-0.65488800	-0.49440400
C	2.34082900	-1.62819100	0.10508800
C	2.09445200	0.53356700	-0.95577800

C	4.47044100	-0.88342000	0.08897200
H	2.78304800	-2.21110100	0.37916300
C	3.97639700	1.22370500	-0.98817600
H	1.90053500	1.52525000	-1.54043700
C	4.89927900	0.35314400	-0.40373700
H	5.18626700	-1.56926300	0.53412000
H	4.30245900	2.18181000	-1.38341400
H	5.94722500	0.63174000	-0.33935200
O	0.35643000	-1.63055500	1.25418200
C	-0.37032700	-1.71250400	2.47996300
H	0.09799700	-2.52563500	3.03784000
H	-0.30069800	-0.78206200	3.05005000
H	-1.42564700	-1.95576400	2.30777300
H	0.85883000	1.15238500	1.00562200

C	3.70279300	-1.39458500	0.25444000
H	1.90040900	-2.55775600	0.44495500
C	3.46629100	0.77110400	-0.80842100
H	1.46206600	1.27204800	-1.43838800
C	4.27743300	-0.19341500	-0.19658500
H	4.34545900	-2.13819900	0.71510000
H	3.87731700	1.70281200	-1.17762800
O	5.62049800	-0.07335400	0.00343800
O	-0.53836600	-1.83521200	1.17414600
C	-1.32149200	-1.89870900	2.36528100
H	-0.99626600	-2.80747300	2.87539300
H	-1.14730300	-1.03013400	3.00642500
H	-2.39213600	-1.97616800	2.14096100
H	0.32472900	0.87420500	1.11572600
C	6.27662200	1.10640800	-0.43016800
H	7.32700600	0.97322600	-0.16604300
H	6.19228700	1.24029700	-1.51605200
H	5.88698700	1.99661000	0.07970200

9c

Atom	X	Y	Z
C	-3.00053100	0.48221500	-0.24248400
C	-2.31946500	-0.72477000	-0.32486700
C	-2.90432300	-1.80087800	-0.99029400
C	-4.16991100	-1.63038800	-1.55790200
C	-4.84345000	-0.40511900	-1.46249600
C	-4.26169000	0.67679900	-0.79801500
S	-2.02446400	1.69735700	0.62239500
N	-0.89945900	0.50477900	1.11566600
C	-0.93990400	-0.71346600	0.32427600
H	-2.38143000	-2.74897800	-1.06399500
H	-4.63822900	-2.45950400	-2.08028500
H	-5.82740900	-0.29344500	-1.90822500
H	-4.77310800	1.63025700	-0.71485800
O	-1.40253200	2.64887200	-0.30485100
O	-2.72438600	2.21634800	1.79533200
O	-0.01462500	-0.74046800	-0.75899800
C	1.32693500	-0.50492900	-0.53312800
C	2.15656000	-1.46904900	0.05733400
C	1.86036100	0.69995400	-1.01061800
C	3.51968400	-1.21690500	0.18436800
H	1.73223500	-2.40258800	0.40363400
C	3.22486900	0.95172900	-0.88911200
H	1.19996500	1.42529400	-1.47380300
C	4.03890000	-0.00958400	-0.28824700
H	4.18217900	-1.94605400	0.63480000
H	3.65773100	1.87647300	-1.25086200
O	-0.64990200	-1.83531500	1.10955300
C	-1.42236600	-2.02229100	2.29808600
H	-1.03081400	-2.93364500	2.75323700
H	-1.30586300	-1.18167700	2.98723300
H	-2.48484000	-2.16124200	2.06804000
H	0.02653700	0.89273400	1.26656600
N	5.48350900	0.25210000	-0.15451300
O	6.17146700	-0.60951900	0.38849900
O	5.91399100	1.31590700	-0.59319500

11a

Atom	X	Y	Z
O	-0.00005100	2.35443300	0.00000000
C	0.00000200	1.08200400	0.00000000
C	0.00000700	0.28817800	1.21398600
C	0.00000700	0.28817800	-1.21398600
C	0.00000700	-1.10364700	1.20269300
H	-0.00003200	0.83087200	2.15864000
C	0.00000700	-1.10364700	-1.20269300
H	-0.00003200	0.83087200	-2.15864000
C	0.00004600	-1.83326100	0.00000000
H	0.00001600	-1.64148500	2.15341600
H	0.00001600	-1.64148500	-2.15341600
H	-0.00002100	-2.92106400	0.00000000