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# Reaction Mechanism of Oxidation, Hydroxylation, and Epoxidation by Hypofluorous Acid: A Theoretical Study of Unusual H-Bond-Assisted Catalysis

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The oxidation of organic molecules by hypofluorous acid (HOF) was studied extensively and systematically by Rozen et al. Therefore, it seems appropriate to refer to the process as Rozen oxidation. An entire set of model molecules was selected for quantum chemical investigation of the oxidation mechanism: a C═C double bond in ethylene, sulfur and selenium in dimethyl derivatives, nitrogen and phosphorus in trimethyl derivatives, as well as methyl azides. In the gas phase, van der Waals complexes between HOF and the previously mentioned species easily are formed, but these complexes are reluctant to undergo oxidation. The addition of another HOF molecule connected with the formation of a cyclic complex (i.e., substrate and two molecules of HOF) seems to be decisive for the oxidation process. The attempt to substitute the second HOF molecule with $H_2O$ demonstrated the superiority of HOF. Complexes of this kind decompose along the reaction path smoothly (i.e., with a low activation energy) to the respective oxidation product. A potential role of the hydroxyl cation ($HO^+$) in the oxidation step is mentioned. Besides an oxidation product, one HOF molecule is released (an essential feature of catalysis), and furthermore, hydrogen fluoride is formed. It was suggested by Sertchook et al. (*J. Phys. Chem. A* **2006**, *110*, 8275) that the interaction between the substrate to be oxidized and HOF is catalytically influenced by the HF molecule. The mechanism suggested here is more feasible and, particularly at the early stages of the oxidation process, decisive. Also, the role of acetonitrile, used as a solvent by Rozen et al., is discussed in terms of a continuum model. Moreover, passing from potential energies to Gibbs energies is considered.

## Introduction

The account of hypofluorous acid, HOF, began in the 1930s and for years has been linked to various uncertainties. The history of that effort, associated with attempts to form and isolate HOF, was described by Appelman.[1a] Studier and Appelman isolated[1b] HOF as a white solid melting at −117 °C. Its structural features were obtained from its rotational spectrum.[1c] Further physical characteristics and an outline of HOF reactivity also were explored (cf. ref 1d,e). The photochemistry of HOF was investigated thoroughly in different environments represented by solid matrices.[2] Photochemical transformations of HOF in, for example, $N_2$, CO, and $CH_4$ matrices yielded $N_2O$, $CO_2$, and $CH_3OH$ (besides $CH_3$ and $CH_3\cdots HF$), respectively.

Another important and extensive wave of interest in the oxidation power of HOF was initiated by Rozen et al. in the mid-1970s[3a] and has resulted in dozens of papers and reviews.[3b−d] In particular, three breakthroughs in Rozen et al.'s papers should be mentioned: (1) convincing evidence that it is not dangerous to use elemental fluorine under appropriate conditions; (2) remarkable stabilization of HOF in an acetonitrile solution, which has turned out to be the most valuable tool for preparative purposes; and (3) smooth, rapid, and high-yielding preparation of well-defined oxidation products of representatives of all the main classes of organic compounds under mild conditions.[4] Specifically, the $CH_3CN{\cdot}HOF$ complex oxidizes readily, for example, secondary alcohols to ketones,[4a] various kinds of amino compounds to nitro compounds[4b,c] (including electron-deficient anilines[5] and amino acids[4d]), hydroxylate tertiary C-H groups,[4e] and epoxidate olefines,[4f] including the tetra-substituted and fluorinated[4h] olefines. The number of reactions that can be handled easily by hypofluorous acid continues to increase, but the reaction mechanism is still not fully understood. For its investigation, mainly the isotopic labeling of $H^{18}OF$ was used.[4a,6] According to these references, the transferred O atom comes from HOF in different ways. One such way is the transformation of methyl ethers to ketones by the nonclassical three-center/two-electron carbonium ion mechanism[4a] or the transformation of alcohols to ketones or esters by means of the dioxirane mechanism.[6] On the basis of ref 7, high dissociation energies of the HOF molecule to O ($^3P$ and $^1D$) + HF (61.6 and 16.2 kcal/mol) or F + OH (51.0 kcal/mol) are expected to exclude these ways of oxygen transfer in Rozen oxidations.

Spectroscopic investigation of the $CH_3CN{\cdot}HOF$ complex confirmed its existence.[8] The same is true for the low-temperature X-ray structure analysis of the complex; a complex with HF, $HF{\cdot}CH_3CN$, also was studied, and its structure was established. It should be noted that in the absence of the stabilization effect of $CH_3CN$, HOF decays to HF and $(1/2)O_2$ ($\Delta H = -16$ kcal/mol).[1a]

*Ab initio* quantum chemistry treatments of the HOF dimer were performed, as a result of which two stable cyclic structures with six and five atoms in the cycle of comparable energy were localized.[9a] The bonding in hypohalous acids was studied on

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the basis of a topological analysis of the electron localization functions,[9b] and the difference between $HO^+F^-$ and $HO^-X^+$ (X = Cl, Br, or I) was interpreted. It is worth mentioning that $OH^+$ assumes in a set of 19 oxygen-containing species the highest (calculated) electron affinity, namely, 12.4 eV.[10] This means that $OH^+$ is an extremely powerful oxidation agent. This special position of HOF already had been discussed years before HOF was prepared and studied.[11] The coupled cluster method with the inclusion of relativistic corrections was used for the study of the thermochemical and spectroscopic properties of HOF.[7] Moreover, it was shown that the isomerization of HOF into fluorosyl hydride, HFO, via a cyclic activated complex, was highly improbable.[12a] The same systems and, moreover, radical cations thereof were studied a few years earlier.[12b]

Until 2006, there had been only limited experimental attempts and no theoretical studies concerning the oxidation mechanism of HOF for organic molecules. The reaction course of the epoxidation of ethylene by HOF was studied using the classical methods of quantum chemistry and particularly variously parametrized density functional theory procedures.[13a,b]

This work remedies the lack of attention and is organized as follows: the Computational Details describes the computational techniques employed in this study. In the first part of the Results and Discussion, we deal with the energetics of different van der Waals (vdW) complexes including the HOF molecule and some other species. In the second part, the universal aspects of the proposed mechanism are discussed. The next four parts concern the mechanism of oxygen transfer onto various centers: the C═C bond, S in sulfides, and N in amines and azides. The results of the proposed mechanism are summarized in the Conclusion.

## Computational Details

All stationary points on the potential energy surfaces were optimized at the B3LYP/aug-cc-pVDZ level. The DFT/B3LYP approximation was selected on the basis of general experience that the GGA (generalized gradient approximation) functionals tend to underestimate barrier heights of chemical reactions, whereas the amount of the Hartree−Fock exchange to hybrid functionals contributes to their overestimation.[14] Therefore, a partial cancellation of errors can be expected in this case.

As the density functionals fail to describe the vdW complexes held by dispersive forces (D), we also tested the effect of these forces on formation energies and barrier heights using the empirical DFT(B3LYP)+D[15] approach implemented within Turbomole 5.8.[16] It is noteworthy that the DFT+D approach has been parametrized for a large set of vdW molecules to reproduce interaction energies, which were calculated at the CCSD(T)/CBS level.[15] This analysis confirms that the structure of the complexes being studied is mostly stabilized by electrostatics.

We chose the aug-cc-pVDZ basis set, which seems to be appropriate for the studied systems. For example, passing from the aug-cc-pVDZ to the aug-cc-pVTZ basis set is related to a change of 0.15 kcal/mol in the case of reaction 1. Further corroboration of our choice can be found in ref 17.

The transition states were localized using eigenvalue following (EF) or synchronous transit-guided Newton−Raphson (QST2 and QST3) procedures as implemented in the Gaussian 03 program package.[18] Furthermore, Fukui's intrinsic reaction coordinate (IRC) calculations were carried out to examine as to whether the optimized transition states connect the expected reactants and products. Alternatively, we used relaxed scans along the reaction coordinate. With regard to estimating the reaction Gibbs energies, $\Delta G$, the rotational−vibrational enthalpic and entropic contributions were obtained from frequency analyses of vibrational modes of reactants, transition states, and products (ideal-gas approximation). Therefore, $\Delta G$ is equal to the sum of these three terms: $\Delta E + \Delta H_{\mathrm{nonel}} - T\Delta S_{\mathrm{nonel}}$, where $\Delta E$ is the difference between the electronic energies, $\Delta H_{\mathrm{nonel}}$ is the nonelectronic enthalpic contribution, and $T\Delta S_{\mathrm{nonel}}$ is the entropic contribution. An alternative equation can be expressed in terms of partition functions $q$ (rot is rotational, vib is vibrational, and tr is translational): $\Delta E + \Delta\mathrm{ZPVE} - RT\ln(q_{\mathrm{rot}}q_{\mathrm{vib}}q_{\mathrm{tr}})$, where ZPVE stands for zero-point vibrational energy.

**SCHEME 1: Thermodynamic Cycle Used for Calculation of Gibbs (Formation or Activation) Energy, $\Delta G$, Corresponding to Oxygen Transfer from HOF to Substrate in Acetonitrile-like Bath ($\epsilon_r = 36.65$)[a]**

$$\begin{tikzcd}
R(g) \arrow[r, "\Delta E + \Delta\mu"] \arrow[d, swap, "\Delta G_{\mathrm{solv}}"] & P(g) \arrow[d, "\Delta G'_{\mathrm{solv}}"] \\
R(l,\varepsilon) \arrow[r, swap, "\Delta G"] & P(l,\varepsilon)
\end{tikzcd}$$

[a] Difference between electronic energies ($\Delta E$) along with enthalpic and entropic corrections included in the term $\Delta\mu$ ($\Delta\mu = \Delta E + \Delta\mathrm{ZPVE} - RT\ln(q_{\mathrm{rot}}q_{\mathrm{vib}}q_{\mathrm{tr}})$) determines the gas-phase Gibbs energy of oxidation. Solvation free energies $\Delta G_{\mathrm{solv}}$ are taken into account by implicit-solvent approach COSMO. R and P represent reactant and product, respectively.

To include the effect of acetonitrile-like solvent ($\epsilon = 36.65$) on $\Delta G$, we reoptimized the gas-phase structures using the self-consistent reaction field method with the polarized continuum model[19] and took advantage of the thermodynamic cycle as described in Scheme 1.

All intermolecular interaction energies were corrected for the basis set superposition error using counterpoise corrections.[20] All energies include ZPVE. Atom charges and charge transfers were obtained from a natural bond orbital (NBO) analysis[21] employing the B3LYP/aug-cc-pVDZ approach.

## Results and Discussion

**Energetics of Complexes with HOF.** As will be shown, the action of the HOF molecule on a substrate was preceded by the formation of intermolecular complexes (e.g., HF···HOF and HOF···HOF). From this point of view, it seems expedient to compare the interaction energies, $\Delta E_{\mathrm{int}}$, of several different complexes formed by the molecules that are abundantly present in the solution (e.g., HF, $H_2O$, $CH_3CN$, and HOF). The values of $\Delta E_{\mathrm{int}}$ of the complexes calculated in the gas phase and in the implicit acetonitrile-like solvent that are likely to be most relevant are presented in Table 1. The respective optimized structures are depicted in Figure 1. After comparing the values obtained at the DFT+D and DFT levels, the conclusion was drawn that the dispersion term is not the dominant factor that would stabilize the complexes. It is plausible to assume that permanent multipole interactions are mostly dominant and that the simple DFT approach provides satisfactory results.

Trimers have higher stability energies than dimers for the number of building units. The most stable complex is the one with the HOF···HF···HOH ring (structures C and C′ in Figure 1), whereas the cyclic HOF···HOF dimer (structures F and F′ in Figure 1) has the lowest stabilization energy. However, the difference between stabilization energies of these structures is significantly lower when the estimate of nonelectronic terms of the enthalpic and entropic contributions (and, therefore,

**TABLE 1: Formation (Stabilization) Energies per Number of Building Units ($\Delta E_{int}/n$), Formation Gibbs Energies ($\Delta\Delta G_{int}/n$) Relative to $\Delta G_{int}/2$ of Referent $CH_3CN\cdots HOF$ Complex, and Relative Change in Interaction Entropy Term ($T\Delta\Delta S_{int}/n$) Related to Same Referent System Collected for Several Complexes[a]**

| | $\Delta E_{int}/n$ (kcal/mol) | | $\Delta\Delta G_{int}/n$ (kcal/mol) | $T\Delta\Delta S_{int}/n$ (kcal/mol) |
|---|---|---|---|---|
| structure | DFT+D | DFT | DFT | DFT |
| A | −3.44 | −3.45 | 1.40 | 2.55 |
| A′ | −2.74 | −2.64 | 2.69 | |
| B | −3.95 | −3.96 | 0.68 | 2.58 |
| B′ | −3.24 | −3.64 | 1.71 | |
| C | −4.64 | −4.66 | −0.33 | 2.84 |
| C′ | −4.94 | −4.92 | 0.31 | |
| D | −3.79 | −3.39 | −0.61 | 3.20 |
| D′ | −2.23 | −1.70 | 2.60 | |
| E | −1.28 | −1.29 | 1.11 | 5.00 |
| E′ | −0.85 | −0.83 | 1.16 | |
| F | −0.97 | −0.96 | 2.65 | 3.81 |
| F′ | 0.15 | 0.19 | 3.49 | |

[a] Corresponding geometries of systems are depicted in Figure 1. Gas-phase values (A, B,...) and values in solutions (A′, B′,...) are presented, calculated at the B3LYP(+D)/aug-cc-pVDZ level.

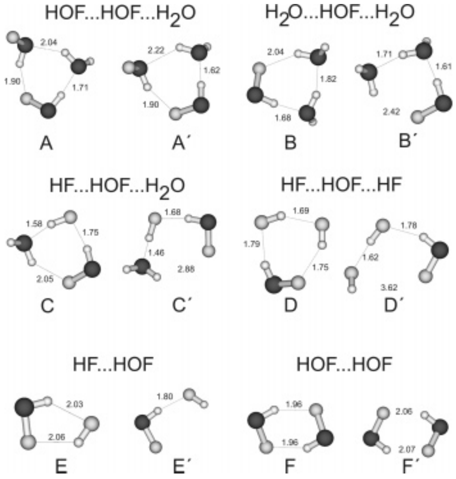


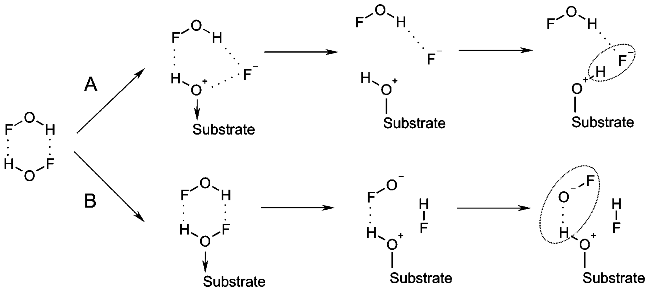
**Figure 1.** Structures of vdW complexes involving HOF molecules. The intermolecular distances are measured in Ångstroms. The assigned capital letters without or with primes correspond to the geometries calculated in the gas phase or in implicitly acetonitrile-like solvent. Large dark balls represent O atoms. Large and small gray balls represent F and H atoms, respectively. The calculations were carried out employing the B3LYP(+D)/aug-cc-pVDZ approach.

$\Delta G_{nonel}$) to differences of the total Gibbs energies, $\Delta G_{int}$, is taken into account. These contributions are more significant for trimers than for dimers, apparently due to the entropic effects. As a result, $\Delta G_{int}$ indicates that the formation of vdW complexes costs a comparable amount of energy with respect to the free molecules.

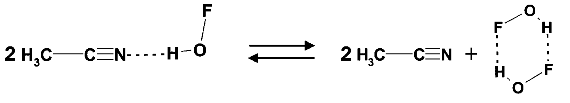
The H-bonded $FOH\cdots NC{-}CH_3$ complex is surprisingly stable ($\Delta E_f = -6.56$ kcal/mol in the gas phase and $-7.70$ kcal/mol in COSMO; $\Delta G_{int} = 2.22$ kcal/mol in the gas phase and 5.64 kcal/mol in COSMO) as compared to the other vdW molecules shown in Table 1 (see also the significance of $\Delta\Delta G_{int}$), which can explain as to why the role of acetonitrile as an inert solvent necessary for the preparation of a stable acting agent is so important.

In a reaction mixture, the dynamic equilibrium of $FOH\cdots NC{-}CH_3$ with the other previously mentioned systems as well as with the $FOH\cdots$substrate and the $FOH\cdots FOH\cdots$substrate complexes was expected because of the rather small differences between their formation energies. For example, note that the energy of reaction 1 is equal to 11.7 kcal/mol at the B3LYP/aug-cc-pVDZ level and 11.9 kcal/mol at the B3LYP+D/aug-cc-pVDZ level.

**SCHEME 2: Discussed Reaction Pathways of Epoxidation, Oxidation, and Hydroxylation[a]**



[a] A branch represents the proposed mechanism of oxygen transfer, the B branch being an alternative but significantly less likely process.



(1)

**General Scheme of Catalysis.** Before discussing particular reaction models, a reaction mechanism will be proposed that seems to be shared by each of the following cases. In the previously mentioned study focused on ethylene epoxidation,[13] the authors demonstrated the autocatalytic properties of HF forming with HOF a cyclic three-molecular $HF\cdots HF\cdots HOF$ or two-molecular $HF\cdots HOF$ system in a transition state. On the basis of the B97-1/aug-pc2 calculations, they suggested that the gas-phase Gibbs activation barriers $\Delta G^{\ddagger}$ amount roughly to 10.5 and 15.6 kcal/mol at 298 K, respectively. We, however, investigated the catalytic role of the reactant, HOF, forming a cyclic or linear two-molecular $HOF\cdots HOF$ system. On the basis of our models, we attempted to stress the general aspect of this unusual H-bond-assisted oxidation (hydroxylation).

In Scheme 2, two proposed mechanisms of oxygen transfer onto the substrate are displayed. In both, it is assumed that the approach of the second HOF molecule to the $substrate\cdots HOF$ complex causes a reorientation of all the molecules involved in the system, thus giving rise to a hydrogen-bond-assisted transition state (TS). In this state, the long distance between the fluorine and the oxygen atoms of the attacking HOF molecule (1.48−1.73 Å) along with its distribution of NBO partial charges (in the free HOF molecule, F: −0.15 |e| and O: −0.32 |e| and in the TS, F: −0.17 to −0.53 |e| and O: −0.33 to −0.43 |e|) suggest the role of electrophilic $HO^{\delta+}$ as an acting agent, as previously stated.[9b] According to the A path in Scheme 2, the leaving fluoride anion is suggested to be simultaneously stabilized by an H-bond with the second HOF molecule. Consequently, a key role in catalysis is believed to be played by a charge transfer from the electron lone pair (or $\pi$ orbital) of the substrate to the $\sigma^*$(O-F) orbital, resulting in heterolytic cleavage of the fluoride anion, which is stabilized by assisting HOF. However, there is no apparent electron redistribution leading to the release of the F-H molecule from the $HO{-}F\cdots H{-}OF$ complex, as outlined by the B path in Scheme 2. Therefore, it can be concluded that the proposed reaction mechanism proceeds in two steps, the first of which involves the transfer of $HO^+$ onto the substrate and the deprotonation of the HO group by the $F^-$ anion, whereas the second, HOF molecule does not participate directly in the bond breaking/forming. In the context of the putative self-catalytic property of the HOF molecule forming (non)cyclic vdW dimer, it is noteworthy to mention the very elegant mechanism of the $Br_2$ + $Cl_2$ → 2BrCl reaction, which does not occur in the bimolecular process, but another $Cl_2$ molecule is needed to form a six-centered benzene-like vdW structure and to enable the concerted transformation of the three pairs of bonds with a very low activation barrier.[22]

Considering the putative role of the $\sigma$*(O-H) orbital and entropy, which is supposed to hinder the three-molecular complexes against two-molecular ones, it is assumed that our proposed system can be more effective than those dealt with in ref 13a. However, we are aware of the probable competition between catalysis by reactant and autocatalysis. The following sections deal with different reaction models demonstrating the universality of the proposed reaction mechanism in further detail.

**Epoxidation of Ethylene.** The powerful reactivity of hypofluorous acid will first be illustrated on the epoxidation of ethylene. As to the reaction rates, the experimental evidence suggests that the mechanism has to enable the system to pass through a rather low-energy transition state. However, the calculated activation barrier for the simple model gas-phase system HOF···$C_2H_4$ seems to be too high for the reaction course to be rapid ($\Delta E^\ddagger \approx 14-29$ kcal/mol depending on the density functional used[13a]). As was mentioned in the preceding section, Sertchook et al.[13a] demonstrated that the height of activation barriers is significantly reduced with the assistance of other molecules. They revealed the significance of the HF or $CH_3CN$ molecules, which form a vdW complex with reactive HOF. Subsequently, systems such as HF···HOF···$C_2H_4$, HF···HF···HOF···$C_2H_4$, and $CH_3CN$···HOF···$C_2H_4$ have to reach activation energies of approximately 7.3, 3.5, and 11−20 kcal/mol, respectively. The values of $\Delta G^\ddagger$ at 298 K are higher (≈10−15 kcal/mol), apparently due to the entropic effects. The partial loss of entropy is, however, most pronounced in the Gibbs formation energies, which is expected to handicap the three-molecular systems (e.g., HF···HF···HOF···$C_2H_4$), despite their lowest $\Delta E^\ddagger$ value. From this viewpoint and with respect to the following discussion, the role of the HOF molecule as a self-catalyst seems to be very attractive.

In the gas phase, two HOF molecules temporarily form a circle with an oxygen atom coordinated to the double bond of ethylene (structure F in Figure 1). The transition state in such an arrangement lies 3.7 (B3LYP), 4.1 (B3LYP-D), or 10.1 (MP2) kcal/mol above the initial complex. Considering the system at 298 K, the respective $\Delta G^\ddagger$ values are as follows: 8.1, 8.6, and 14.1 kcal/mol. The entropy portion $|T\Delta S^\ddagger_{\mathrm{nonel}}|$ contributes by approximately 85% to the $|\Delta H^\ddagger_{\mathrm{nonel}}| + |T\Delta S^\ddagger_{\mathrm{nonel}}|$ term at the B3LYP level.

As to the mechanism of the oxygen-transfer process, oxygen is transferred onto the double bond of ethylene via a transition state, in which the three atoms (C, C, and O) form vertices of an isosceles triangle (C−C: 1.36 Å and C−O: 2.19 Å) and follow its asymmetrical deformation (equal to 287*i* and 278*i* $\mathrm{cm}^{-1}$ in a frequency analysis of the gas-phase and solvated structure, respectively) when the oxygen atom approaches a carbon atom, which is rehybridized from $sp^2$ to $sp^3$. According to the *ab initio* study of Berski et al.,[9] a negligible charge transfer occurs between the HOF molecules in the dimer. However, the strong formation of a classical hydrogen bond in FOH···$F^-$ coupled with a slight charge transfer from the fluoride anion to the $\sigma$*(O-H) orbital during reaction could be the driving force of the whole reaction.

**TABLE 2: Energetics of Selected Structures of All Reaction Models Discussed in This Paper[a]**

| system | $\Delta E_f$ | $\Delta\Delta G_f$ | $\Delta E_f'$ | $\Delta\Delta G_{f'}$ | $\Delta E^\ddagger$ | $\Delta G^\ddagger$ | $\Delta E_{R\to P}$ |
|---|---|---|---|---|---|---|---|
| 1 | −5.8 | 11.1 | −3.9 | 4.4 | 4.2 | 8.1 | −75.5 |
| 1[b] | | | −1.8 | 4.5 | 18.2 | 19.6 | −67.5 |
| 2 | −4.7 | 14.6 | −0.8 | 9.7 | 19.7 | 22.6 | −28.4 |
| 3 | −14.7 | 4.1 | −5.0 | 3.1 | 6.5 | 6.5 | −58.2 |
| 4 | −16.8 | 3.9 | −5.1 | 2.8 | 7.1 | 7.2 | −59.9 |
| 5 | −10.9 | 6.9 | −4.5 | 2.3 | 3.0[c] | 4.2[c] | −111.3 |
| 6 | −9.1 | 8.2 | −4.1 | 4.1 | 11.8 | 14.3 | −103.8 |
| 7 | −9.4 | 8.6 | −4.0 | 4.4 | 4.9 | 5.2 | −84.0 |
| 8 | −9.4 | 8.1 | −3.6 | 4.2 | 2.1 | 2.4 | −67.7 |
| 9 | −6.1 | 12.3 | −3.7 | 5.7 | 1.3[c] | 0.7[c] | −79.2 |
| 10 | −9.3 | 8.1 | −3.6 | 4.6 | 1.7 | 3.8 | 65.2 |
| 11 | −4.4 | 12.6 | −3.1 | 5.0 | 0.9 | 0.6 | −62.2 |

[a] Numbers correspond to systems shown in Figure 2. Symbols used for reaction energies are explained in Scheme 2. Relative formation Gibbs energies are related to formation Gibbs energy of the $CH_3CN$···HOF complex ($\Delta\Delta G_f = \Delta G_f(\text{system}) - \Delta G_f(CH_3CN{\cdot}HOF)$). Values are in kcal/mol. [b] $C_2H_4$ + HOF system; not shown in Figure 2. [c] Results obtained from a TS search by relaxed scan.

The inclusion of the implicit solvent model in calculations has a significant effect on the geometry of the localized transition state. While the structure, similar to that of the gas phase, possesses more than one imaginary frequency in its vibrational analysis, the physically appropriate transition state exerts a noncyclic form of the $(HOF)_2$ unit. Moreover, the Gibbs activation barrier at 298 K amounts only to 4.1 kcal/mol ($\Delta E^\ddagger$ = 2.3 kcal/mol), which is more easily achievable than in the gas phase.

Considering the abundance of water in the reaction mixture (roughly 10%), a catalytic effect of water molecules also can be expected. Moreover, Table 1 shows that complexes of HOF with $H_2O$ are thermodynamically more stable than $(HOF)_2$. However, in the gas phase, the calculated activation barrier of 11.0−12.0 kcal/mol (depending on the conformer structure of the initial complex) indicates that the HOF molecule is a significantly better catalyst than the $H_2O$ molecule (the reaction would be kinetically controlled), which can be ascribed to the more pronounced charge transfer in the HOF···HOF than in the HOF···$H_2O$ system.

The reaction in the case of the analogous chlorine-containing system, HOCl···HOCl···$C_2H_4$ (see system 2 in Table 2and Figure 2), has a much higher activation barrier, $\Delta E^\ddagger$ = 19.8 kcal/mol, with the Gibbs activation barrier being 22.6 kcal/mol. Estimating the dependency of the reaction rate on the $\exp(-\Delta G^\ddagger/RT)$ term, the assumption would be that the model reaction would be roughly $3.3 \times 10^6$ times slower at room temperature with HOCl than HOF. This fact emphasizes the exclusivity of HOF as a reactive species.

**Formation of N-Oxide from Amine and P-Oxide from Phosphine.** The oxidation of tertiary amines is another important class of reactions easily carried out by $CH_3CN{\cdot}HOF$, as reviewed in ref 23. The oxidation of trimethylamine has been selected as a model of this class of reactions. The crucial points on the reaction energy profile in the gas phase along with the corresponding pictures of structures are presented in Figure 2. First, an H-bonded FOH···$N(CH_3)_3$ complex with a Gibbs formation energy, $\Delta G_f$, of 6.3 kcal/mol is supposed to coexist in equilibrium with other systems as discussed previously (e.g., FOH···NC−$CH_3$ +$N(CH_3)_3$ = FOH···$N(CH_3)_3$ + NC-$CH_3$ with $\Delta\Delta G_f$ = 4.1 kcal/mol (see system 3 in Table 2)). Because of the equilibrium distribution, the FOH···FOH···$N(CH_3)_3$ complex also was formed with an additional Gibbs energy cost, $\Delta G_{f'}$ = 5.3 kcal/mol (hence, $\Delta\Delta G_{f'}$ = 3.1 kcal/mol for system 3 in Table 2). The oxidation follows the general reaction scheme described

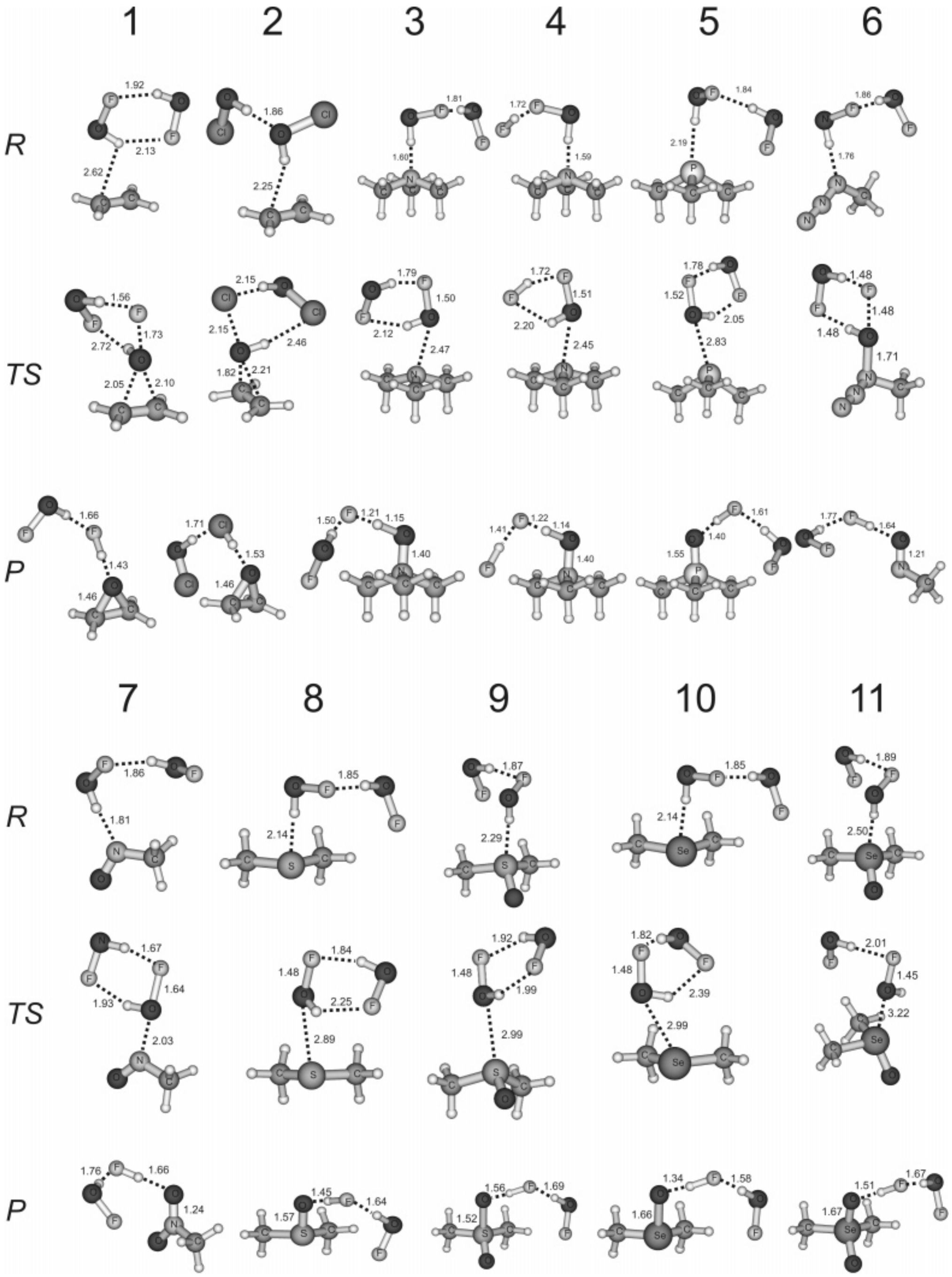
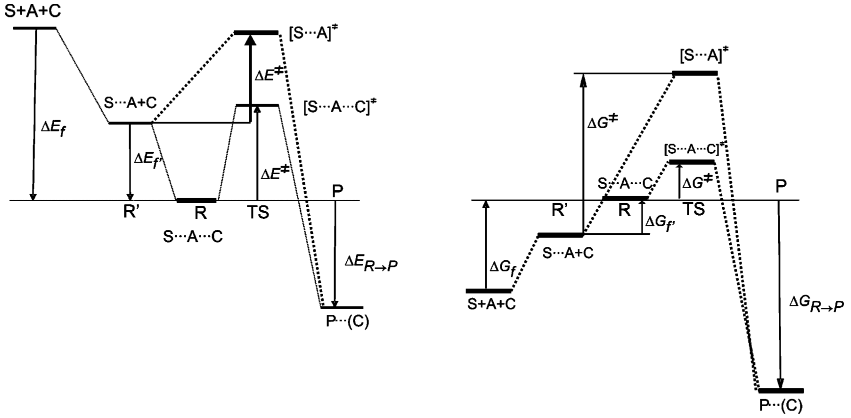


**Figure 2.** Crucial gas-phase structures (R is reactant, TS is transition state, and P is product) on the respective ground-state hypersurfaces. The numbers (corresponding to systems) also refer to Table 2. The bond lengths are expressed in Ångstroms.

previously (see Scheme 2). The critical part of the reaction pathway in the gas phase is associated with the Gibbs energy cost, $\Delta G^{\ddagger} = 6.5$ kcal/mol, which is approximately 5.5 kcal/mol lower than the Gibbs energy barrier for $FOH\cdots N(CH_3)_3$. Interestingly, the HOF dimer retains its cyclic form only in the transition state. As for the solvated system, HOF does not form any cyclic structure. Despite this fact, the catalysis remains very effective. It supports the concept of stabilization of the leaving fluoride anion mainly by H-bond formation. According to the natural bond orbital analysis, this H-bond in the TS is characterized by a slight charge transfer from the fluoride anion to the $\sigma$*(O-H) orbital, coupled with a charge transfer from the electron lone pair of the nitrogen atom of the substrate to the antibonding orbital of the attacking HOF, $n(N) \rightarrow \sigma^*(O\text{-}F)$. The previously described mechanism of catalysis by reactant (HOF) and by product (HF) has a comparable potential energy profile with activation barriers of 6.5 and 7.1 kcal/mol, respectively. The same holds true for $\Delta G^{\ddagger}$. Therefore, it is to be expected that the role of catalysis by HOF decreases during the reaction course as the concentration of hypofluorous acid diminishes; the opposite is true for autocatalysis. However, based on the free-energy results, the reaction catalyzed by HOF is estimated to be 3.4 times faster than when catalyzed by HF ($\approx \exp[-(\Delta G^{\ddagger}_{HOF} - \Delta G^{\ddagger}_{HF})/RT]$).

The phosphines (and relative phosphorus-containing compounds) also were subjected to Rozen oxidations.[24] It was concluded that $HOF{\cdot}CH_3CN$ is a mild, rapid, and effective agent. As to the representative trimethylphosphine, $P(CH_3)_3$, its conversion into $O{=}P(CH_3)_3$ is related to its very low activation barrier, $\Delta E^{\ddagger} = 3.0$ kcal/mol ($\Delta G^{\ddagger} = 4.2$ kcal/mol). The reaction mode in the transition state is the same as the one in the nitrogen-containing system. The lower activation barrier for

**SCHEME 3: Potential Energy and Gibbs Reaction Profiles**[a]



[a] Symbols S, A, and C represent substrate, agent, and catalyst, respectively. Symbols R (reactant), TS (transition state), and P (product) also are presented with respect to Figure 2. Values of corresponding energies for different reaction models are assembled in Table 2.

phosphines than for amines can be explained in terms of the strength of the electron lone-pair bond to nitrogen and phosphorus: the charge transfer, $n(\mathrm{P}) \rightarrow \sigma^*(\mathrm{O\text{-}F})$, is less energy-consuming than the analogous $n(\mathrm{N}) \rightarrow \sigma^*(\mathrm{O\text{-}F})$.

**Formation of N-Oxide (Nitroso Derivatives) and N-Dioxide (Nitro Derivatives) from Azide.** The nitro derivatives also can be prepared from azides by means of the Rozen oxidation.[25] The experimental evidence of nitroso intermediates implies that the oxidation proceeds by a stepwise mechanism.[23] It corroborates the proposed mechanism, one step of which was described previously. Analogously to the two previous models, the $\mathrm{FOH\cdots N^-{=}N^+{=}N{-}CH_3}$ complex is activated by H-bond assistance from another HOF molecule, resulting in the formation of a transition state with a Gibbs activation barrier of 11.8 kcal/mol ($\Delta E^{\ddagger} = 12.4$ kcal/mol; for most of the reaction models, the values of $\Delta E^{\ddagger}$ and $\Delta G^{\ddagger}$ are very similar, thus suggesting that the corresponding step is an almost entropy-independent part of the reaction). The following attachment of $\mathrm{HO^+}$ from HOF is linked with the release of the $\mathrm{N_2}$ molecule. The $\mathrm{(HO\text{-}N\text{-}CH_3)^+}$ intermediate is deprotonated according to the A branch in Scheme 2. The $\mathrm{O{=}N{-}CH_3}$ intermediate is attacked again within the framework of the same four-step scenario: (1) formation of a vdW structure with HOF molecules; (2) formation of the $\mathrm{(HOF)_2}$ cycle and orientation of the O atom toward an electron lone pair of the nitrogen atom, related to the energy cost $\Delta G^{\ddagger} = 5.2$ kcal/mol ($\Delta E^{\ddagger} = 4.9$ kcal/mol); (3) attachment of $\mathrm{HO^+}$; and (4) final deprotonation resulting in the $\mathrm{O_2N{-}CH_3}$ formation.

**Formation of S-Oxide (Sulfoxide) and S-Dioxide (Sulfone) from Sulfide and Se-(Di)oxide from Selenide.** The last class of reactions for which the proposed mechanism will be discussed concerns the oxidation of dialkyl sulfides.[26a] It is necessary to mention that the oxidations of electron-depleted sulfides and thiophenes also have been described.[27] Dimethylsulfide was used as a model system. The two-step formation of the $\mathrm{FOH\cdots FOH\cdots S(CH_3)_2}$ structure led to a lowering of the potential energy by $-12.6$ kcal/mol ($\Delta E_{\mathrm{f}} + \Delta E_{\mathrm{f'}}$ in Table 2). However, $\Delta\Delta G_{\mathrm{f}} + \Delta\Delta G_{\mathrm{f'}}$ (with respect to the $\mathrm{CH_3CN\cdots HOF}$ complex) is roughly 12.3 kcal/mol, which is primarily caused by the lowering of entropy. It appears to be the most energy-consuming part of the reaction model (like with all other reaction models) because the following oxidation of sulfide is associated with only a very low Gibbs activation barrier of 2.4 kcal/mol (system 8 in Table 2). A similar energy profile was obtained for the oxidation of S-oxide to S-dioxide, with a barrier of 0.7 kcal/mol. The two extremely low transition states (structures 8 and 9 in Figure 2) agree with the experimental evidence concerning the very fast oxidation of sulfides to S-dioxide. The exclusive formation of sulfones instead of sulfoxides in the oxidation of sulfides led Rozen et al.[26b] to the hypothesis that the reagent molecules form the cluster (dimer), which tranfers two oxygen atoms onto substrate; this conclusion was also indirectly supported by another experiment, where the dilution of the acetonitrile solution of hypofluorous acid with propionitrile resulted in the exclusive formation of sulfoxide. We developed an experiment-based hypothesis in that the first oxidation step is controlled in a self-catalytic process (HOF···HOF), whereas the second step is autocatalyzed (HOF···HF). Note that a similar conclusion can be made for the oxidations of primary amines to nitro derivatives.

Unlike with sulfur chemistry, no experiments have been published on selenium compounds. On the basis of our calculations, we report the energetics of our model

$$\mathrm{CH_3\text{-}Se\text{-}CH_3} \xrightarrow{\mathrm{HOF}} \mathrm{CH_3\text{-}SeO_2\text{-}CH_3}$$

and predict again two very low-lying transition states (10 and 11 in Figure 2). The estimated Gibbs activation barriers amount to 3.8 and 0.6 kcal/mol and are comparable to those linked with the oxidation of dimethylsulfide. We hope that this prediction will be verified experimentally.

## Conclusion

We have suggested a simple but very effective reaction mechanism of the oxidation (hydroxylation) of various organic compounds by self-catalyzed hypofluorous acid. Unlike an earlier study by Sertchook et al.,[13a] which provided an explanation for the extraordinary oxidative effectivity of HOF based on the autocatalytic properties of hydrofluoric acid formed during the oxidation reaction, we emphasize the self-catalytic role of hypofluorous acid. Although neither the HOF nor the HF catalyst molecules are actively involved in the bond-breaking/forming process, they both stabilize the leaving fluoride anion of the acting hypofluorous acid by means of a strong H-bond. This seems to be sufficient to lower the activation barrier considerably. It is necessary to mention the possibility of catalysis with $\mathrm{H_2O}$ rather than HOF. It was shown, however, that the barrier lowering with HOF is significantly more effective (at least for ethylene epoxidation).

In this paper, we discussed two aspects that can be in favor of HOF. Again, Sertchook et al. proposed the formation of cyclic

HF···HF···HOF as the best reactive unit (i.e., having the lowest activation barrier). We obtained a similar activation barrier for the cyclic HOF···HOF unit. However, assuming mainly the role of the entropy effect on the formation of cyclic three-molecular/two-molecular systems, we have concluded that the formation of HOF···HOF can be more likely. In addition, an H-bond stabilization of the leaving fluoride anion in the transition state is expected to be higher for HOF than HF species due to the stronger electron transfer from $F^-$ on the rather electron-withdrawn H−O bond in HOF.

At the beginning of this study, the idea of the hexagonal structure of the HOF dimer as the reactive unit that is already pre-organized to release HF molecules upon oxidation seemed to be very fruitful. Such a structure would trigger an extensive electron redistribution in a complex during the oxidation process. However, it has turned out that HOF retains its hexagonal structure only in transition states when the reaction proceeds in the gas phase, whereas HOF molecules in solution do not even form any cyclic structure. This emphasizes the importance of the H-bond stabilization of the fluoride anion and that the attacking OH group need not be stabilized by such an H-bond formation. The possibilities concerning the oxidation of C−H bonds in various hydrocarbons are an important but also extensive and intricate subject that is therefore discussed separately.[17]

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