New synthetic route to modafinil drug including desulfobenzhydrylation of sodium carbamoylmethyl thiosulfate: experimental and quantum chemical studies

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A new synthetic route to 2-benzhydrylsulfinylacetamide (**1**), a nootropic drug modafinil, is described. The synthesis includes the alkylation of sodium thiosulfate with chloroacetamide to sodium carbamoylmethyl thiosulfate, the desulfobenzhydrylation of the latter by benzhydrol in formic acid to form benzhydrylthioacetamide (**3a**), and the further oxidation of this thioamide with hydrogen peroxide. According to B3LYP/6-31G** DFT calculations, the key step of the synthesis, namely, desulfobenzhydrylation of salt **6a**, occurs only insignificantly due to the energetically unfavorable direct attack of this salt by benzhydryl formate; the reaction mainly involves the attack by the benzhydrilium carbocation Ph_2CH^+. The oxidation of sulfide **3a** to sulfinylacetamide **1** is efficiently catalyzed by side proton-donor molecules (constituents of the transition states of the reaction). The oxidant can be the anionic form of the reactant (HO_2^- ion), which reacts with sulfide **3a** *via* the unusual noncatalytic mechanism. At the step of transition state formation, this mechanism resembles the S_N2 substitution.

Key words: modafinil, 2-benzhydrylsulfinylacetamide, synthesis, quantum chemical calculations, DFT method, B3LYP density functional, transition states, desulfobenzhydrylation, Bunte salt, sulfoxidation, relay mechanism of prototropic catalysis.

Nootropic drug modafinil (provigil, modalert, alertec) with the chemical structure of 2-benzhydrylsulfinylacetamide (**1**) is a bestseller of the Cephalon company.[1] The drug can, in particular, improve the memory and prolong the waking period without significant adverse effects characteristic of traditional drugs with this effect. Modafinil also possesses some other interesting pharmacological properties[2—4] and is used for the treatment of certain types of sleep disturbance. The exact mechanism of action of modafinil is unknown. It is assumed that, as classical psychostimulant agents, modafinil increases the level of extracellular dopamine, but acts specifically by blocking dopamin reuptake sites.[5,6]

Modafinil is synthesized from chloroacetic acid or its amide and benzhydrol or benzhydryl halides from which *S*-benzhydrylthioacetic acid $BzhSCH_2COOH$ (**2**) (Bzh = $= Ph_2CH$) or its amide **3a** is obtained in some way (usually, by the reaction with thiourea). Amide **3a** is further oxidized to modafinil (**1**) with hydrogen peroxide in acetic acid.[7,8] Sulfoxide **1** can also be obtained from compound **2** following Scheme 1 *via* intermediate formation of benzhydrylsulfinylacetic acid (**4**) and its ethyl ester (**5**).[9,10]

Results and Discussion

We succeeded to develop a new synthetic route to modafinil (**1**) (see Scheme 1, steps *A*—*C*), which is based on the use of sodium carbamoylmethyl thiosulfate (**6a**) (Bunte salt) obtained by the alkylation of sodium thiosulfate with chloroacetamide in an aqueous solution (step *A*).[11] The key step of the synthesis is the desulfo-S-benzhydrylation of salt **6a** (step *B*) by short-term treatment with benzhydrol (**7**) in formic acid at 60 °C resulting in almost quantitative formation of benzhydrylthioacetamide **3a**. In the last step of the process (*C*), compound **3a** is transformed into modafinil (**1**) by oxidation with 33% H_2O_2 in HCOOH at 10 °C. Under these conditions, sulfide **3a** is oxidized rather selectively: no signals of an admixture of the corresponding sulfone are observed in the ^1H NMR and IR spectra of the unpurified reaction product. This favorably distinguishes the reaction we have developed

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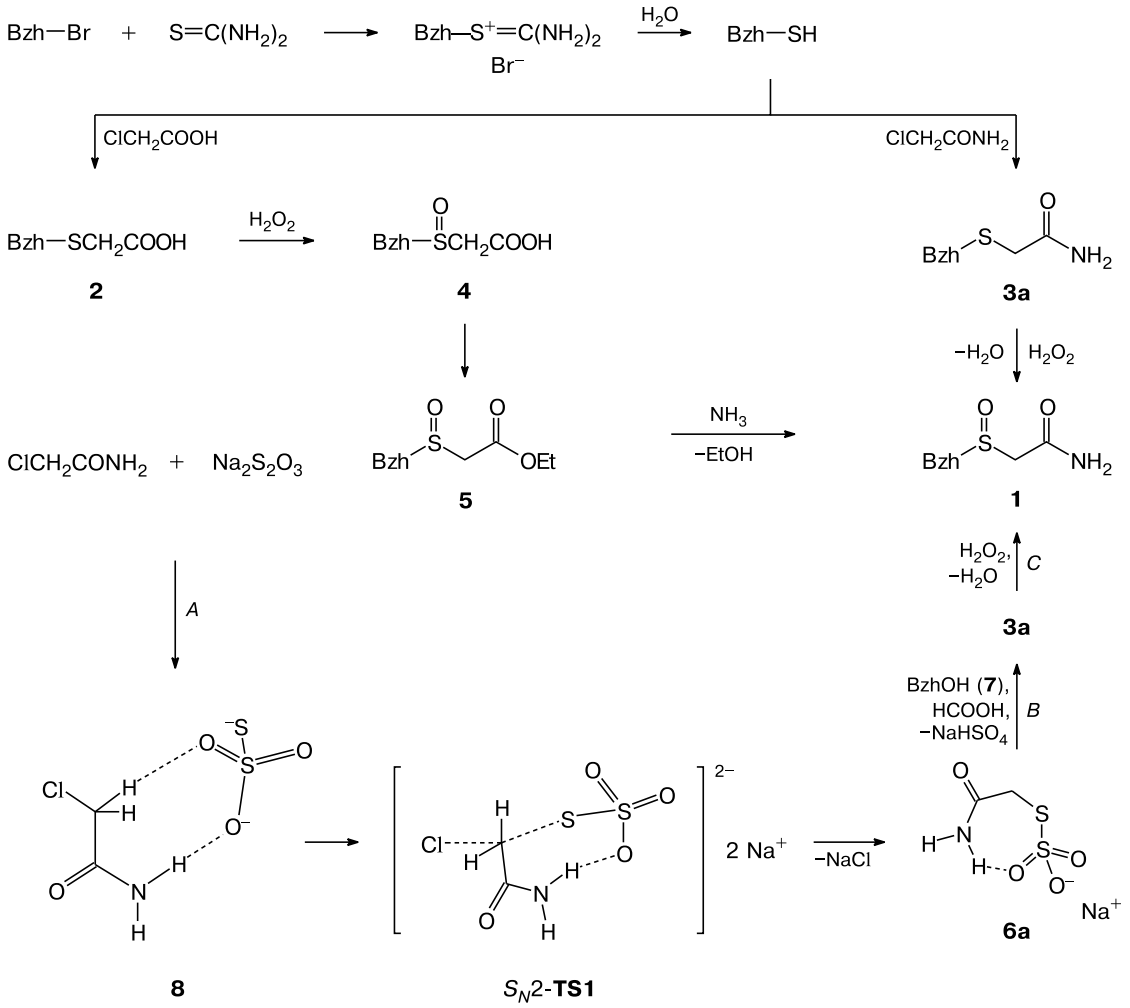
Scheme 1



Bzh = Ph_2CH

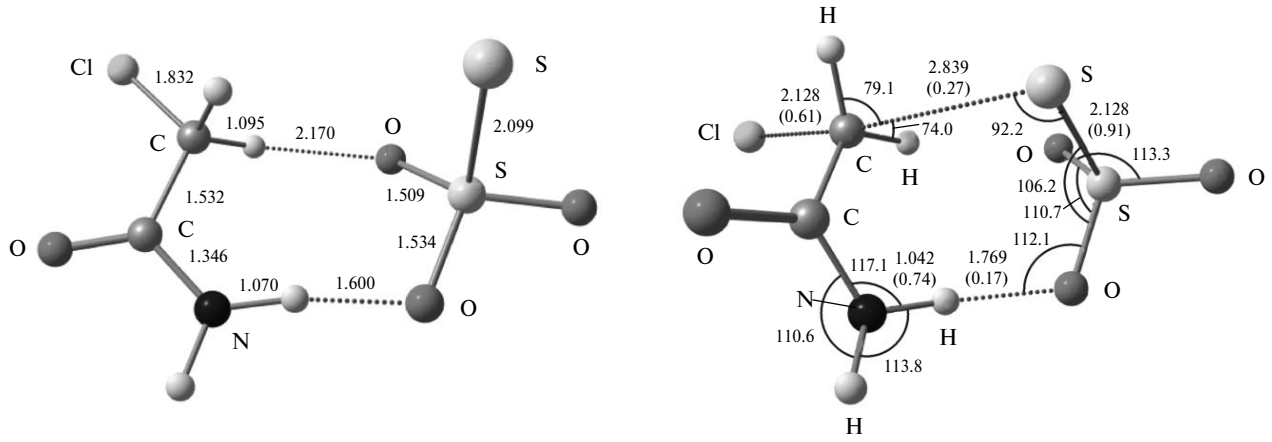
from the analogous oxidation of compound **3a** in acetic acid, which is accompanied by the formation of considerable amounts of sulfone.[8]

Steps *B* and *C* can be combined by performing the process without isolation of amide **3a**. In this case, the single isolated intermediate product is Bunte salt **6a**, and the overall yield of compound **1** after two one-pot steps is 74%.

The carbamoylmethylation of sodium thiosulfate (step *A*), as the alkylation of $Na_2S_2O_3$ with simple primary alkyl halides,[12] is the substitution of the chlorine atom by the highly S-nucleophilic[13] $S_2O_3^{2-}$ anion *via* the S_N2 mechanism (see Scheme 1). Subsequent desulfobenzhydrylation (step *B*) also includes the S-nucleophilic attack where the role of S-nucleophile is played by the O-anion of salt **6a** (**6a**$^-$), which is not characteristic of Bunte salts, while electrophiles are the benzhydrylating agents generated by the BzhOH (**7**)—HCOOH system, namely, benzhydryl formate* (**9a**) and the benzhydrilium cation Bzh^+. The latter is formed upon the heterolytic cleavage of ester **9a** and the O-protonated forms of benzhydrol and dibenzhydryl ester. It is believed that the benzhydrylation of CH-acids,[15,16] nitriles,[17] and thiophenols[18,19] by benzhydrol in formic acid and other acidic media or by benzhydryl acetate in the presence of Lewis acids proceeds similarly involving the Bzh^+ cation. When using Lewis acids, their complexes with the starting reactants play the role of precursors of Bzh^+.[16]

The aforesaid suggests that the Bzh^+ cation also participates in the desulfobenzhydrylation of salt **6a**. In addition, formate **9a** can also directly benzhydrylate the Bunte salt by the S_N2 mechanism. At the same time, the reaction route involving preliminary hydrolytic S-de-

* Secondary alcohols are readily esterified by formic acid in the absence of catalysts (see, *e.g.*, Ref. 14).



8 **TS1**

Fig. 1. Structures of the ion-molecular complex of the reactants (**8**) and the transition state **TS1** of the carbamoylmethylation of the thiosulfate anions with chloroacetamide. Here and in Figs 2—4 shown are selected bond lengths (in Å), bond angles (in deg), and Mulliken bond orders (in parentheses).

sulfonation of salt **6a** resulting in mercaptoacetamide followed by its S-benzhydrylation* is insignificant, because a control experiment showed that compound **6a** is almost not hydrolyzed under the experimental conditions.

In practice, desulfobenzhydrylation of salt **6a** begins with its S-benzhydrylation involving electrophilic attack of anion **6a**$^-$ on the most nucleophilic S^{II} atom.** As a result of the addition to the benzhydryl group, the initially not very strong $CH_2S—SO_3^-$ bond is additionally weakened, which leads to the subsequent fast hydrolytic elimination of the S-sulfo group.

Quantum chemical study of different steps of the synthesis of modafinil. Some of the key steps in Scheme 1 were studied by the B3LYP/6-31G** density functional method. According to calculations, the initial step of the synthesis (carbamoylmethylation of thiosulfate anion by chloroacetamide) involves the formation of the low-lying, relatively early anionic transition state **TS1** (see Scheme, Fig. 1). The S—C—Cl angle characterizing the degree of deviation of the reaction site geometry from trigonal bipyramid is 168.9°. The transition state is formed from a very stable (provided no solvation) ion-molecular complex of the reactants (**8**, $\Delta G^\circ = -36.1$ kcal mol^{-1}, see Fig. 1) stabilized by two hydrogen bonds including the very strong hydrogen bond N—H...O—S 2.662 Å long. The activation energy of the reaction $\Delta^{\neq}G^\circ_{calc}$ relative to this complex in the absence of solvation is very low (5.2 kcal mol^{-1}), indicating very high S-nucleophilicity of the nonsolvated thiosulfate anion.

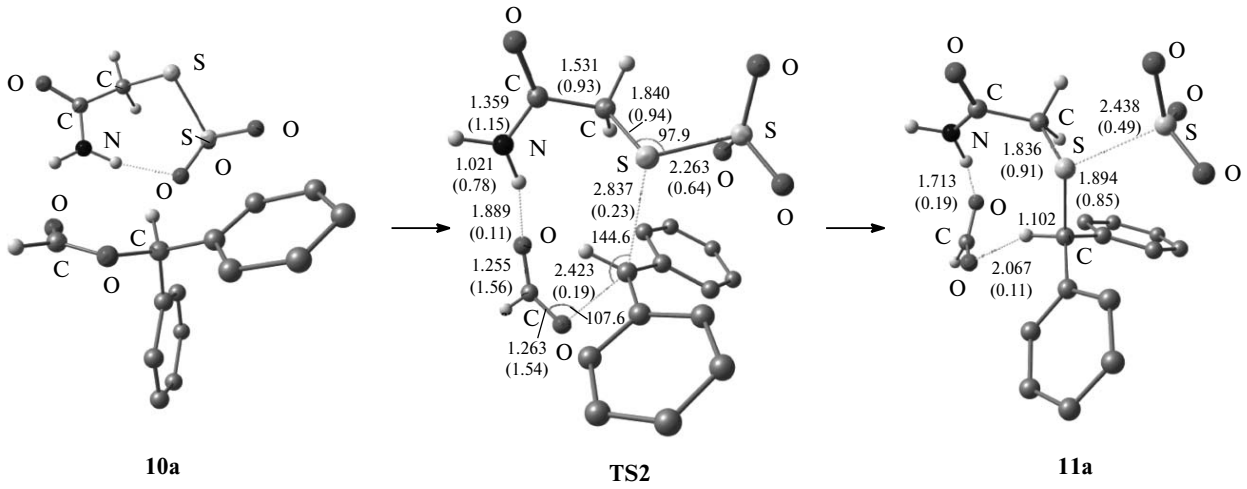
If the second step of the synthesis is the benzhydrylation of the anion of salt **6a** (**6a**$^-$), the reaction may proceed *via* the S_N2 channel through the transition state **TS2** of moderate polarity with $\mu_{calc} = 4.2$ D (Fig. 2). We also studied three comparison reactions, namely, benzhydrylation of methylthiosulfate anion $MeSSO_3^-$ (**6b**$^-$) with formate **9a** and benzylation of anions **6a**$^-$ * and **6b**$^-$ with benzyl formate (**9b**) (Scheme 2, Fig. 2, Table 1). Their transition states **TS3**—**TS5**, respectively, are similar to **TS2**, also being of moderate polarity. Since **TS1**—**TS5** are the transition states of the S_N2-type reactions, their imaginary vibrational modes have the largest amplitudes of antisymmetric vibrations relative to the electrophilic center for those atoms which are nucleophilic centers of the reactions.

The reaction sites of the transition states **TS1**—**TS5** of the reactions proceeding by the S_N2 mechanism are highly distorted trigonal bipyramids whose vertices are occupied by the nucleophilic S^{II} and Cl (O) atoms of the incoming S-nucleophile (thiosulfate or alkyl thiosulfate group) and leaving nucleofuge (Cl^- or $HCOO^-$ anion), respectively; the electrophilic carbon atom of the methylene (methine) group of the electrophile is located at the center. Both key bonds in the transition states **TS1**—**TS5**, S—C and C—Cl (C—O), especially the C—O one, are strongly weakened and characterized by the following Mulliken bond orders: 0.27, 0.61 (**TS1**); 0.23, 0.19 (**TS2**); 0.46, 0.25 (**TS3**); 0.29,

* These are the indirect schemes with the initial step of hydrolysis that are usually used for the desulfo-S-alkylation of Bunte salts.[20—24]

** The S^{II} atom in the Bunte salts is also most basic.[25,26] In spite of a low nucleophilicity of this atom, several Bunte salts containing a carbonyl or thiocarbonyl group near the S_2O_3 fragment undergo intramolecular heterocyclization, probably, due to the nucleophilic attack of these electrophilic groups by the S^{II} atom of the S_2O_3 fragment.[27—29]

* The anion of salt **6a** contains the intramolecular hydrogen bond N—H...OS between the amino group and SO_3 group that closes the seven-membred hydrogen-bonded cycle in this anion (see Scheme 1).



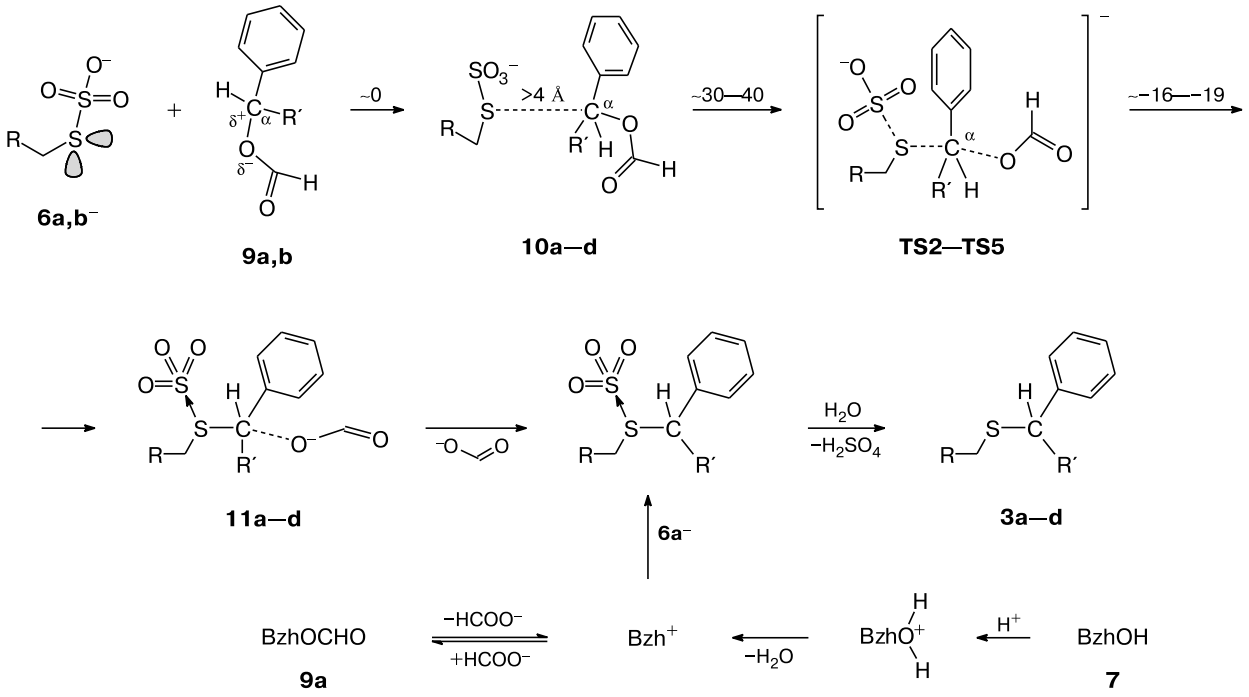
10a **TS2** **11a**

Fig. 2. Pre-reaction complex **10a**, transition state **TS2**, and the post-reaction donor-acceptor complex **11a** in the benzhydrylation of Bunte salt **6a** by the S_N2 mechanism (the H atoms of the phenyl groups are omitted). The ΔG° values relative to the reactants are 1.1 (**10a**), 42.1 (**TS2**), and 23.8 (**11a**) kcal mol^{-1}.

0.19 (**TS4**); and 0.48, 0.25 (**TS5**). Compared to the initial Bunte salts **6a,b**, the S—S bonds in **TS2**—**TS5** are somewhat weaker (the corresponding bond orders are 0.64, 0.58, 0.62, and 0.58; *cf.* 0.71 and 0.66 in salts **6a,b** and 0.91 in the $S_2O_3^{2-}$ anion). The chlorine atom and formate group in **TS1**—**TS5** bear a considerable negative charge.

As for other transition states of S_N2-type reaction with bulky groups near the reaction center,[30a] structural distortion of the reaction sites in **TS2**—**TS5** is first of all due to the influence of the steric factor, thus being maximum for the benzhydryl-containing states **TS2** and **TS4** (here the S^{II}—C_α—O angles deviate from 180° to the greatest

Scheme 2



R = $CONH_2$ (**6a**), H (**6b**); R′ = Ph (**9a**), H (**9b**); R = $CONH_2$, R′ = Ph (**3a**, **10a**, **11a**, **TS2**); R = $CONH_2$, R′ = H (**3b**, **10b**, **11b**, **TS3**); R = H, R′ = Ph (**3c**, **10c**, **11c**, **TS4**); R = R′ = H (**3d**, **10d**, **11d**, **TS5**)

Note. Numbers above arrows indicate the range of changes in the calculated Gibbs free energy ΔG° of gas-phase transformations.

Table 1. Quantum chemical data for the reactions studied by the B3LYP/6-31G** DFT method

Structure	R	R´	$-E^a$	$-G^{\circ b}$	$\Delta^{\neq}G^{\circ}$ (ΔG°)^c /kcal mol^{-1}	μ_{calc} /D	$-\nu_i$ /cm^{-1}
			au				
H_2O	—	—	76.382605	76.380405	—	2.2	—
H_2O_2	—	—	151.475859	151.472861	—	1.8	—
HO_2^-	—	—	150.824969	150.834669	—	2.3	—
$S_2O_3^{2-}$	—	—	1021.9399380	1021.9560846	—	1.5	—
$ClCH_2CONH_2$	—	—	668.8149385	668.782431827	—	1.9	—
8	—	—	1690.8304130	1690.7959668	(−36.1)	22.9	—
3a	$CONH_2$	Ph	1108.330844	1108.121066	—	2.1	—
6a	$CONH_2$	—	1230.37012	1230.329571	—	6.0	—
6b	H	—	1061.729747	1061.713267	—	3.5	—
9a	—	Ph	690.770802	690.597990	—	1.9	—
9b	—	H	459.860726	459.760002	—	2.4	—
10a	$CONH_2$	Ph	1921.158677	1920.925848	(1.1)	11.3	—
10b	$CONH_2$	H	1690.246971	1690.085640	(2.5)	8.7	—
10c	H	Ph	1752.517552	1752.309971	(0.8)	11.8	—
10d	H	H	1521.609719	1521.474146	(−0.5)	6.7	—
11a	$CONH_2$	Ph	1921.122765	1920.889575	(23.8)	5.9	—
11b	$CONH_2$	H	1690.220343	1690.060944	(18.0)	5.1	—
11c	H	Ph	1752.490935	1752.281077	(18.9)	5.2	—
11d	H	H	1521.584718	1521.4479977	(15.9)	5.1	—
13	$CONH_2$	Ph	1259.214427	1258.995940	(−25.2)	5.7	—
14 · H_2O	$CONH_2$	Ph	1259.313733	1259.096607	—	3.5	—
TS1	—	—	1690.8246714	1690.7876180	5.2	—	193
TS2	$CONH_2$	Ph	1921.093531	1920.860534	42.1	—	145
TS3	$CONH_2$	H	1690.192530	1690.030987	36.8	—	344
TS4	H	Ph	1752.461703	1752.254662	35.5	—	159
TS5	H	H	1521.559498	1521.422832	31.6	—	320
TS6	$CONH_2$	Ph	1336.186497	1335.933444	25.7	3.9	289
TS7	$CONH_2$	Ph	1412.596535	1412.321850	20.6	2.9	280
TS8	$CONH_2$	Ph	1449.491791	1449.232875	15.7	1.5	502
TS9	$CONH_2$	Ph	1259.189859	1258.970557	15.9[d]	6.3	230

[a] The energy of the structure without vibrational, thermochemical, and entropy corrections.
[b] The calculated free energy of the structures at 298 K.
[c] The free activation energy of the reaction corresponding to the presented transition state; the ΔG° values of the pre(post)-reaction complexes relative to the starting reactants are given in parentheses.
[d] The activation energy relative to reactant encounter complex **13**.

extent, being 144.6 and 146.1°, respectively). In the benzyl-containing transition states **TS3** and **TS5**, these angles are much larger; 161.6 and 163.5°, respectively. In addition, in the transition states **TS2** and **TS4**, the S—C_α (2.837 and 2.691 Å) and C_α—O (2.423 and 2.439 Å) bonds are significantly longer (*cf.* 2.369, 2.308 Å for **TS3** and 2.188, 2.241 Å for **TS5**).

The transition states of the carbamoylmethylation reactions (**TS2** and **TS3**) are characterized by the direct binding of the incoming and leaving groups through hydrogen bonds between their spatially approached fragments NH_2 and CO. The formation of these bonds 2.882 (**TS2**) and 2.805 Å (**TS3**) long results in closure of the reaction sites of these transition states to form the nine-membered N,S,O,O-macroheterocycles (see, *e.g.*, Fig. 2).

Bimolecular nucleophilic substitution in the systems **6** + **9** begins with the formation of almost ergoneutral pre-reaction ion-molecular complexes **10a—d** with ΔG° = = −0.5—+1.5 kcal mol^{-1} (see Table 1) and is completed by the formation of three-component complexes **11a—d** (see Scheme 2, Table 1 and Fig. 1) consisting of sulfide **3a** or **3b**, trioxide SO_3, and anion $HCOO^-$. The molecular components of the complexes are bound to each other by the relatively weak donor-acceptor bond >S→SO_3, whose order depends only slightly on the nature of the substituents R and R´ and is close to 0.50, while the formate anion is retained by hydrogen bonds. The carbamoylmethyl-containing associates **11a,b** contain two such bonds formed involving the NH_2 and $C_\alpha H$ groups as proton donors and forming the structural fragment N—H...OCHO...HC_α. Other associates contain only the stabilizing OCHO...HC_α bond, whose formation is favored by a considerably high acidity of the C_α—H bond. Thus, in complexes **11**, sulfur trioxide showing no unusual behavior acts as a Lewis acid

as in, *e.g.*, the $C_5H_5N{\rightarrow}SO_3$ complex (reagent for the sulfonation of acidophobic substrates[31]) and in the zwitterionic form of sulfaminic acid $H_3N^+{-}SO_3^-$.[32]

Destabilization of the S—S bond upon complexation, which favors fast desulfonation of complexes **11**, is confirmed by a noticeable decrease in the orders of these bonds on going from the initial Bunte salts **6a,b** (S—S bond orders are 0.71 and 0.66, respectively) to **11**.

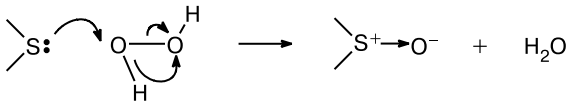
Benzhydrylation of anion $\mathbf{6a}^-$ with formate **9a** by the S_N2 mechanism is energetically unfavorable and characterized by a high activation barrier ($\Delta^{\neq}G^{\circ}_{calc}$ = = 42.1 kcal mol^{-1}). This is, in particular, due to the low nucleophilicity of the S^{II} atom of the alkylthiosulfate anions caused by the influence of the adjacent sulfo group (strong electron acceptor). The nucleophilicity of these anions with the formally neutral sulfur atom is much lower than that of the S-anionic nucleophile $S_2O_3^{2-}$, which is usually used for the synthesis of these anions. In addition, steric shielding of the reaction center by the bulky benzhydryl group plays an important role. The significance of this factor is well seen when comparing this reaction with the other three substitution reactions studied, whose transition states **TS3**—**TS5** are much less sterically hindered and, hence, have substantially lower energies $\Delta^{\neq}G^{\circ}_{calc}$ of 36.8, 35.5, and 31.6 kcal mol^{-1}, respectively.

On going from the gas phase to solutions, the anionic transition state **TS2** of low polarity, corresponding to the second step of the synthesis of modafinil, should retain or even increase its energy, because its solvation is worse than that of the starting reactants (*cf.* published data[30b,33—36] for other anionic transition states of ion-molecular reactions). This is the more valid for polar media in which the starting anion is solvated much more strongly than the considerably larger anionic transition state. Therefore, benzhydrylation of Bunte salt **6a** by the S_N2 mechanism in solutions should be very slow as well. However, since in fact benzhydrylation is rather fast even under mild temperature conditions, it is reasonable to conclude that it mainly proceeds by the S_N1 mechanism with the electrophilic attack of the Bzh^+ carbocation on the anion $\mathbf{6a}^-$. In addition to lesser steric hindrance of the corresponding transition state compared to **TS2**, this reaction route is favored by the relative thermodynamic stability of the Bzh^+ cation (as a consequence, Bzh^+ is formed in considerable concentrations in the reaction system), its high reactivity, and the high polarity of the reaction medium (HCOOH).

Note that the already mentioned benzhydrylation of CH-acid enols and nitriles with benzhydrol,[15—17] which readily proceeds in HCOOH, does not occur in acetic acid. Evidently, this is due to the low acidity of AcOH and high nucleophilicity of the $MeCOO^-$ ion. That is why the Bzh^+ carbocation is almost not generated in this solvent. In particular, this cation is not formed from benzhydryl acetate, because the acetate ion is too poor nucleofuge,[37] being considerably weaker in this respect than the formate group.

The completing step of the synthesis of modafinil (oxidation of sulfide **3a** with hydrogen peroxide in HCOOH) belongs to the processes that are sometimes considered as a specific kind of S_N2 nucleophilic substitution at oxygen (see Ref. 38 and references cited therein). Meanwhile, this strongly contradicts the commonly accepted non-oxidative character of rS_N2-type reactions (Scheme 3).

Scheme 3



However, at present this type of sulfoxidation reactions is usually considered as the O,S-transfer of the oxygen atom from the H_2O_2 molecule to the sulfur atom of sulfide with simultaneous (and considerably more energy-expendable) one-proton O,O-transfer within the H_2O_2 molecule (see, *e.g.*, Ref. 39).

In the absence of catalysts, sulfoxidation with hydrogen peroxide requires extremely high activation energies of about 50—60 kcal mol^{-1}.[40—43] Therefore, this reaction usually occurs in the catalytic regime, being catalyzed by various proton-donor molecules, for instance, water molecules (their catalytic action is due to incorporation into the transition state of the reaction). Since the number of incorporated catalytic molecules is variable, the catalytic oxidation is usually a multichannel process with different reaction channels having substantially different activation energies.

The catalytic action of proton-donor molecules is due to a decrease in the energy of the most energy-consuming step of the elementary reaction act, namely, one-proton O,O-transfer in H_2O_2, which was convincingly demonstrated[39] for the $Me_2S{-}H_2O_2{-}H_2O$ system. The mechanism of catalysis mechanism consists in the change in the proton transfer regime from the direct to the relay proton transfer. In the latter case, the proton migrates indirectly along a cyclic chain of hydrogen bonds[38,39] rather than moves directly from one oxygen atom of H_2O_2 to the other, which is very unfavorable. As a result, the activation barriers to oxidation decrease substantially, as a whole, to quite appropriate levels.

It is believed that the relay proton transfer is the basis of sulfoxidation,[44,45] epoxidation,[46a] Bayer-Villiger oxidation, and Criegee rearrangement,[46b] which proceed involving other proton-donor molecules (perfluoroalkanols, phenol, and alkanoic and perfluoroalkanoic acids) as catalysts. In particular, epoxidation in perfluoroalkanols is accelerated by about 10^5 times compared to the non-catalyzing solvents,[46a] which is provided by the incorporation of one to four catalyst molecules into the transition state of the reaction.

The catalytic mechanism is also characteristic of the sulfoxidation of compound **3a** with hydrogen peroxide, which is also catalyzed by water molecules. The potential energy surfaces (PES) of tri- and tetramolecular reaction systems consisting of molecules **3a** and H_2O_2 and one or two H_2O molecules exhibit points corresponding to relatively low-energy transition states **TS6** and **TS7** of the catalytic oxidation reaction catalyzed by one or two H_2O molecules, respectively (Fig. 3). Along with the direct O,O proton transfer, the catalyzed relay proton transfer occurs in these transition states. The structures of the reaction sites and the stoichiometry of the transition states located are analogous to those of the mono- and dihydrate transition states of the catalytic oxidation of Me_2S with hydrogen peroxide.[39] Even more efficient is the catalyzed oxidation of sulfide **3a** with formic acid, which together with water forms a mixed reaction medium. Transition state **TS8** (see Fig. 3) of this, third catalytic reaction channel is also formed through the relay proton transfer provided by one catalyst molecule HCOOH. It is most likely that acetic acid is also a catalyst of oxidation. As already mentioned, the sulfoxidation of compound **3a** with hydrogen peroxide is also carried out in acetic acid.[7,9]

As follows from analysis of the geometry of the transition states **TS6**—**TS8**, the catalytic oxidation of sulfide **3a** with hydrogen peroxide always begins with the attack of the lone electron pair of the sulfur atom on the adjacent oxygen atom of the H_2O_2 molecule, similarly to the oxidation of other sulfides with this reagent.[40] This attack is likely facilitated by the electrostatic attraction of the in-

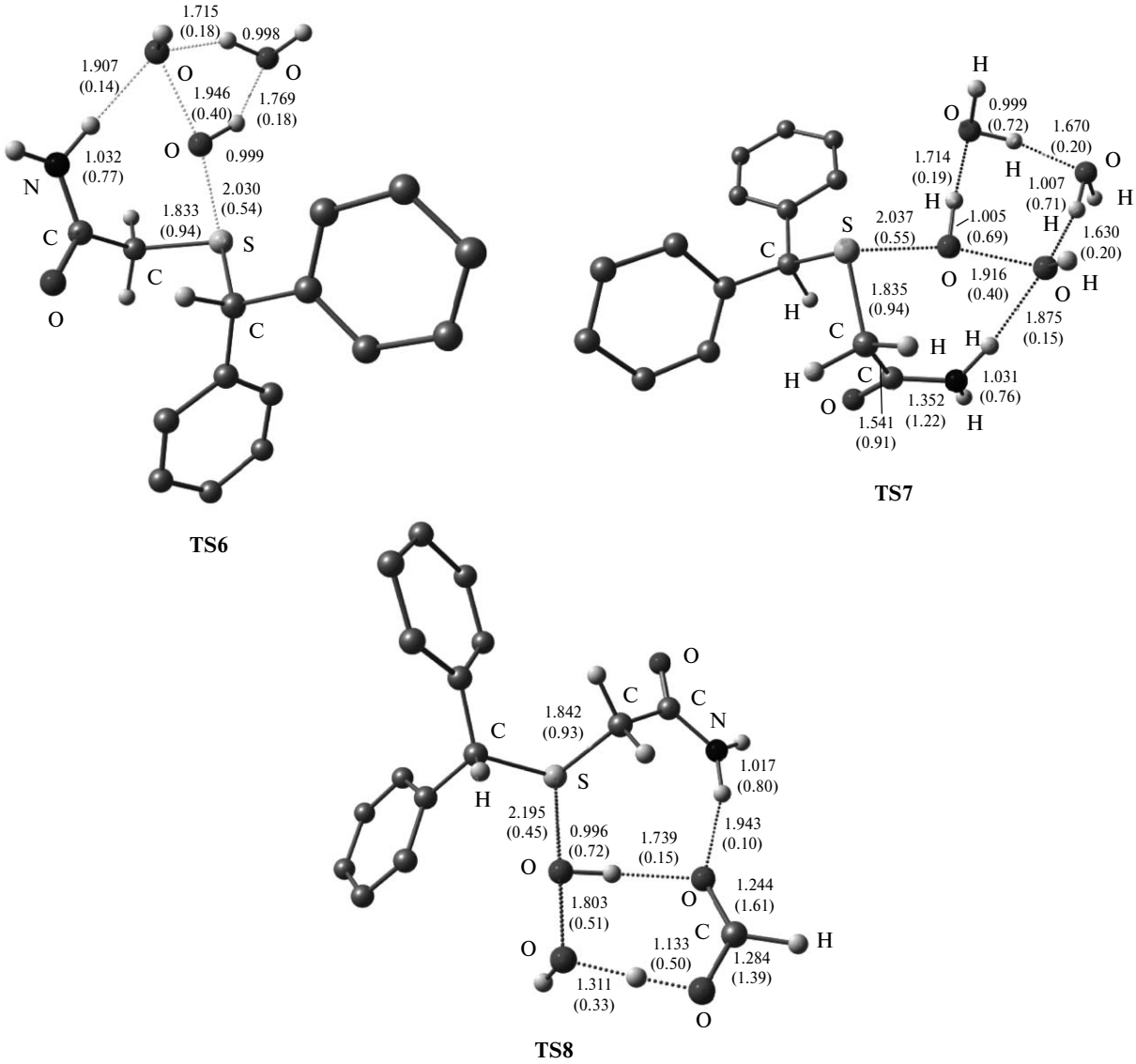


Fig. 3. Transition states of the oxidation of benzhydrylthioamide **3a** with hydrogen peroxide catalyzed by one (**TS6**) or two (**TS7**) H_2O molecules or by the HCOOH molecule (**TS8**).

teracting S and O atoms due to their unlike electric charges (the sulfur atom of sulfide **3a** bears a positive charge of about 0.1 (according to Mulliken)).

All three reaction channels observed are relatively low energy-consuming. The transition states are in the following order with respect to the $\Delta^{\neq}G^{\circ}_{calc}$ values (in kcal mol^{-1}): **TS6** (25.7) > **TS7** (20.6) > **TS8** (15.7). Thus, as for the reaction of hydrogen peroxide with Me_2S,[39] two water molecules catalyze the oxidation of sulfide more efficiently than one H_2O molecule. The relatively low $\Delta^{\neq}G^{298}_{calc}$ values of the three considered reaction channels agree well with the experimentally observed ease of sulfide **3a** oxidation to modafinil (**1**) in HCOOH, which is a rather fast process, even at low temperatures (see above), being additionally an exothermic process.

As the oxidation of other sulfides with hydrogen peroxide, the reaction considered is an autocatalyzed process in which the role of the catalyst is played by a product (water). Therefore, according to the available data,* similar reactions in aprotic media occur with an induction period and a self-acceleration period.

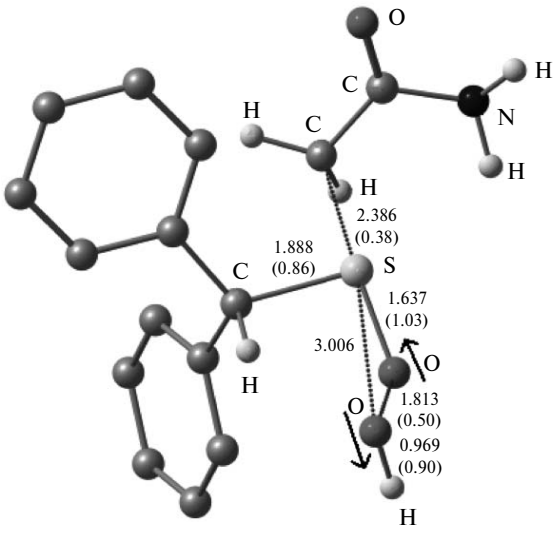
Since formic acid has a considerable acidity, an additional reaction channel involving the H_3O^+ ion as a catalyst[40] can make some contribution to the oxidation of compound **3a** in formic acid. It seems likely that other reaction routes, namely, the oxidation of sulfide **3a** with performic acid and the oxidation initiated by the outer-sphere one-electron oxidation of the substrate with H_2O_2 molecules, are less significant. Particularly, the formation of HCOOOH in the reversible reaction

$$HCOOH + H_2O_2 \rightleftharpoons HCOOOH + H_2O$$

proceeds rather slowly (at 26.5 °C, which is higher than in our experiments) and at considerably higher concentrations of HCOOH (90—100%) the reaction with 30% H_2O_2 ceases only within ~1 h).[47] The outer-sphere electron transfer observed for a series of systems of the amine—diacyl peroxide type[48] is hindered for hydrogen peroxide owing to its relatively low one-electron redox potential.

The energy barrier to sulfoxidation can in principle be reduced noncatalytically, *viz.*, by transition of the reaction to the regime of oxidation with the anionic form of the reactant (HO_2^- ion), which, unlike the oxidation with the neutral form of the reactant, requires no accompanying energy-consuming proton transfer. Evidently, the reaction mechanism can to some extent be adjusted in this fashion on going to strong alkaline media, which favor the ionization of H_2O_2.[49]

The transition state of oxidation of sulfide **3a** with the HO_2^- ion (**TS9**) is shown in Fig. 4. A similar transition



TS9

Fig. 4. Transition state **TS9** of the oxidation of sulfide **3a** with the HO_2^- anion. Arrows show the direction of migration of the oxygen atoms of the HO_2^- anion during the transformation of the transition state into the reaction products: the C anion of modafinil **14** and the water molecule. The O—S—C_α angle formed with the participation of the attacking oxygen atom is 147.3°.

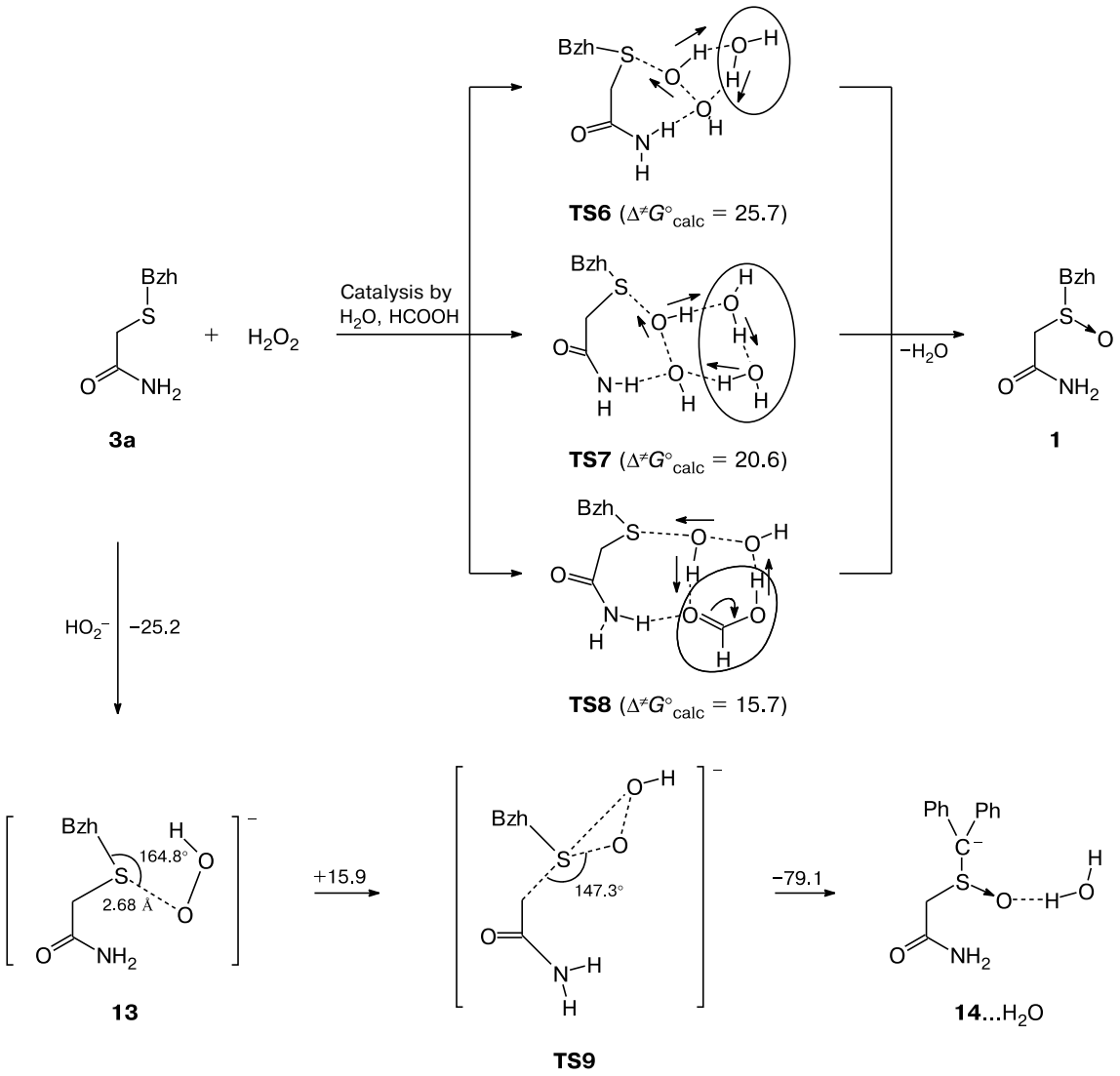
state was found for the oxidation of methyl benzyl sulfide with the hydroperoxide ion (**12**).

The oxidation of sulfides **3a** and **12** with the HO_2^- anion proceeds by rather unusual mechanism. When the transition state is formed, especially in the case of compound **3a** (Scheme 4), the reaction strongly resembles the S_N2 nucleophilic substitution. The nucleophile and electrophile are the HO_2^- ion and the sulfide molecule, respectively (sulfides are considered as nucleophiles in the "S_N2-like" oxidation of sulfide with the neutral form of the reactant (see Scheme 3)).

We studied in more detail the reaction of compound **3a** with the HO_2^- ion, which is initiated by the formation of strongly exoergic pre-reaction ion-molecular complex **13** with the stabilization energy $\Delta G^{\circ}_{calc} = -25.2$ kcal mol^{-1}. During the subsequent transformation of this complex into transition state **TS9**, the HO_2^- ion with strong nucleophilic properties due to the α-effect of two adjacent lone electron pairs,[33] attacks the positively charged sulfur atom of the substrate and the S—CH_2 bond. As in conventional S_N2-substitution, this bond is attacked from the back. More exactly, the small lobe of the sp^3-hybrid AO of the S atom involved in the formation of this bond is attacked. Bringing together of the reaction centers, S and O atoms, results in the formation of the S—O bond, which becomes stronger, and the S—CH_2 bond is substantially weakened in the transition state (bond order 0.38, bond length 2.386 Å; the corresponding parameters of the formed S—OOH bond are 1.03 and 1.637 Å).

* Indeed, it was experimentally established that thioxane oxidation with H_2O_2 in anhydrous dioxane or *N*-methylacetamide occurs with self-acceleration or is accelerated upon the addition of water.[38]

Scheme 4



Note. Arrows indicate the direction of migration of the O and H atoms during the process; ellipses separate the atoms of the H_2O and HCOOH molecules acting as catalysts from the H_2O_2 molecule; numbers on arrows show the change in the free energy on going from one structure to another.

Thus, up to the formation of **TS9** the oxidation proceeds in such a way as if it is the S_N2 reaction with the HO_2^- and $CH_2CONH_2^-$ anions as the incoming and leaving groups, respectively. However, after having passed the transition state, the character of the reaction abruptly changes from substitutive to a more favorable oxidative one. As a result, the CH_2CONH_2 group, which was going to detach, is retained and the OH^- anion bound by the weak SO—OH bond (bond order 0.50) is eliminated from the SOOH fragment instead. The formation of sulfoxide **1** thus started also does not complete, because the OH^- ion ceases deprotonation of the $C_\alpha H$ group of modafinil. As a result, the C-anion (**14**) is formed in the elementary reaction act instead of molecule **1**. Evidently, the deprotonation of modafinil is favored by its relatively high CH-acidity, high nucleophilicity of the unsolvated OH^- ion, and a long distance from the undoubtedly more "acidic" N—H bond. The S—CH_2 bond, which is strongly weakened in the transition state, becomes stronger and returns to its normal state simultaneously with the deprotonation.

Since the oxidation of amide **3a** with the HO_2^- ion requires no accompanying energy-consuming proton transfer in the reactant, it proceeds rather easily. The transition state **TS9** of the gas-phase reaction is barrierless relative to the reactants, whereas there is a rather high energy barrier ($\Delta^{\neq}G^{\circ}_{calc}$ = 15.9 kcal mol^{-1}) relative to pre-

reaction ion-molecular complex **13**. In the liquid phase the energy characteristics of sulfide oxidation with this ion can evidently change over a wide range due to the strong solvation of the ions participating in the reaction, first of all, the HO_2^- ion.

Thus, the results of our study suggest that the synthetic potential of Bunte salts as nucleophiles, first of all, with respect to highly reactive electrophiles that react *via* the S_N1 mechanism, was underestimated and that the relay proton transfer plays a unique catalytic role in various organic reactions including those that at first glance seem to be rather far from typical prototropic transformations.

Experimental

NMR spectra were recorded on a Varian XL-300 instrument with an operating frequency of 300 MHz in $CDCl_3$. IR spectra were measured on a Varian Excalibur 3100 FT-IR spectrometer in the solid phase. Calculations of the geometries and free Gibbs energies of molecules, ions, and transition states and the IRC calculations were performed using the PC Gamess/Firefly program for quantum chemical calculations.[50] The energy characteristics are given with a correction to the vibrational energy using a scaling factor of 0.961.[51] The gas-phase standard Gibbs free energies $G°$ for $T = 298.15$ K and $p = 1$ atm (10^5 Pa) were calculated in the ideal gas approximation assuming harmonic character of atomic vibrations and the absence (for the systems considered) of thermally accessible electron-excited states by the standard equation

$$G° = E + G_{corr},$$

where E is the quantum chemically calculated energy of the molecule at $T = 0$ K ignoring the zero-point vibrational energy correction, and G_{corr} is the thermal correction for normal conditions and representing the sum of the translational, vibrational, and rotational contributions. The G_{corr} value was calculated by the equation

$$G_{corr} = H_{corr} - TS_{corr}.$$

The necessary thermal corrections to the enthalpy and entropy (H_{corr} and S_{corr}) applied to macroscopic molecular ensembles were calculated by the statistical mechanics methods starting from the properties of individual molecules.[52]

Sodium carbamoylmethyl sulfate (6a). A mixture of $Na_2S_2O_3 \cdot 5H_2O$ (500 g, 2.01 mol) and chloroacetamide (200 g, 2.14 mol) in water (500 mL) was heated with stirring at 60—70 °C until the amide was dissolved completely. The heating was stopped and the reaction mixture was allowed to cool gradually to room temperature. Then the mixture was cooled to 10 °C, and salt **6a** was filtered off, washed with methanol, and dried at 70—80 °C. The yield was 278 g (72%). The compound has no distinct m.p. and decomposes gradually at temperatures above 200 °C (*cf.* Ref. 11: m.p. 180—203 °C). The yield of the salt can considerably be increased by vacuum evaporation of the mother liquor, this gives a mixture of **6a** with NaCl.[53] ^{1}H NMR, δ: 3.90 (s, 2 H, CH_2); 7.24, 7.36 (both br.s, 1 H each, NH). Found (%): C, 14.65; H, 2.83; N, 8.55. $C_2H_4NNaO_4S$. Calculated (%): C, 14.91; H, 2.50; N, 8.69.

2-Benzhydrylacetamide (3a). A mixture of benzhydrol **7** (18.4 g, 0.1 mol), salt **6a** (28 g, 0.15 mol), 80% HCOOH (100 mL), and water (25 mL) was heated with stirring at 60 °C until complete homogenization (~20 min). Then the mixture was cooled to room temperature and treated with water (100 mL). The precipitate of thioacetamide **3a** was filtered off and dried at room temperature. The yield was 24.0 g (92%, based on BzhOH), m.p. 109—110 °C (see Ref. 9). ^{1}H NMR, δ: 3.09 (s, 2 H, CH_2); 5.18 (s, 1 H, CH); 5.76, 6.52 (both br.s, 1 H each, NH); 7.21—7.29 (m, 2 H, *p*-H_{Ar}); 7.29—7.37 (m, 4 H, *m*-H_{Ar}); 7.38—7.43 (m, 4 H, *o*-H_{Ar}). Found (%): C, 70.32; H, 5.77; N, 5.49. $C_{15}H_{15}NOS$. Calculated (%): C, 70.01; H, 5.87; N, 5.44.

2-Benzhydrylsulfinylacetamide (1). ***A.*** A solution of thioacetamide **3a** (5.1 g, 0.02 mol) in 80% HCOOH (20 mL) and water (5 mL) was treated with vigorous stirring and cooling for 1 h with 33% H_2O_2 (2.5 mL), adding it by 0.5-mL portions and controlling the temperature of the reaction mixture to be at most than 10 °C. Then water (40 mL) was added, and compound **1** was filtered off, washed with water, and dried at room temperature. The yield was 5.1 g (93%), m.p. 164—165 °C (Pr^iOH—DMF).[9] ^{1}H NMR, δ: 3.18, 3.30 (both d, 1 H each, CH_2, $J_{gem} = 11.9$ Hz); 5.32 (s, 1 H, CH); 7.17 (s, 1 H, NH_2); 7.21—7.57 (m, 11 H, 2 Ph + 1 H of NH_2 group). IR, ν/cm^{-1}: 3310, 3163 (NH_2); 1683 s (C=O); 1030 vs (>S=O) (the spectrum exhibits no absorption bands of the SO_2 group at 1120 and 1309 cm^{-1} characteristic of the spectrum of $BzhSO_2CH_2CONH_2$ in which these bands are strong). Found (%): C, 65.99; H, 5.78; N, 5.34. $C_{15}H_{15}NO_2S$. Calculated (%): C, 65.91; H, 5.53; N, 5.12.

B. A suspension of BzhOH (18.4 g, 0.1 mol) and thiosulfate **6a** (28.0 g, 0.15 mol) in 80% formic acid (100 mL) and water (25 mL) was heated with stirring at 70—80 °C to complete homogenization (~15—20 min). Then the reaction mixture was cooled to 5 °C, and H_2O_2 (11 mL, $d = 1.135$) was added with stirring in such a manner that the temperature of the reaction mixture would be at most 10 °C. After the exothermic reaction ceased, the mixture was diluted with water (200 mL), and coarsely crystalline sulfoxide **1** was filtered off and dried. The yield was 20.2 g (74% based on BzhOH), m.p. 166—167 °C (EtOH).[9] The samples obtained by procedures *A* and *B* show no depression of melting point of the mixed probes.

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