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Micropollutant oxidation studied by quantum chemical computations: methodology and applications to thermodynamics, kinetics, and reaction mechanisms

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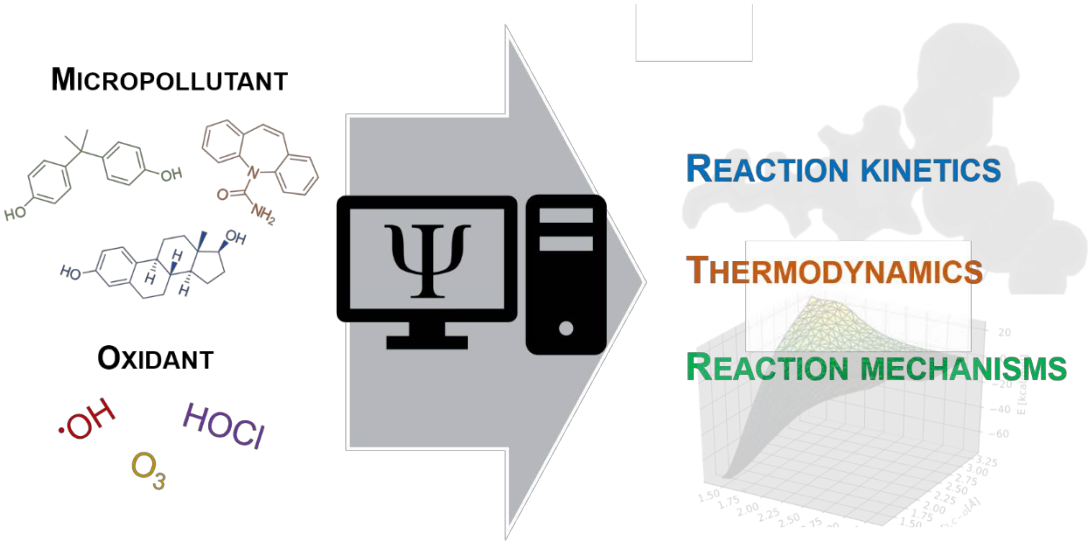
MICROPOLLUTANT
OXIDANT
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HOCl
O_3
REACTION KINETICS
THERMODYNAMICS
REACTION MECHANISMS

15

CONSPECTUS

The abatement of organic micropollutants during oxidation processes has become an emerging issue for various urban water systems such as drinking water, wastewater and water reuse. Reaction kinetics and mechanisms play an important role in terms of efficiency of these processes and the formation of transformation products, which are controlled by functional groups in the micropollutants and the applied oxidants. So far, the kinetic and mechanistic information of the underlying reactions was obtained by experimental studies, additionally, predictive quantitative structure activity relationships (QSARs) were applied to determine reaction kinetics for the oxidation of emerging compounds. Since this experimental approach is very laborious and there are tens of thousands potential contaminants, alternative strategies need to be developed to predict the fate of micropollutants during oxidative water treatment. Due to significant developments in quantum chemical (QC) computations in recent years and increased computational capacity, QC-based methods have become an alternative or a supplement to the current experimental approach.

This article provides a critical assessment of the current state-of-the-art of QC-based methods for the assessment of oxidation of micropollutants. Starting from a given input structure, QC computations need to locate energetic minima on the potential energy surface (PES). Starting from these minima, useful thermodynamic and kinetic information can be estimated by different approaches: Experimentally determined reaction mechanisms can be validated by identification of transition structures in the PES, which can be obtained for addition reactions, heavy atom transfer (Cl^+, Br^+, $O^{\cdot}$) and H-atom transfer (simultaneous proton and electron transfer) reactions. However, transition structures in the PES cannot be obtained for e^--transfer reactions (SI, Text S8).

Second order rate constants *k* for the reactions of micropollutants with chemical oxidants can be obtained by *ab initio* calculations or by quantitative structure activity relationships (QSARs) with various QC descriptors. It has been demonstrated that second order rate constants from *ab initio* calculations are within factors 3-750 of the measured values, whereas LFER-based methods can achieve factors 2-4 compared to the experimental data. The orbital eigenvalue of the highest occupied molecular

orbital (E_{HOMO}) is the most commonly used descriptor for LFER-based computations of *k*-values.

In combination with results from experimental studies, QC computations can also be applied to investigate reaction mechanisms for verification/understanding of oxidative mechanisms, calculation of branching ratios or regioselectivity, evaluation of the experimental product distribution and assessment of substitution effects. Furthermore, other important physical-chemical constants such as unknown equilibria for species, which are not measurable due to low concentrations or pK_a values of reactive transient species can be estimated. With further development of QC-based methods, it will become possible to implement kinetic and mechanistic information from such computations in *in silico* models to predict oxidative transformation of micropollutants. Such predictions can then be complemented by tailored experimental studies to confirm/falsify the computations.

INTRODUCTION

Reactions of chemical oxidants with micropollutants

Chemical oxidants (e.g., chlorine, ozone, chlorine dioxide, etc.) have been applied in water treatment since more than a century, first for disinfection and later for micropollutant abatement.[1] Chemical oxidants react mainly with water matrix components such as the dissolved organic matter (DOM),[1] however in this article, we will focus on the oxidative abatement of micropollutants, which has become a major issue for drinking water, in water reuse systems, and enhanced municipal wastewater treatment systems.[1] Typically, oxidation does not lead to a complete mineralization of target micropollutants but to transformation products with initially similar structures as the parent compounds.[1] Biologically active target compounds are inactivated by these relatively minor changes in their molecular structures.[1] For extended oxidation of micropollutants low molecular weight compounds will be formed, with limited or no structural similarities to the target compounds, which may be of toxicological concern.[1]

Assessment of oxidation processes

So far, the efficiency of oxidation processes has been mainly assessed experimentally. There is a large body of information on the kinetics and mechanisms of the reactions of functional groups and micropollutants with chemical oxidants.[1] However, a purely

experimental approach for kinetic and mechanistic studies is labor-intensive and time consuming. If only a fraction of the about 100'000 commercially available chemicals can be found in water treatment systems (especially wastewater and water reuse), it will be almost impossible to determine reaction kinetics, mechanisms and transformation products experimentally (Figure 1).[1]

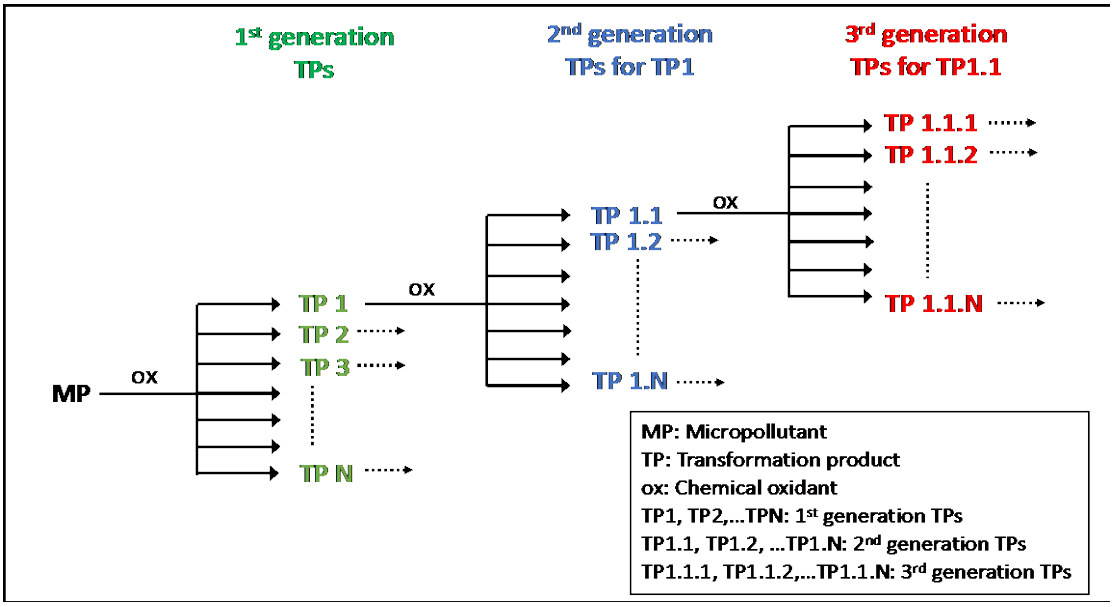

Figure 1. Reactions of chemical oxidants with synthetic organic compounds (MPs). A simplified reaction scheme illustrates the complexity for the formation of TPs. Dashed arrows: Analogous reactions to TP1, TP1.1 and TP1.1.1 (not shown).

Rather, a focus on fundamental kinetic and mechanistic aspects with the main oxidant-reactive functional groups is promising. This knowledge can then be extrapolated to realistic systems to assess transformation product formation based on the knowledge of functional groups of the reaction targets.[1]

Predictive methods for oxidation kinetics and mechanisms

It is evident that prognostic tools are needed to estimate kinetic parameters and determine mechanisms for oxidant-target compound reactions for the huge number compounds.

Reaction kinetics

Second-order rate constants for the reactions of organic compounds with oxidants such as hydroxyl radical, ozone, chlorine, bromine, chlorine dioxide, ferrate(VI) and permanganate have been experimentally determined and compiled.[2-9] Based on this information, second-order rate constants for the reactions of emerging compounds with oxidants can be estimated by quantitative structure activity relationships (QSAR). This approach has been successfully applied for activated aromatic compounds, olefins and amines for the oxidants ozone, chlorine, chlorine dioxide and ferrate(VI) with Hammett and Taft sigma coefficients.[10] Overall, predicted second-order rate constants within a factor of 1/3-3 of the measured values can be obtained, similar to the margin of different experimental studies. However, for complex chemical structures, Hammett or Taft coefficients are sometimes difficult to obtain.[10] Furthermore, second-order rate constants for the reactions of hydroxyl radical with organic compounds have been estimated by the group contribution method.[11] The advent of modern quantum chemical (QC) methodologies (e.g., density functional theory, DFT) and the high-performance computing provided an affordable means for theoretical investigations on oxidative reactions. Therefore, an alternative for estimating second-order rate constants is based on QC computations (see below).[12] This approach has the advantage that it is independent of Hammett or Taft sigma values, which are not available for all chemical structures.

Reaction mechanisms

Transformation pathways during oxidative treatment of micropollutants can be determined by labor-intensive experiments by analyzing transformation products by a suite of analytical tools.[1] Such information has been applied to build computer-assisted pathway prediction systems based on reaction rules for ozone and hydroxyl radical.[13-14] For other oxidants applied in water treatment (e.g., chlorine, chlorine dioxide, permanganate, etc.), no comprehensive compilations of mechanistic information are available and it is more difficult to predict reaction products. Generally, the uncertainty of predictions increases with the extent of transformation of the target compound, i.e., from the first-generation products to higher generation products (Fig. 1). Based on the reaction mechanisms provided in literature, it is often difficult to judge the likelihood of specific reactions among multiple pathways.

It has been demonstrated, that QC computations can complement or even substitute experimental kinetic and mechanistic studies on the oxidation of organic compounds.[15-16] The goals of this paper are to (i) discuss the state-of-the-art of QC

138 computations for oxidative processes, (ii) give examples and a critical evaluation of
139 the work that has been performed in this field, and (iii) assess the practical
140 implications of this approach.

QUANTUM CHEMICAL COMPUTATIONS: STATE-OF-THE-ART

General considerations

QC computations[17] simulate isolated molecules or complexes, as opposed to a solution containing molecules in high numbers. A typical input file and output is exemplified in Figure 2.

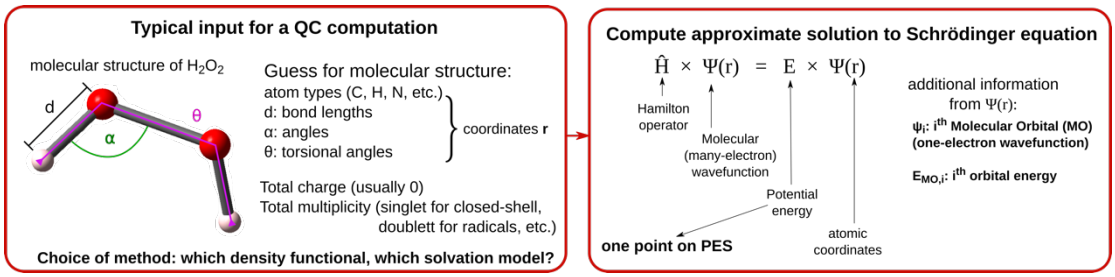

Figure 2: Required input for a QC computation and resulting information.

The approximate solution of the time-independent electronic Schrödinger equation depends on the atomic coordinates *r* (bond lengths, angles, and torsional angles) as parameters only (Born-Oppenheimer approximation) and yields the potential energy E for a given set of coordinates (Figure 2). These 3N-6 degrees of freedom (N=number of atoms) define a potential energy surface (PES, Figure 3). The reactant and product species of a reaction are defined by differences in *r* only, and the number of atoms has to remain balanced for calculation of energy differences. From a given input structure, a computer program will find the closest energetic minima (stationary structures) on the PES, corresponding to observable chemical species. Based on this, further analyses can lead to information on kinetics, thermodynamics, and reaction mechanisms, which is elucidated in Figure 4.

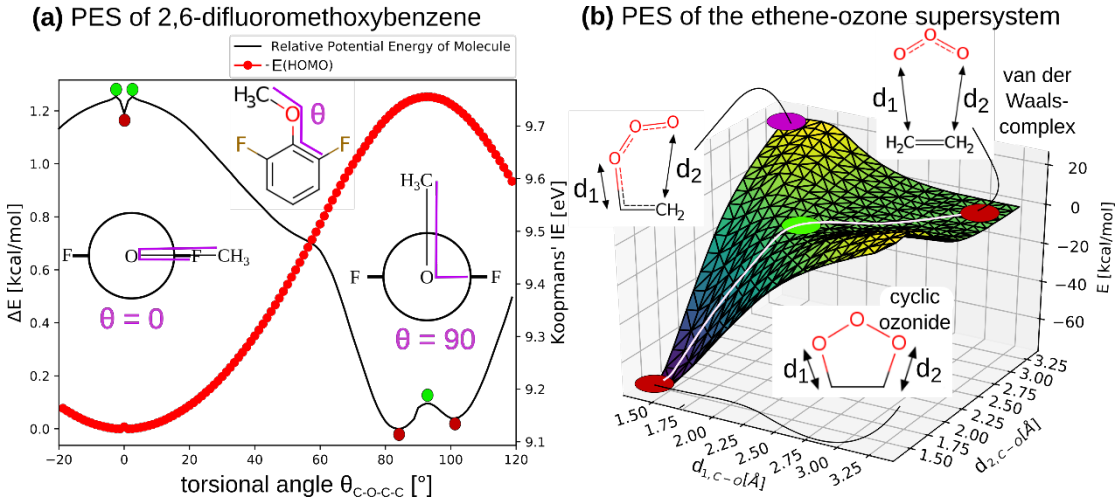

Figure 3: The 3N-6-dimensional PES can be collapsed to one or two dimensions by systematically varying *one or two coordinates*, and optimizing the rest of the system. (a) *Dihedral angle* of the H_3C-O-C-CF torsion of 2,6-difluoromethoxybenzene (b) *Two $r_{C\text{-}O}$ distances* of the O_3-ethene supersystem. Minima on the PES are marked in red, the transition structure connecting the minima in green. (b) also shows the potential structure for a monodentate adduct (purple) and the minimum energy path/"reaction coordinate" connecting reactants and products in white (computational details: Supporting Information(SI) Text S7).

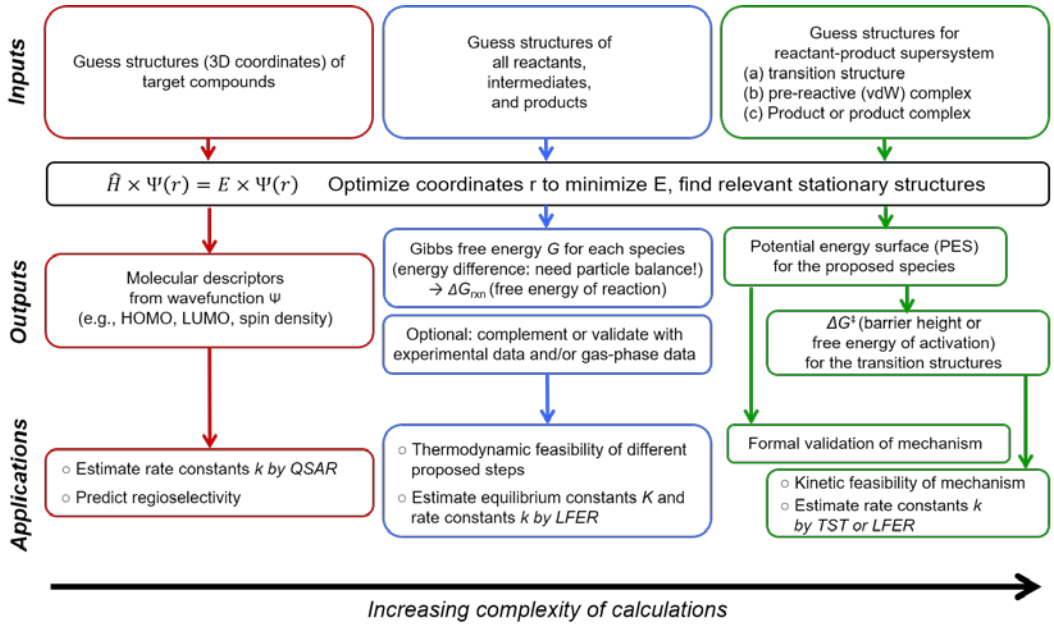

Figure 4: Calculation schemes with various complexities for obtaining the relevant QC parameters of different applications as discussed in the manuscript. LFER: Linear free energy relationship, TST: Transition state theory

Evaluation of ΔG_{rxn} (thermodynamic feasibility and equilibria)

Gibbs free energy (G or free energy hereafter) can be used to evaluate thermodynamic feasibility or equilibria of a reaction (Figure 4, middle). This is implemented following the thermodynamic cycle summarized in eq. (1), yielding the aqueous free energy of reaction ΔG_{rxn}.

$$\Delta G_{rxn} = \sum G_{products,gas} + \sum \Delta G_{products,solv} - \sum G_{reactants,gas} - \sum \Delta G_{reactants,solv} \quad (1)$$

Only structures of individual species need to be provided, and can usually be easily proposed. Moreover, the computation can be divided into a gas phase component and a free energy of solvation ΔG_{solv},[18] allowing for the use of highly accurate methods (e.g., coupled cluster[19]) or experimental values for gas phase ΔG_{rxn}. The accuracy of such calculations strongly depends on the model chemistry used for both the gas phase and the solvation parts.

For gas phase energetics, the "gold standard" CCSD(T) method[19] (SI, Text S1) can achieve an accuracy of 1 kcal/mol (≅experimental accuracy) for many problems of organic chemistry, and should be used whenever affordable. Table 1 illustrates that the uncertainty in thermodynamic properties stems primarily from the solvation model, especially for ionic compounds. However, for some of the primary and secondary oxidants bearing "multireference character" (including Cl_2O,[20] ClO_2,[20] O_3,[21] $O_3^{\cdot-}$, and $^1O_2$),[21] and any singlet diradical intermediates (SI, Text S9), gas phase results alone may already be equally uncertain. For example, free energy calculations involving O_3 as a reactant suffer from a systematic error in ΔG_{rxn} of ~4 kcal/mol in the gas phase electronic energy component when computed by CCSD(T), and even worse with contemporary DFT methods.[21] More sophisticated methods are necessary to reach 1 kcal/mol accuracy,[19, 21] which are not affordable for any target compounds of interest. Careful method evaluation using smaller model compounds can be used to select methods with reasonable results for real systems (SI, Text S1 for a discussion of accuracy versus computer time).

In many difficult cases, lacking thermodynamic data can be compiled from experimental data. Gas phase reaction energies, but also experimental pK_a values, redox potentials, or other equilibrium constants (linked to free energy differences through $\log(K) = \Delta G/RT$) can be used in thermodynamic cycles to estimate desired free energy differences or free energies of solvation needed for aqueous phase calculations. This requires that the other components of the thermodynamic cycle are

computed close to experimental accuracy. Table 1 provides some examples of achievable accuracies for such thermochemical simulations.

Table 1: Typically achievable average accuracies for thermodynamic parameters from QC computations.[a]

Thermodynamic parameter	**Accuracy**
ΔG_{rxn} (gas phase)	CCSD(T)/composite: ~1-2 kcal/mol[19] (~4 kcal/mol)[d21] DFT: 2-4 kcal/mol[24]
ΔG_{solv} (neutral species)	Implicit solvation:[d] 1-2 kcal/mol[25]
ΔG_{solv} (ionic species)	Implicit solvation:[d] 3-7 kcal/mol[25]
pK_a	Implicit solvation only:[d] ~6 pH units[26] Implicit solvation with some explicit water molecules:[e] ~1 pH unit[26]
IE (gas)[b]	CCSD(T)/composite: ~1-2 kcal/mol[27-28] DFT: ~3-5 kcal/mol[28]
$\Delta G°$[c]	Implicit solvation:[d] ~0.3 V (~7 kcal/mol)[29] Explicit solvation:[d] ~0.2 V (~4 kcal/mol)[30]

[a]Results should be compared to experimental data of similar systems (e.g., equilibrium constants of halogen oxides[22]), or can be correlated to experimental data of a congeneric series (e.g., one-electron oxidation potentials of anilines[23] see SI, Text S1)

[b]gas phase adiabatic ionization energy

[c]half-cell standard reduction potential

[d]reduced accuracy for multi-reference species

[e]SI, Text S2 for details on implicit and explicit solvation

Computational validation of proposed reaction mechanisms

For further mechanistic validation, stationary structures on the PES of combined reactants need to be identified: (a) The pre-reactive complex of the reactants, (b) the product (complex), and (c) a transition structure (first order saddle point on the PES) connecting the reactant with the product side through a minimum energy path (Figure 3b).

This is possible if the minimum energy path can be easily expressed by atomic coordinates (e.g., by one or two interatomic distances). However, oxidants react by different mechanisms including electron transfer (ET) (Table 2) or variations thereof, where transition structures cannot be identified like this (Table 3).

When describing bond formation/cleavage, common QC methods suffer from a poor description of largely elongated bonds,[17, 19] resulting in inaccurate energetics, and in the worst case in qualitative differences in the PES described by different methods (SI, Text S3). Such extreme problems should only arise when a molecular diradical is involved.

Frequently, the initial reaction of an oxidant with a target compound will not lead to the experimentally observed "primary" product, but to metastable intermediate(s) that cannot be observed experimentally (Figure 1). However, only computing a complete pathway from reactant to product can support a proposed reaction mechanism, which can be quite laborious. Computed $\Delta G^{\ddagger}$ (barrier height or free energy of activation) can be used as an additional criterion concerning the kinetic feasibility of a computed mechanism, and can provide some insight into the kinetic control of the formation of possible products.

Table 2: Common oxidants in water treatment and the corresponding reaction mechanisms

Oxidant	**Proposed reaction mechanisms**
O_3	Addition, H-atom transfer, e^--transfer, O-transfer
HOCl	Cl^+-transfer, e^--transfer
Cl_2O	Cl^+-transfer, e^--transfer
HOBr	Br^+-transfer, e^--transfer
ClO_2	e^--transfer
$^{\bullet}OH$	Addition, H-atom transfer, e^--transfer
Fe(VI)	e^--transfer, addition, oxygen-transfer
$^1O_2$	Addition

Table 3: Feasibility of PES computations to identify transition structures

Mechanism	**PES / minimum energy path**
Addition	Yes
(Heavy) atom transfer (Cl^+, Br^+, $O^\bullet$)	Yes
H-atom transfer	Yes (if proton and electron are transferred simultaneously)
e^--transfer	No (including proton-coupled electron transfer and similar)

Kinetics of reactions: Second-order rate constants *k*

Kinetic experiments for a bimolecular reaction between a target compound (Red) and an oxidant (Ox) measure an apparent second-order rate constant k_{app} ($M^{-1}s^{-1}$, typically determined at 298K and 1atm), which is a lump sum of different microscopic reactivities (eq. 2):

$$-\frac{d}{dt}[Red] = k_{app}[Red_{tot}][Ox_{tot}] = \sum_i^n \sum_j^m \sum_l^o k_{ijl}[Red_i][Ox_j] \qquad (2)$$

where "tot" signifies total concentrations. The triple summation corresponds to (*i*) speciation in the target compound, (*j*) speciation in the oxidant, and (*l*) different reaction channels for a species-specific reaction. Therefore, k_{ijl} is a microscopic rate constant specific to a certain *i-j* species pair and a channel *l*. Simulated rate constants are computed from a specific molecular geometry, thus correspond to k_{ij} (species-specific) or k_{ijl} (channel-specific). In experiments, in contrast, pH-dependent speciation for the target compound and oxidant can be typically deconvoluted with the pK_a, while other species-specific (e.g., conformers) and channel-specific *k* remain indistinguishable (SI, Text S4). Therefore, a careful comparison between theoretical and experimental *k* is required for verification.

ab initio calculations of k by Transition State Theory (TST)

Identified transition structures allow the calculation of $\Delta G^{\ddagger}$ (Figure 4, right), which is linked to the rate constant through TST, using the Eyring-Polanyi equation (Table 4). Calculation of absolute microscopic rate constants requires detailed knowledge of the reaction mechanism(s)/transition structures, along with further corrections to the rate

expression.[31] There are several limitations to this approach: (a) Calculations including "problematic" oxidants such as O_3 (and probably also ClO_2, Cl_2O, $CO_3^{\cdot-}$) suffer from shortcomings of the used electronic structure method. (b) Ionic transition structures can be significantly stabilized by water molecules (which are lacking from the usually employed implicit solvation models) or may be catalyzed by proton transfer to and from neighboring water molecules, (c) limitations of the Eyring-Polanyi equation or similar approaches (e.g., the transmission coefficient is unknown for solution-phase reactions, and well-defined quasi-equilibria are assumed) (SI, Text S5). Estimation of log(*k*) close to experimental accuracy (~1 log(*k*)) would typically require an accuracy in $\Delta G^{\ddagger}$ of < 2 kcal/mol, which can never be warranted (Table 1). If computed and experimental log(*k*) differ by > 2, this could still be due to the technical limitations of the simulation, or the rate-determining step of the reaction was not properly identified on the PES.

For ET reactions, transition structures are not easily identified, and rate expressions such as the Marcus or Sandros-Boltzmann equation are often used (Table 4). They express $\Delta G^{\ddagger}$ as a free energy difference and a fitting parameter (assumed to be constant for the studied reactions). Computational estimation of redox properties is too inaccurate[27, 29-30] to calculate absolute rate constants.

Table 4: Simplified rate constant expressions relevant to nucleophile-electrophile interactions (SI, Text S5).

Eyring-Polanyi	**Marcus**	**Sandros-Boltzmann**	**Klopman-Salem**
$log(k) \propto -\frac{\Delta G^{\ddagger}}{RT}$	$log(k) \propto -\frac{(\lambda + \Delta G^{o})^2}{4\lambda k_B T}$	$log(k) \propto \frac{\Delta G + s}{RT}$	$log(k) \propto \frac{\beta^2_{HOMO-LUMO}}{E_{HOMO,nuc} - E_{LUMO,elec}}$
$\Delta G^{\ddagger}$: free energy of activation	$\Delta G°$: difference in electrode potentials (free energy of electron transfer) λ: reorganization energy (fitting parameter in	ΔG: free energy of reaction *s*: fitting parameter to a set of experimental rate constants	E_{HOMO}: HOMO[a] energy on nucleophile E_{LUMO}: LUMO[b] energy on electrophile β: HOMO-LUMO resonance integral

	experimental work) k_B: Boltzmann constant		

[a]HOMO: Highest occupied molecular orbital; [b]LUMO: Lowest unoccupied molecular orbital

k estimation from molecular descriptors D

A more common, pragmatic approach to estimate *k* is by regression models (e.g., QSAR) (eq. 3):

$$\log(k_a) = \sum c_b \times D_{a,b} + C \qquad (3)$$

where *k* is the second-order rate constant for the reaction between a target compound *a* and a specific oxidant, $D_{a,b}$ is the b^{th} descriptor derived from the molecular structure of the target compound *a*, c_b are coefficients fitted to experimental *k* values of a specific oxidant, and *C* is a constant. A comparison to common rate expressions (Table 4) shows that *D* has to be proportional to $\Delta G^{\ddagger}$ or its electrochemical formulations, irrespective of the reaction mechanism.

Conceptual scope and limitations of QC descriptors

Among different descriptors, the orbital eigenvalue of the highest occupied molecular orbital (E_{HOMO}, contained in Ψ) of the target compound is the most commonly used. This is not surprising, as it relates to all relevant rate expressions (Table 4):

(i) The Klopman-Salem equation describes the ease of bond-making between a nucleophile (target compound) and an electrophile (oxidant) by a donor-acceptor orbital interaction. This electron flux from the HOMO of the nucleophile to the LUMO of the electrophile is most favorable when this HOMO-LUMO energy gap is small.

(ii) The Marcus and Sandros-Boltzmann equations relate the rate constant of an electron transfer reaction to the free energy change and a fitting parameter (λ or *s*). The free energy change is caused by removing an electron from the target compound, and transferring it to the oxidant, corresponding to the adiabatic ionization energies (IE/oxidation potential) and electron affinities (EA/reduction potential) of the reactants (eq. 4):

$$\Delta G° = \text{IE(reductant)} + \text{EA(oxidant)} \qquad (4)$$

Koopmans' theorem[32-33] states that the $-E_{HOMO} \cong$ IE of a molecule, and $-E_{LUMO} \cong$ EA, which are however vertical (non-adiabatic) quantities. In the Marcus theory, the difference between vertical and adiabatic electron transfer energies is the reorganization energy λ.

When considering a regression model of a single oxidant, its reduction potential or EA remain constant, and thus any form of computed IE of the target compound can be linked to electron transfer and/or bond-making reactions. Orbital energies have also been used as descriptors for H-atom transfer reactions, and these can be expected to be strongly correlated for a congeneric series (e.g., "phenols").[34] Thus, descriptors related to the IE are not mechanism-specific.

There are several caveats noteworthy when estimating k with QC descriptors. Orbital/ionization energies cannot account for steric effects, and imply that the rate-determining step of the reaction is the initial attack of the oxidant on the target compound. Moreover, when considering all relevant species according to eq. 2, in contrast to protonation state, conformational speciation remains undetected experimentally, but can have a large impact on calculated rate constants. Figure 3a shows the evolution of $-E_{HOMO}$ with the torsional angle of the methoxy group of 2,6-difluoromethoxybenzene. The competition between mesomeric effects and steric hinderance leads to two minima of PES that are only ~1.5 kcal/mol apart. However, the change in $-E_{HOMO}$ is 8-fold (12 kcal/mol). Similar effects can be expected whenever a torsion is associated with the disruption of mesomeric effects. Consequently, algorithms that automatically generate a single guess structure for a molecule have to be used cautiously (different conformations may need to be considered when necessary).

Besides speciation, different reaction channels can contribute to the observed reactivity of two well-defined species (k_{ij} vs. k_{ijl}). This can refer to different mechanisms (e.g., ET vs. Cl^+-transfer, Table 2), but also a reaction at different sites within an organic molecule. The used descriptors (IEs, orbital energies, bond dissociation energies) are usually not mechanism-specific enough to distinguish reaction channels. However, regioselectivity (different reactive sites) can be described. Ψ contains descriptors to predict the likely sites of oxidation reactions in target compounds. Examples beyond MOs (natural bond orbitals,[35] the average local ionization energy IE_L,[36] and the spin density of an oxidized target compound) are

given in Figure 5. Additionally, calculated bond dissociation energies (X-H, X=C, O, N, S, not shown) can reveal the most reactive sites for H-abstraction.

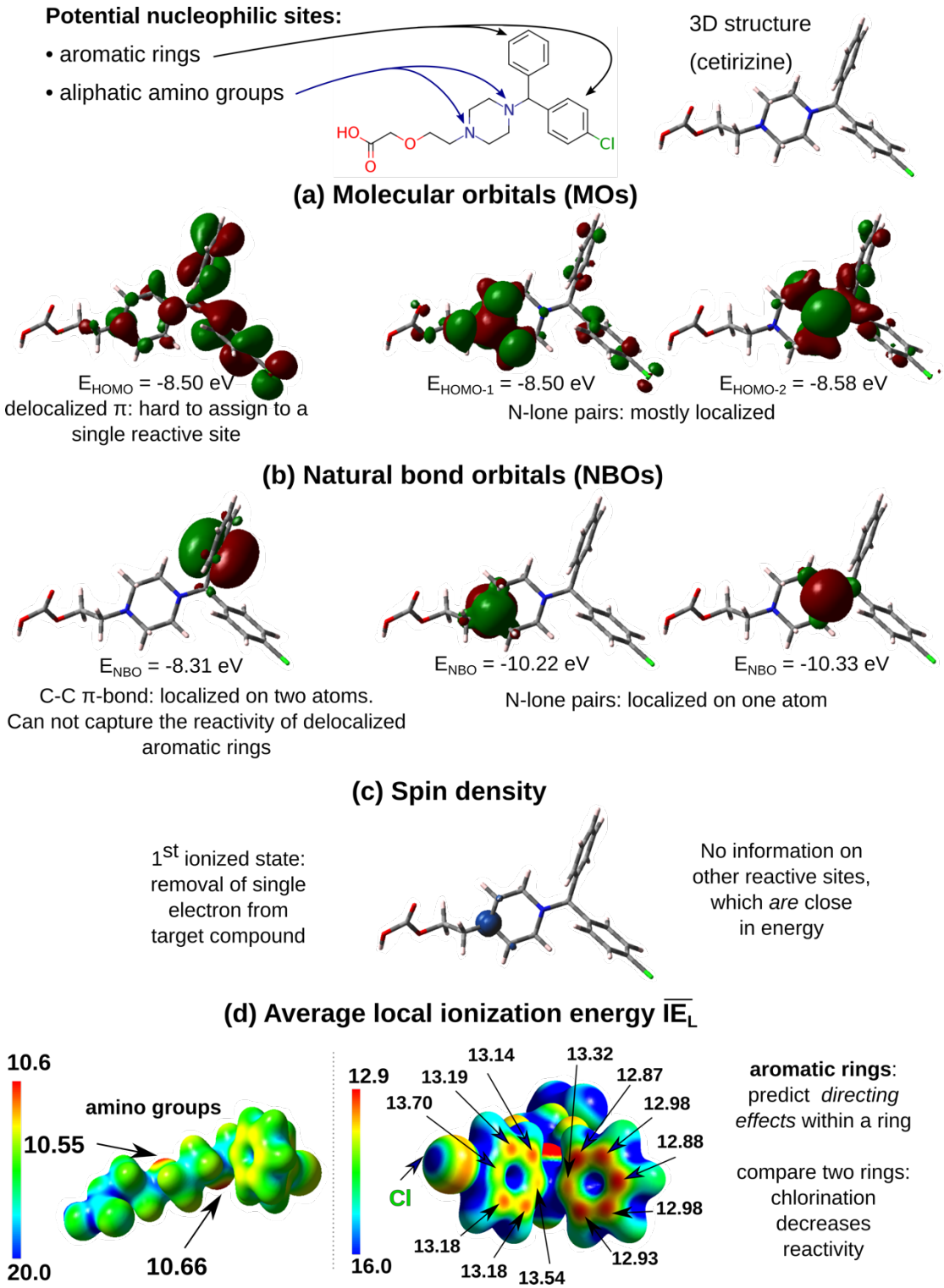

Figure 5: Insight into regioselectivity of cetirizine (SI, Text S6 for details). (a) MOs are often delocalized over several reactive sites, (b) NBOs are perfectly localized on one or two atoms, but fail to capture delocalization effects, (c) indicates the location

of the unpaired electron in a radical, (d) is a Koopmans-type ionization energy projected onto a surface. Descriptors (a)-(d) predict a higher reactivity of the left amino group.

APPLICATION OF QUANTUM CHEMICAL COMPUTATIONS FOR KINETIC AND MECHANISTIC OXIDATION STUDIES

Reaction kinetics

QSAR models using QC descriptors have been proposed for several oxidants (Table 5).

Table 5: Examples of QSAR models for the determination of second-order rate constants that use QC descriptors.

Oxidant	Target compounds	Descriptors	Rate constants
O_3	aromatics[12, 37]	E_{HOMO}	k_{ij}
O_3	olefins and amines,[12]	E_{NBO}	k_{ij}
O_3	phenols[38]	VIE[a]	k_{ij}
O_3	aromatics[37]	ΔG of adduct formation	k_{ij}
$HO_2^{\cdot}/O_2^{\cdot-}$	various[39]	E_{HOMO}/ E_{LUMO}	k_{app}
$^{\cdot}OH$	various[40]	E_{HOMO}	k_{ij}
$^{\cdot}OH$	various[41-42]	$\Delta G^{\ddagger}$ *(LFER)*[b]	k_{ijl}
$^1O_2$	olefins, aromatics, amines[43]	E_{HOMO}	k_{app}
$^1O_2$	phenols[44]	ΔG^{o} [c]	k_{ij}
Carbonate radical	phenols, N-containing compounds[44-45]	ΔG^{o} [c]	k_{ij}
Carbon-, chlorine- and oxygen-derived radicals	various inorganic species or disproportionation[42, 46]	$\Delta G^{\ddagger}$ *(LFER)* [b]	k_{ijl}

[a]VIE: Vertical ionization energy, [b]LFER: Linear Free Energy Relationship, [c]half-cell standard reduction potential

Most of the proposed correlation models used experimental k_{ij} (protonation-state specific), which collectively include all reaction channels. E_{HOMO} and E_{NBO} were

shown to be strongly correlated with the corresponding Hammett or Taft constants from the QSAR approach,[12] wherefore these descriptors are regarded as proxies reflecting the electron-donating/withdrawing effects of substituents on a reaction center. Ideally, the two types of descriptors should be mutually replaceable. QC descriptors yield sometimes results inferior to Hammett/Taft constants, which we ascribe partly to shortcomings in the electronic structure methods used to compute these descriptors. As $-E_{HOMO}$ can be interpreted as an IE, differing quality of both descriptors can be expected from different methods, which is exemplified in Figure 6. Systematic errors may cancel within a group of congeneric target compounds, but more general models benefit from using methods that produce somewhat realistic ionization/orbital energies.[33] The same argument holds for thermodynamic descriptors such as bond dissociation energies or product formation energies. When considering congeneric classes of compounds, QSAR-predicted rate constants agree with experimental k_{ij} within a factor of 2-4.[12] However, the scope of such QSAR models is limited by the structures comprised in the experimental training data set.

As an alternative to QSAR, absolute k computed from $\Delta G^{\ddagger}$ by TST were within a factor of 3-750 from experimental values, depending on the oxidants, reaction types and models employed.[12, 31,41, 47]

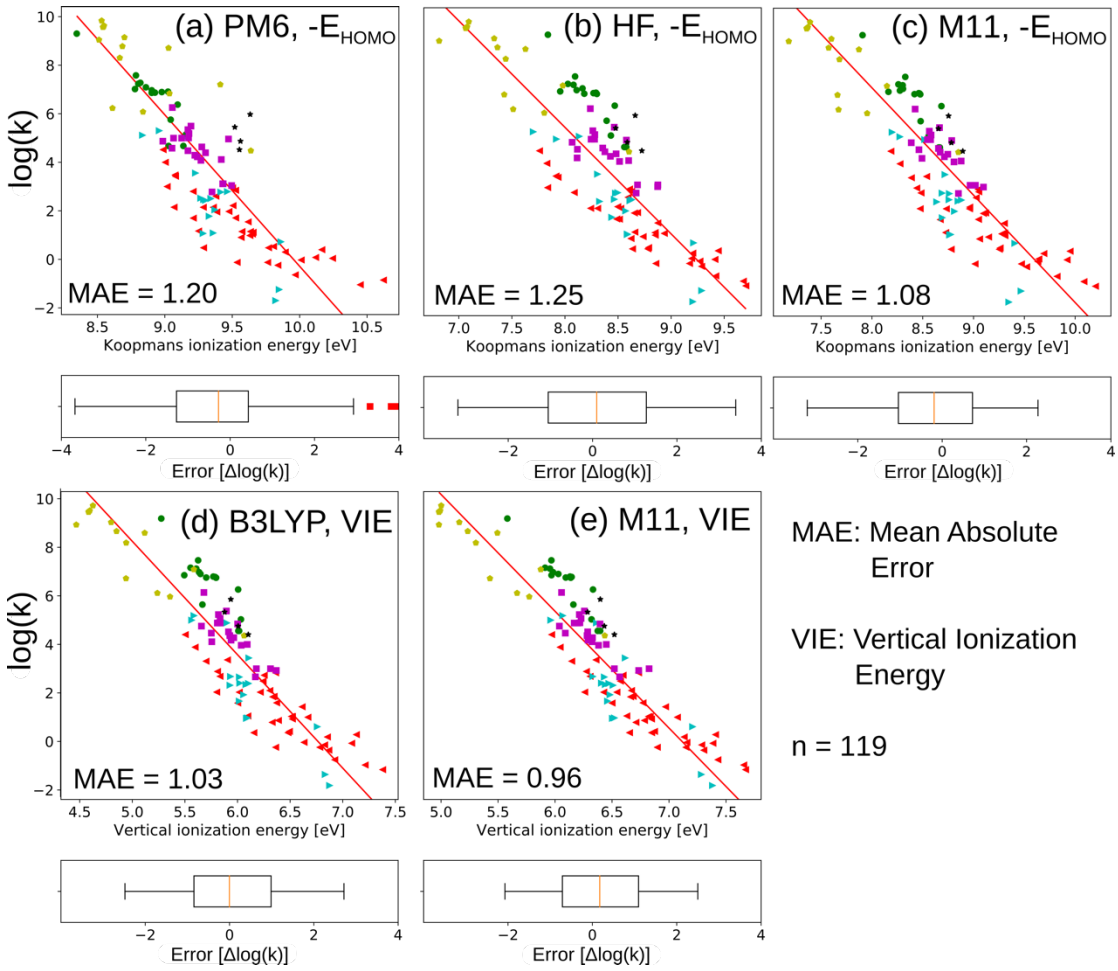

Figure 6: Univariate QSAR models for the log(*k*) for the reactions between ozone and aromatic compounds. Descriptors are E_{HOMO} calculated by (a) the semi-empirical PM6 model, (b) the Hartree-Fock model, (c) the long-range corrected M11 density functional, (d) and (e) explicitly calculated VIE using B3LYP and the generally more accurate M11 functional (SI, Text S7).

Reaction mechanisms and thermodynamic properties

Mechanistic insights allow (qualitative) conclusions on the types of compounds undergoing a studied type of reaction. QC data provide information on what types of intermediates can be formed, and if they are connected on the PES. This knowledge can be used to determine the likelihood of the formation/type of transformation products (Table 6). Reaction mechanisms often involve equilibria, which can be estimated based on QC free energy calculations (Table 7).

Table 6: Illustrative examples of QC studies of oxidative reaction mechanisms

Reaction	Calculation type(s)	Gained information
N,*N*-dimethylsulfamide + O_3[47]	$\Delta G/\Delta G^{\ddagger}$	Verification/understanding of Br^--catalyzed mechanism
Acetone + $^{\bullet}OH$[48]	$\Delta G/\Delta G^{\ddagger}/k$ of 88 possible elementary reactions from reactants to experimentally observed products	Comparison of theoretically simulated time-dependent concentration profiles of the target substance and oxidation products with experimental observations
Ratinidine + mono-/dichloramine[49]	$\Delta G/\Delta G^{\ddagger}$	Proposition of nitric oxide as reactive nitrosating agent (refuted by experiment)[50]
p-substituted phenols + O_3[38]	$\Delta G/\Delta G^{\ddagger}$ of reactions following the initial addition of O_3	Qualitative attribution of observed products to substituent-specific reaction mechanisms
Ibuprofen + $^{\bullet}OH$[51]	$\Delta G/\Delta G^{\ddagger}$ of primary attack	Regioselectivity/branching ratio: H-abstraction, $^{\bullet}OH$ addition
Carbamazepine + HOCl[52]	$\Delta G/\Delta G^{\ddagger}$	Elucidation of mechanisms leading to experimentally observed products

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426 Table 7: Illustrative examples of estimated thermodynamic data

System	Calculation types(s)	Gained information
HOCl/HOBr[22]	ΔG	Estimates of unknown equilibria between

		HOX/XOX/X_2 (X=Cl,Br)
Halamines[53]	ΔG/LFER	Estimated pK_a of chlor-/bromamines
Phenols[38]	ΔG/LFER	Estimated pK_a of phenols
Sulfonamides[23]	ΔG/LFER	Estimated $\Delta G°$ (redox potential)

PRACTICAL IMPLICATIONS AND OUTLOOK

Reaction kinetics

The abatement of organic micropollutants by oxidation processes is governed by reaction kinetics. Second-order rate constants for oxidation reactions can be determined experimentally or estimated by conventional QSAR methods. Both approaches have limitations. Alternatively, QSAR-based approaches with QC descriptors or *ab initio* estimations can be applied. QSAR-type approaches provide typically reasonable results for second-order rate constants within a factor of 2-4 from measured values. This is similar to differences between experimental studies. *ab initio* calculations of *k* have shown some success for $^{\bullet}$OH and other radicals. The application to other oxidants is largely unexplored, deserving systematic studies, and the reasons for the poor agreement with experiments need to be elucidated.

QSAR models with QC descriptors have been developed for the estimation of rate constants for ozone and hydroxyl radical. For chlorine, chlorine dioxide, and ferrate (VI), QSAR models using Hammett or Taft constants were successfully developed.[6] Therefore, molecular descriptors representative of a substituent effect may manifest a close correlation with rate constants, similar to E_{HOMO} or E_{NBO} for ozone.[3] A concurrent use of other QC descriptors such as bond dissociation energies could lead to multivariate models that surpass current QC-based QSARs.

Formation of transformation products

Prediction of transformation products formed from micropollutants during oxidative water treatment is still a challenge. *ab initio* predictions are currently not possible, but QC computations can assist predictions of transformation products on several levels: (i) Confirmation of postulated reaction products by Gibbs free energy calculations, (ii) assessment of the feasibility of postulated transient products, which are not accessible experimentally, (iii) evaluation of reaction pathways with multiple reaction channels, (iv) calculation of regioselectivity and (v) calculation of physical chemical properties (e.g., pK_a, standard reduction potentials).

In a recently developed pathway prediction system, reactions of organic moieties with ozone from experimental studies were compiled and integrated into a software using a chemoinformatics tool, applying reaction rules to predict transformation products. This *in silico* prediction system also includes an option for prediction of second-order reaction rate constants based on QSAR-type correlations of second-order rate constants with molecular orbital energies of target substances.[13] However, on-the-fly theoretical thermodynamic computations for different reaction channels remain to be implemented. They are currently limited due to the lack of a reliable and affordable model chemistry/software for target substances, oxidants, intermediates, and products.

Outlook

Testing the thermodynamic feasibility of a proposed reaction mechanism based on ΔG_{rxn} is relatively easy, and should become a standard approach whenever a mechanism is proposed based on experimental results. In such analyses we need to consider that intermediate steps can be endergonic, and that kinetic control of the reaction may lead to the thermodynamically less favorable products.

Detailed mechanistic studies, including the calculation of $\Delta G^{\ddagger}$, have been mostly limited to hydroxyl radical, for which the chemistry is the most well-understood to date. With further experimental mechanistic studies, it should be possible to gain a better understanding of the reactivity of other oxidants reacting by addition or atom transfer (e.g., HOCl/HOBr/Cl_2O/O_3). Moreover, theoretically proposed mechanisms with $\Delta G^{\ddagger}$ can be further verified provided that experimental $\Delta G^{\ddagger}$ for the corresponding reaction channel can be obtained from the temperature dependence of the reaction rate (i.e., from the Arrhenius equation). Eventually, such mechanistic insight based on a combined experimental and computational approach could lead to pathway prediction systems that cover oxidants beyond O_3.

SUPPORTING INFORMATION

Computational details; further reading on calibration of QC methods, implicit and explicit solvation models, influence of the model chemistry on mechanistic calculations, speciation in reaction kinetics, rate expressions for oxidation reactions, regioselectivity and (de-)localization of molecular orbitals, the reaction coordinate of electron transfer reactions, multireference character and singlet diradicals; 4 Figures, 1 Table.

BIOGRAPHICAL INFORMATION

Peter R. Tentscher received a PhD in chemistry from EPFL, The Swiss Federal Institute of Technology, Lausanne, followed by post-doctoral stays at EPFL and Eawag. He is currently a visiting scientist at Aalborg University. His research interests are in computational chemistry and aqueous oxidation chemistry.

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Urs von Gunten received a PhD in Chemistry from the ETH, the Swiss Federal Institute of Technology in Zurich and is currently a full professor at EPFL and a senior researcher at Eawag, the Swiss Federal Institute of Aquatic Science and Technology. His main interests are kinetic and mechanistic studies of disinfection and abatement of micropollutants during oxidative processes.

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