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PAPER

Base-catalyzed reactions of environmentally relevant *N*-chloro-piperidines. A quantum-chemical study†

Davor Šakić,[a] Hendrik Zipse[b] and Valerije Vrček*[a]

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Electronic structure methods have been applied to calculate the gas and aqueous phase reaction energies for base-induced rearrangements of *N*-chloropiperidine, *N*-chloro-3-(hydroxymethyl)piperidine, and *N*-chloro-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine. These derivatives have been selected as representative models for studying the chemical fate of environmentally relevant chloramines. The performance of different computational methods (MP2, MP4, QCISD, B3LYP and B2PLYP) for calculating the thermochemistry of rearrangement reactions was assessed. The latter method produces energies similar to those obtained at G3B3(+) level, which themselves have been tested against experimental results. Experimental energy barriers and enthalpies for ring inversion, nitrogen inversion and dehydrochlorination reactions in *N*-chloropiperidine have been accurately reproduced when solvent effects have been included. It was also found that the combined use of continuum solvation models (*e.g.* CPCM) and explicit consideration of a single water molecule is sufficient to properly describe the water-assisted rearrangement of *N*-chlorinated compounds in basic media. In the case of *N*-chloro-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine, which represents the chlorinated metabolite of the antidepressant paroxetine, several different reactions (intramolecular addition, substitution, and elimination reactions) have been investigated. Transition state structures for these processes have been located together with minimum energy structures of conceivable products. Imine **4A** is predicted to be the most stable reaction product, closely followed by imine **4B** and oxazinane **8**, while formation of isoxazolidine **7** is much less favourable. Calculated reaction barriers in aqueous solution are quite similar for all four processes, the lowest barrier being predicted for the formation of imine **4A**.

Introduction

Reactions of chlorine and chlorinating agents with organic micro pollutants during water treatment procedures can result in different chloramine byproducts,[1] some of them with carcinogenic and/or mutagenic properties.[2] Of special importance are pharmaceuticals and personal care products (PPCP), which have been frequently detected in municipal wastewaters in recent years.[3,4] Upon water chlorination procedures the amine-containing pharmaceuticals undergo rapid reaction with $HOCl/Cl_2$ to form chlorinated compounds, including chloramine derivatives. It has been reported that, for example, β-blocker metoprolol,[5] antibacterial agent sulfamethoxazole,[6] or fluroquinolone antibiotics[7] on treatment with chlorine easily form the corresponding chloramines in surface waters.

These *N*-chloramine derivatives are rather unstable and can undergo rearrangement reactions quite different from the degradation pathways of the parent (not chlorinated) amine-containing pharmaceutical compounds. All rearrangement processes of *N*-chloramines (see Scheme 1),[8] such as Grob fragmentation,[9] elimination (dehydrochlorination),[10] nucleophilic substitution,[11] or N-centered radical formation,[12] may play an important role in the fate of pharmaceutical residues in an aqueous environment. Therefore, a discussion on the environmental risks of nitrogenous pharmaceuticals in chlorinated water must be directed towards the free amino compound as well as its *N*-chloramine derivatives. It has recently been shown that products of the aqueous chlorination of pharmaceuticals can range from "unusual"[13] to "unexpected",[14] but could also be more toxic than the parent compounds.[15]

Recently, we have studied rearrangements of open-shell systems obtained after N–Cl homolysis in *N*-chloropiperidine (Scheme 1).[16] In order to provide a more comprehensive picture of reaction possibilities, the corresponding reactions in the closed-shell piperidine systems are investigated in this work. Piperidine itself represents a suitable model for pharmaceuticals as many of these include this heterocyclic moiety in their structures. In addition to these model studies, important reaction pathways have

[a]*Faculty of Pharmacy and Biochemistry, University of Zagreb, A. Kovacica 1, HR-10000, Zagreb, Croatia. E-mail: valerije@pharma.hr; Fax: +385-1-4856201; Tel: +385-1-6394441*
[b]*Department of Chemistry and Biochemistry, LMU München, Butenandstr. 13, D-81377, München, Germany. E-mail: zipse@cup.uni-muenchen.de*
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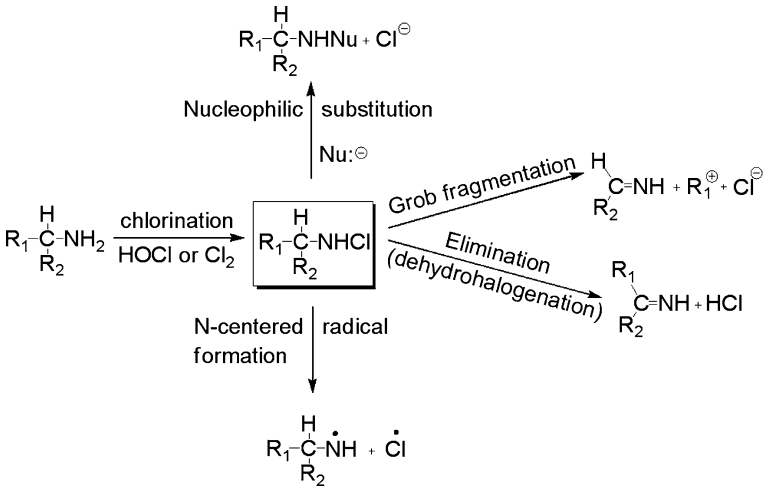
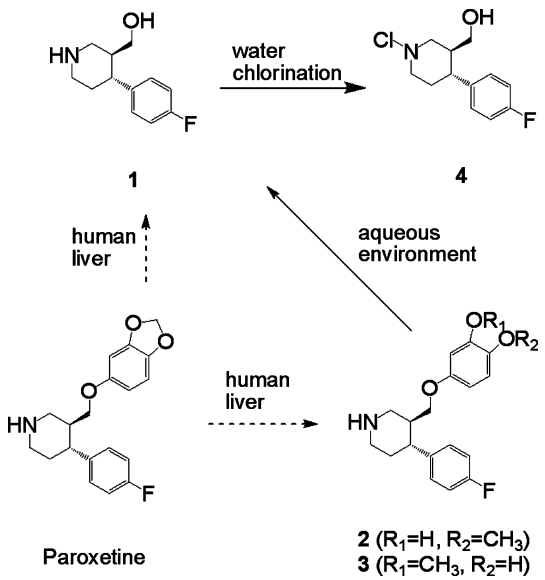


Scheme 1 Different rearrangement reactions in *N*-chloramines.

also been analyzed for the *N*-chlorinated derivative of paroxetine. This antidepressant is an important representative of an emerging group of pharmacologically active 4-aryl piperidines (Scheme 2). Recent studies have shown that paroxetine and its metabolites[17–20] have the potential to accumulate in waste waters,[3,21] but also in the tissue of fish[22] as a result of discharges of this antidepressant into surface waters from municipal wastewater treatment plants. Therefore, interest in conducting the environmental risk assessment of paroxetine continues unabated.[23–27]



Scheme 2 Paroxetine and its metabolites/degradation products.

To properly asses the risk of *N*-chlorinated derivatives of paroxetine, a better understanding of their environmental/chemical fate is imperative. Therefore, we set out to investigate computationally several possible reaction mechanisms that include *N*-chlorinated derivatives of paroxetine, which are relevant to environmental chemistry of this therapeutically important antidepressant.

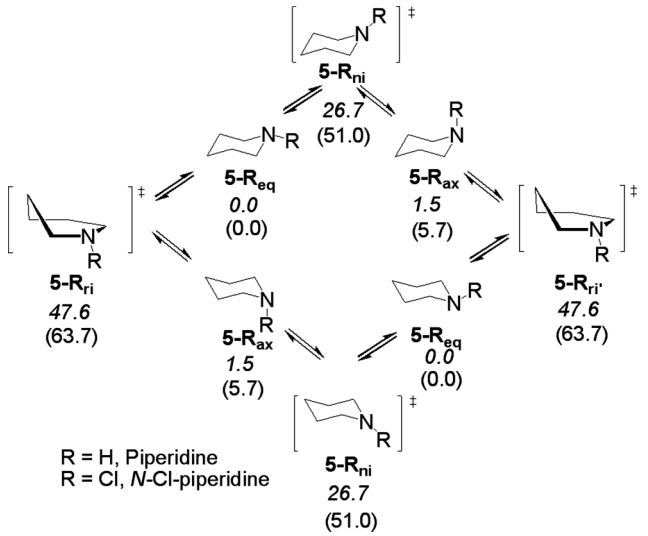
Paroxetine undergoes extensive metabolism in the liver forming three main metabolites (Scheme 2): the product of benzodioxol elimination, (3*S*,4*R*)-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine (**1**), and the two isomers (3*S*,4*R*)-4-(4-fluorophenyl)-3-[3-hydroxy-4-methoxyphenoxy)methyl]-piperidine (**2**) and (3*S*,4*R*)-4-(4-fluorophenyl)-3-[4-hydroxy-3-methoxyphenoxy)methyl]-piperidine (**3**).[28] In the aqueous environment both the parent compound and the two isomers **2** and **3** can undergo[29] cleavage of the ether bond generating the final product **1** (Scheme 2).[30] Therefore, the 4-aryl-piperidine derivative **1** represents the target intermediate which enters the environment where the subsequent degradation processes give rise to different sets of products.[31]

During chlorination of water, the amino compound **1** is converted rapidly and quantitatively to its *N*-chloro derivative **4** (Scheme 2). This *N*-chloramine derivative **4** can undergo various rearrangements (see below) which results in a number of different degradation products. Neither experimental nor computational studies have been published on rearrangement pathways of *N*-chloramine **4**, which could be relevant to the chemical fate of paroxetine in chlorinated water. Quantitative studies have, however, been performed on parent compound *N*-chloropiperidine (**5-Cl**) (Schemes 3 and 4).[32–35]

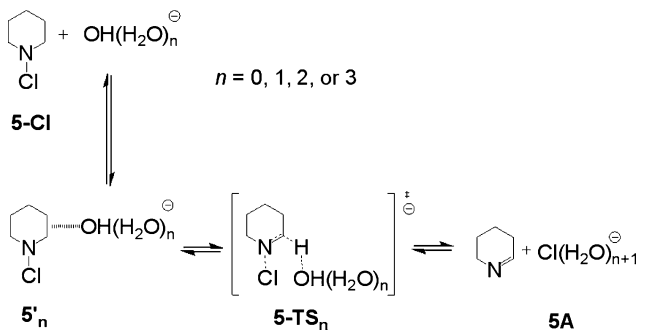
Results and discussion

1. *N*-Chloropiperidine

The performance of a variety of methods for calculating the thermochemistry of different processes in the parent piperidine (**5-H**) and *N*-chloropiperidine (**5-Cl**) was assessed. We use G3B3(+) as our reference procedure in order to evaluate the efficiency of other high-level methods (see ESI†). The accuracy of G3B3(+) has been tested by calculating energy barriers and reaction energies for conformational (ring inversion) and configurational (nitrogen inversion) processes in **5-H** and **5-Cl**. These two processes in piperidines, for which experimental values are known, connect their axial and equatorial (**5-R_{ax}** and **5-R_{eq}**; where R = H or Cl, resp.) forms (Scheme 3). In addition, the energy barrier for base-induced elimination in **5-Cl** has been calculated at G3B3(+) level and compared to the experimental determined reaction barrier. In both cases the combination of G3B3(+) energies with thermochemical corrections calculated at the B3LYP/6-31+G(d)



Scheme 3 Nitrogen and ring inversion processes in piperidine (R = H) and *N*-chloropiperidine (R = Cl). Relative energies (G3B3(+) + ΔG_{solv}; in kJ mol^{-1}) for two chair conformations **5-R$_{eq}$** and **5-R$_{ax}$** and transition state structures **5-R$_{ni}$** and **5-R$_{ri}$** are in italics (piperidine, R = H) and in parentheses (N–Cl-piperidine, R = Cl).



Scheme 4 Reaction pathways calculated for dehydrochlorination in *N*-chloropiperidine.

level and with solvation free energies from CPCM/B3LYP/6-31+G(d) procedure yields results that are in good agreement with experimental values (Table 1). Out of all methods tested (see ESI†), only B2PLYP/aug-def2-TZVPP//B3LYP/6-31+G(d) gives similar results as the G3B3(+) scheme (Table 1). This perturbatively corrected double hybrid functional is quite cost-effective and the calculated results are in line with experimental values. For comparison, the computationally much more demanding MP4/6-31+G(d)//B3LYP/6-31+G(d) method overestimates experimental barriers for conformational inversion processes in **5-H** and **5-Cl**, whereas the energy barrier for dehydrohalogenation in **5-Cl** is somewhat underestimated (Table 1). Therefore, B2PLYP has been used (see below) for energy calculations on paroxetine metabolite **4** and its rearrangement products, which are too large for G3B3(+) composite calculations. The G2 and G3 composite techniques have been used in conjunction with geometry optimizations at DFT level in theoretical studies of a number of elimination processes.[36] The 6-31+G(d) basis set used here is a frequent choice for the description of charged systems[37] and has been employed in recent studies of base-catalyzed reactions.[38]

1.1. Conformational properties. In case of piperidine and *N*-chloropiperidine two possible chair conformations have been located: **5-R$_{ax}$** with the hydrogen (chlorine) atom in axial position and **5-R$_{eq}$** in which hydrogen (chlorine) is equatorial (Scheme 3). In agreement with experimental studies the equatorial conformer was calculated to be more stable in both cases (Table 1).[32,33] The preference for equatorial orientation of chlorine in **5-Cl** is in analogy to the situation in chlorocyclohexane, where the equatorial conformer is preferred over the axial one by 2.2–2.7 kJ mol^{-1}.[39]

In order to undergo fast dehydrochlorination *N*-chloropiperidine must adopt a conformation which allows antiperiplanar elimination of H and Cl (Scheme 3). Indeed, we have calculated (G3B3(+) + ΔG_{solv}) that the energy barrier for *anti*-elimination in **5-Cl$_{ax}$** is 37.1 kJ mol^{-1} lower than the barrier for *syn*-elimination in **5-Cl$_{ax}$** (see ESI†).[40]

Therefore, prior to the elimination step the chlorine atom must be in axial position. This can be achieved by configurational or conformational change **5-Cl$_{eq}$** -> **5-Cl$_{ax}$**, *i.e.* nitrogen inversion or ring inversion process, respectively (Scheme 3). In accord with experimental results we have calculated the nitrogen inversion to be

Table 1 Thermochemical parameters (relative energies in kJ mol^{-1}) calculated for different chemical processes in **5-R** (R = H or Cl) at various levels of theory[a]

		Method[b]				
Chemical Process	Thermochemical parameter	MP4/6-31+G(d) + ΔG_{solv}[c]	MP2(full)/ G3large + ΔG_{solv}[c]	B2PLYP/aug-def2tzvpp + ΔG_{solv}[c]	G3B3(+) + ΔG_{solv}[c]	*Exp.*
5-Cl$_{eq}$ -> **5-Cl$_{ax}$**	ΔG_r at 298.15 K	+8.8	+7.0	+7.7	+5.7	*+6.3*
5-H$_{eq}$ -> **5-H$_{ax}$**		+1.9	+2.1	+1.6	+1.5	*+1.5*
5-Cl$_{eq}$ -> **5-Cl$_{ri}$** -> **5-Cl$_{ax}$**	$\Delta G^{\#}$ (ring inversion) at 298.15 K	+70.3	+64.8	+58.4	+63.7	*+55.4*
5-H$_{eq}$ -> **5-H$_{ri}$** -> **5-H$_{ax}$**		+50.4	+52.0	+45.2	+47.6	*+43.5*
5-Cl$_{eq}$ -> **5-Cl$_{ni}$** -> **5-Cl$_{ax}$**	$\Delta G^{\#}$ (N inversion) at 175.15 K	+57.2	+50.1	+47.1	+51.0	*+49.0*
5-H$_{eq}$ -> **5-H$_{ni}$** -> **5-H$_{ax}$**		+28.5	+26.8	+24.6	+26.7	*+25.5*
5-Cl + OH$^-$(H$_2$O)$_n$ ->	$\Delta H^{\#}$ (elimination) at 298.15 K	+78.3[d]	+96.9[d]	+87.4[d]	+82.5[d]	
5-TS$_n$ -> **5A + Cl$^-$(H$_2$O)$_{n+1}$**[e]		+78.4	+100.1	+88.5	+84.2	*+90.9*
		+81.8	+102.9	+87.2	+87.0	

[a] For a number of different computational methods see ESI.† [b] All energies have been calculated for B3LYP/6-31+G(d) geometries. [c] Solvation energies calculated with CPCM/B3LYP/6-31+G(d) method. Single point energy calculation with continuum model have been performed in the model solvent ε = 8.93 (dichloromethane) for the ring and nitrogen inversions, and in the model solvent ε = 78.4 (water) for elimination reaction. [d] First row, *n* = 1; second row, *n* = 2; third row, *n* = 3. [e] Sum of energies for **5-Cl$_{eq}$** and OH$^-$(H$_2$O)$_n$ set to zero in each case.

the more favorable process.[32,34] The transition state structures **5-Cl$_{ni}$** and **5-Cl$_{ri}$** for nitrogen and ring inversions, respectively, have been located and characterized by imaginary frequencies (see ESI†) which correspond to the respective conformational changes in *N*-chloropiperidine.

1.2. Base-induced elimination. Dilute solutions of *N*-chloropiperidine at alkaline pH are relatively stable. For example, 0.2 mM *N*-chloropiperidine in pH 10 borate buffer decreased only 3% over 24 h at 30 °C.[41] Recently it was found that the energy barrier for dehydrochlorination of N–Cl-piperidine in alkaline aqueous media is $\Delta H^{\#}$(298.15 K) = 90.9 kJ mol^{-1}.[35] We have successfully reproduced this experimental result by using high-level computational models. The energy barrier of 87.0 kJ mol^{-1} (G3B3(+) + ΔG_{solv}) is calculated when base-catalyzed reaction between N–Cl-piperidine and hydroxide ion was considered (Scheme 4). The hydroxide ion as a reactant was represented as a cluster with *n* explicit water molecules (where *n* = 0, 1, 2, or 3) in line with previous studies.[42–44]

If no water is coordinated to hydroxide ion (*n* = 0), the transition state **5-TS$_0$** for E2 reaction could not be located on the corresponding gas-phase PES. This is contrary to the case described for the related *anti*-elimination reaction F^- + cyclohexyl chloride in the gas phase where both reactive complex and transition state are stationary points.[45] In our case only the symmetrical (C_s point group) reactive complex **5′$_0$** has been located as a stationary point, while all other starting geometries converged to the more stable elimination product complex (see ESI†). A relaxed PES scan was performed in order to obtain a constrained geometry of the first-order stationary point, which corresponds to the transition state for elimination. Following the coordinate along the hydroxyl oxygen and β-hydrogen interaction distance (*R*), the transition state **5-TS$_0$** was located at *R* = 1.58 Å. This transition state is less than 6 kJ mol^{-1} above the energy of reactant complex **5′$_0$** and the calculated energy barrier for the elimination reaction is 62.3 kJ mol^{-1} (G3B3(+) + ΔG_{solv}). These results confirm that the calculated PES for elimination without explicit water deviates significantly from experimental values (Scheme 5).

The solvent effects on chemical processes in **5-Cl** are implicitly described by the CPCM/B3LYP/6-31+G(d) continuum method, whereas specific solvent interactions were examined by successive addition of explicit water molecules, followed by optimization of the resulting complex geometries. Water molecules were placed in a variety of locations to sample the different arrays of hydrogen-bonding networks available between N-chloropiperidine and hydroxide cluster $OH^-(H_2O)_n$.[46] Several water configurations for reactive complexes **5′$_n$** were located in each case where *n* = 1, 2, or 3. For example, in the case of the reactive complex with one explicit water (**5′$_1$**) four different minima were located (see more details in ESI†). The number of possible configurations increases with increasing number of water molecules (*n*) in hydroxide cluster $OH^-(H_2O)_n$, but only the most stable structures were considered in this study.

When solvated (by using CPCM/B3LYP/6-31+G(d) model) all reactive complexes **5′$_n$**, consisting of either one, two, or three (*n* = 1, 2, or 3) discrete water molecules interacting with incoming OH^-, become energetically very unfavorable relative to separated reactants (Scheme 5). For example, reactive complex **5′$_3$** is 42.7 kJ mol^{-1} less stable than the separated reactants **5-Cl** and $OH^-(H_2O)_3$. Therefore, these complexes are not relevant in the calculation of energy barriers for elimination reactions in *N*-chloropiperidine in water. The calculated reaction barriers for hydrochloride elimination indicate that at least one water molecule must be included explicitly for an optimal approximation of the first solvation shell, while the resulting cluster is solvated by a dielectric continuum (CPCM model; ε = 78.4) to take into account the bulk effect of water.[47] The corresponding transition state **5-TS$_1$** for E2 reaction (Fig. 1) is located +87.4 kJ mol^{-1} (B2PLYP/def2-aug-TZVPP//B3LYP/6-31+G(d) +ΔG_{solv}) above the separate reactants **5-Cl** and $OH^-(H_2O)_1$, suggesting that this model is adequate to reproduce the experimental result ($\Delta H^{\#}_{298}$ = +90.9 kJ mol^{-1}).

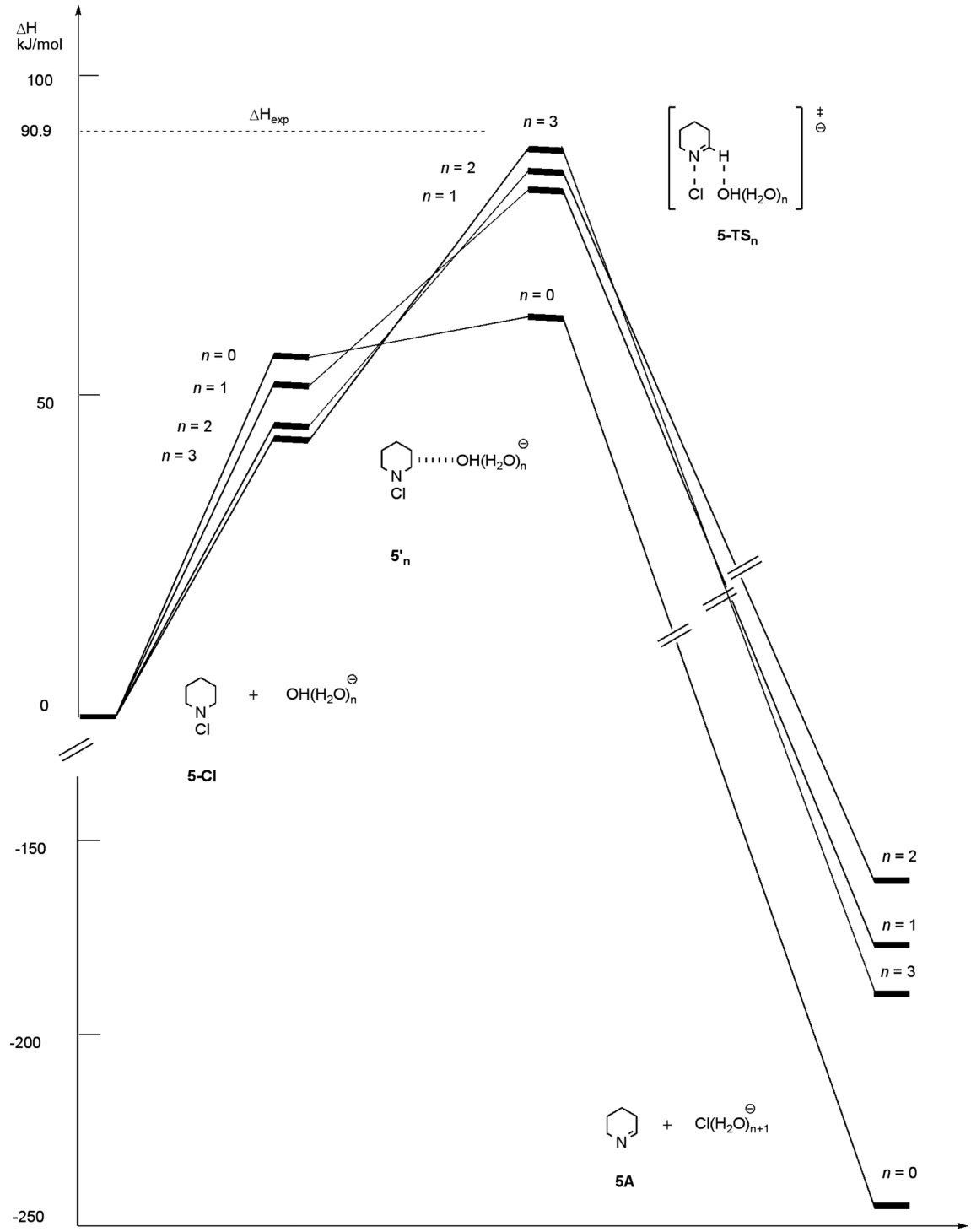
To summarize this part, prior to the elimination step *N*-chloropiperidine **5-Cl$_{eq}$** undergoes configurational change (most probably pyramidal nitrogen inversion) to conformer **5-Cl$_{ax}$**, which is more suitable for base–promoted E2 elimination. Transition states **5-TS$_n$** (where *n* = 0, 1, 2, or 3) for 1,2-elimination are reached by making/breaking four bonds between five atomic centers in a concerted fashion (Fig. 1). The final products of these exothermic reactions (ΔH_{298} is between –162.7 and –244.1 kJ mol^{-1}, depending on number *n*; see Scheme 5) are piperideine (**5A**) and chloride ion represented as water cluster $Cl^-(H_2O)_{n+1}$.[48] Both the configurational/conformational equilibrium **5-Cl$_{eq}$** <-> **5-Cl$_{ax}$** and the subsequent elimination reaction **5-Cl$_{ax}$** -> **5-TS$_n$** -> **5A** are correctly described by the hybrid cluster-continuum method employed in this study.

2. *N*-Chloro-3-(hydroxymethyl)piperidine

The agreement between experimental and computational results for *N*-chloropiperidine (for which both stereochemical and elimination processes were examined) suggests that the same computational approach can be applied to model the analogous dehydrochlorination reaction in chloramine **6** and in the targeted paroxetine metabolite **4** (see below).

Introduction of the hydroxymethyl group at C3-position of the piperidine ring (the same structural motif is incorporated in **4**, see below) significantly reduces the energy barrier for the dehydrochlorination process. At the G3B3(+) (+ ΔG_{solv}) level the calculated enthalpy of activation is 70.5 kJ mol^{-1} (Table 2), which is 12 kJ mol^{-1} less than the barrier (**5-Cl$_{eq}$** + $OH^-(H_2O)$ -> **5-TS$_1$** -> **5A**) calculated for elimination of HCl from N-chloropiperidine (a closely similar energy barrier difference of 11.5 kJ mol^{-1} is obtained by using the B2PLYP/aug-def2-TZVPP + ΔG_{solv} model). Therefore, due to the presence of the –OH substituent in **6** a significant rate enhancement of the elimination process can be expected. This is in agreement with earlier experimental findings, where a dramatic acceleration of the decomposition process in *N*-chlorinated carbinolamines, in comparison to N-chlorinated amines lacking the hydroxyl moiety, has been observed.[50]

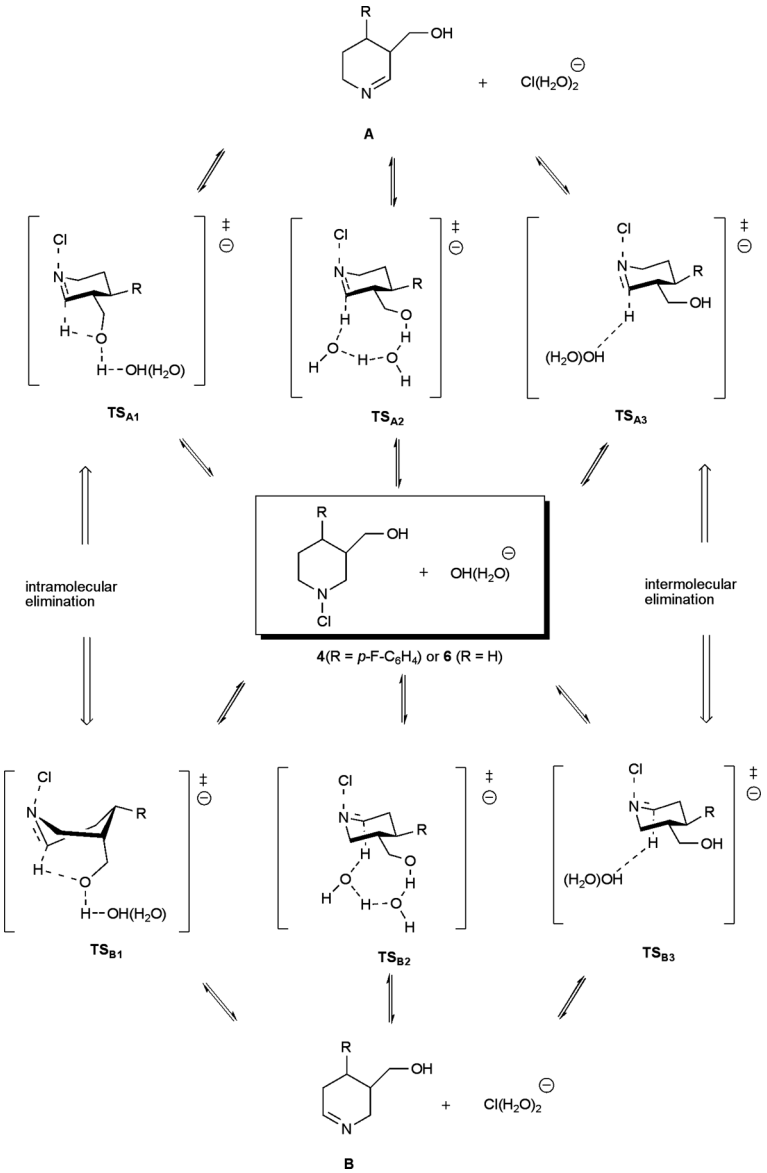
Due to the introduction of the hydroxymethyl group in the piperidine ring system the elimination reaction mechanism becomes more complex. Several different reaction pathways can, in principle, be operative as illustrated in Scheme 6. In order to find out whether an intermolecular (water-assisted Zaitsev-type elimination) or an intramolecular mechanism is favored in dehydrochlorination of **6**, we have attempted to locate transition structures for both reaction channels. Four corresponding



Scheme 5 Schematic potential energy profile (G3B3(+) + ΔG_{solv}) for dehydrochlorination in N-chloropiperidine (**5-Cl$_{eq}$**).

transition states were successfully found: **6-TS$_{A1}$** and **6-TS$_{B1}$**, in which the β-hydrogen atom at either C2- or C6-position, respectively, is transferred directly to the oxygen atom of hydroxymethyl group (intramolecular mechanism); and **6-TS$_{A3}$** and **6-TS$_{B3}$**, in which an explicit water molecule is directly (analogously to the case of **5-Cl**; see Fig. 1) involved in the removal of the β-hydrogen atom at C2- or C6-position, respectively (intermolecular mechanism).

In structure **6-TS$_{A1}$** (and **6-TS$_{B1}$**) two water molecules are hydrogen bonded to the $-CH_2OH$ group (Fig. 2), but none is directly involved in the removal of the β-hydrogen atom, whereas in **6-TS$_{B3}$** (and **6-TS$_{A3}$**) no direct interaction between C3-hydroxymethyl group and $OH^-(H_2O)$ cluster is present. Out of these four structures the transition state **6-TS$_{A1}$** for intramolecular elimination has been calculated as the most stable (Table 2). In



Scheme 6 Three different base-promoted elimination mechanisms examined in N-chlorinated compounds **4** and **6**.

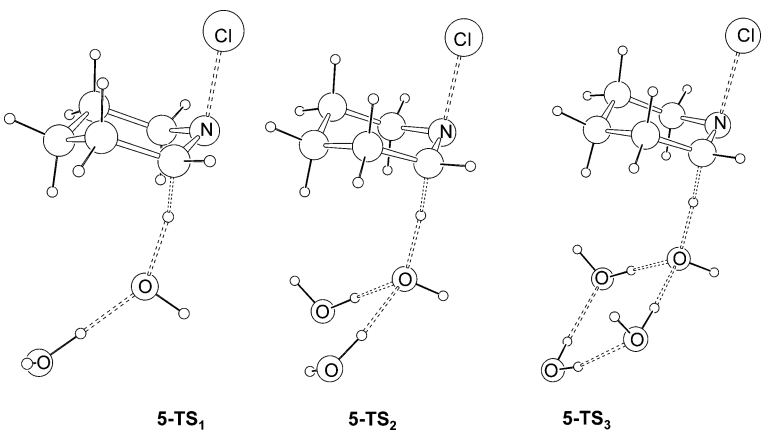


Fig. 1 B3LYP/6-31+G(d) optimized transition state structures for reaction (*anti*-elimination) between *N*-chloropiperidine and hydroxide cluster $OH^-(H_2O)_n$ where $n = 1$, 2, or 3. Only the most stable structures for each case are shown.

Table 2 Relative energies ΔH (in kJ mol^{-1}; at 298.15 K) for stationary points in the elimination processes of **6**, calculated at different levels of theory[a]

Structure[b]	B3LYP/6-31+G(d) $+\Delta G_{solv}$[c]	B2PLYP/aug-def2-TZVPP $+\Delta G_{solv}$[c]	G3B3(+) $+\Delta G_{solv}$[c]
$\mathbf{6}_{eq}$	0.0[d]	0.0[d]	0.0[d]
6-TS$_{A1}$	+50.2	+75.5	+77.1
6-TS$_{B1}$	+65.1	+88.5	+83.0
6-TS$_{A2}$	+57.6	+78.7	+74.0
6-TS$_{B2}$	+51.1	+75.8	+70.5
6-TS$_{A3}$	+68.4	+86.8	+80.7
6-TS$_{B3}$	+70.8	+88.9	+82.5
6A	−243.8	−243.9	−197.8
6B	−250.9	−249.6	−203.4

[a] All energies have been calculated for B3LYP/6-31+G(d) geometries. [b] Only lower energy isomers were included. [c] Solvation energies calculated with CPCM/B3LYP/6-31+G(d) method. Single point energy calculation with continuum model have been performed in the model solvent $\varepsilon = 78.4$ (water). [d] Sum of energies for $\mathbf{6}_{eq}$ and $OH^-(H_2O)$ set to zero.

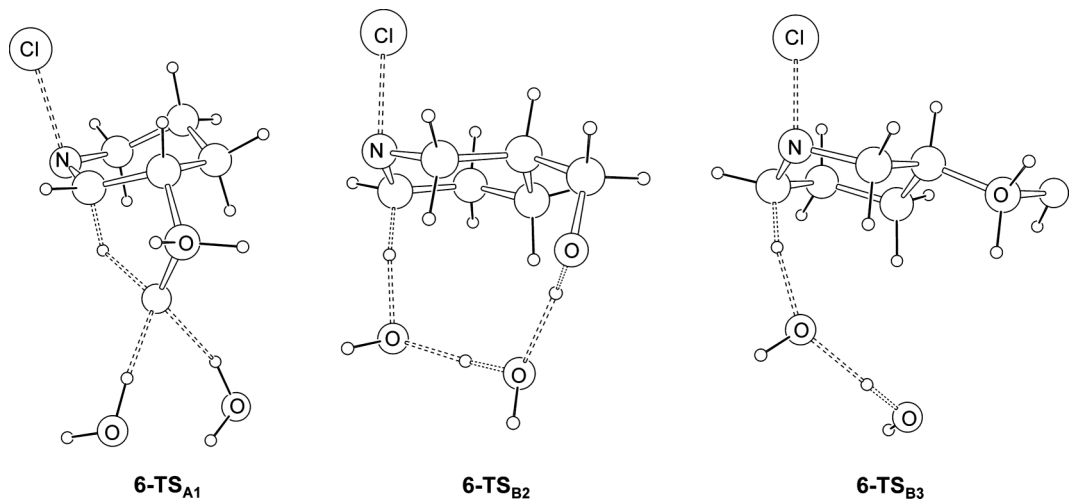


Fig. 2 B3LYP/6-31+G(d) optimized transition state structures for intramolecular (**6-TS$_{A1}$** and **6-TS$_{B2}$**) and intermolecular mechanism (**6-TS$_{B3}$**) for dehydrochlorination of *N*-chloro-3-hydroxymetyl-piperidine (**6**).

accordance with earlier experimental and computational studies, intramolecular dehydrohalogenation is thus the most favorable decomposition pathway in alkaline aqueous chemistry of β-carbinolamines.[50,51]

In addition, we have located two more transition structures **6-TS$_{A2}$** and **6-TS$_{B2}$** for elimination in which explicit water molecules are inserted between the hydroxymethyl group and β-hydrogen atom (C2-H or C6-H, resp.) forming 9- or 11-membered ring structures, respectively (Fig. 2). Interestingly, these transition structures have been calculated (at the G3B3(+) level) to be more stable than **6-TS$_{A1}$**, suggesting that this "bridging" mechanism of elimination could also be operative.

In conclusion, at least three different modes of water assistance are possible in elimination processes in **6**: the one, in which water is directly involved in elimination of C6-hydrogen atom (intermolecular elimination); the mechanism, in which water molecules are hydrogen bonded to hydroxymethyl group (intramolecular elimination); and the "bridging" mechanism, in which water assists the elimination step by forming nine- or eleven-membered rings in the corresponding transition state structures **6-TS$_{A2}$** and **6-TS$_{B2}$**, respectively.

3. *N*-Chloro-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine

For the smaller systems studied here (**5-Cl** and **6**), we have shown that a combination of solvent continuum model (CPCM) and one explicit water molecule is sufficient to properly describe the water-assisted rearrangement of *N*-chlorinated compounds in basic aqueous media. Since the G3B3(+) approach is too expensive for paroxetine metabolite **4**, the final energy calculations for all structures are performed by using MP4(FC)/6-31+G(d)//B3LYP/6-31+G(d) and B2PLYP/aug-def2-TZVPP//B3LYP/6-31+G(d) models. The latter method produces energies very similar to those obtained at G3B3(+) level, which themselves have been tested against experimental results (see Table 1).

Several base-promoted processes have been observed in the aqueous decompositions of *N*-chlorinated alcoholamines including pharmaceuticals.[13,49] The two main reaction paths were found to be intramolecular dehydrohalogenation and Grob fragmentation.[50–52] As the *N*-chloramine **4** cannot undergo Grob-like fragmentation, the intramolecular dehydrochlorination is the most feasible rearrangement mechanism in an alkaline aqueous environment (see Scheme 5). It has been shown earlier that bimolecular eliminations, in which OH^- assists in base-promoted

eliminations, are much slower processes in comparison to intramolecular dehydrohalogenations, in which a free hydroxyl group catalyzes the reaction.

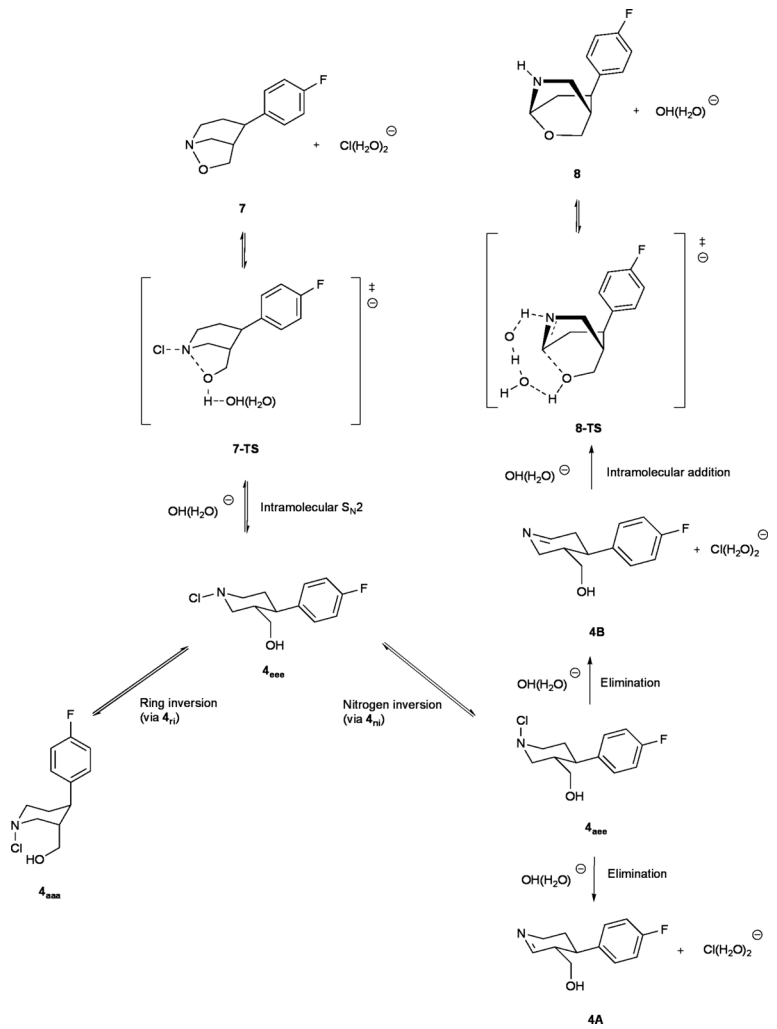
The fact that the hydroxyl group of (N–Cl)-alcoholamine **4** is relatively acidic allows the possibility of an intramolecular elimination, *i.e.* an abstraction of a β-hydrogen atom would take place following a pre-equilibrium deprotonation of the hydroxyl group of the alcoholamine.

Again, a hybrid cluster-continuum model suitable to describe intramolecular dehydrochlorination in **4** has been used to perform a detailed analysis of all possible reaction pathways (Schemes 6 and 7).

A similar competition between ring and nitrogen inversion in *N*-chlorinated piperidine systems has recently been described in the course of azasugar synthesis. It has been shown that regioselective dehydrochlorination of *N*-chloropiperidine azasugars is controlled by the switchable configuration at the chloramine nitrogen atom.[53] The importance of detailed mechanistic and stereochemical insights in dehydrochlorination reactions has also been shown in the case of *N*-chlorinated macrolide antibiotics.[54,55] It has been found that the relative rate of dehydrochlorination reaction may well depend on the conformational properties of 6-membered ring systems, in which both hydroxyl and chlorinated amino groups are located.

Elimination pathways in **4** can be described using the same mechanistic scheme already used for chloramine **6** (Scheme 6). Three different mechanisms of dehydrochlorination were considered: intermolecular, in which the hydroxide/water complex is directly involved in removal of β-hydrogen atom; intramolecular, in which deprotonation is assisted directly by the hydroxymethyl group at C-3; and the bridged mechanism, in which water molecules are inserted in between hydroxymethyl group and β-hydrogen atom (either C2-H or C-3 H atom). For each mechanism the corresponding transition state structures could successfully be located (Fig. 3).

It is found that dehydrochlorination in paroxetine metabolite **4** is 15.3 kJ mol^{-1} more favorable than the analogous process in parent *N*-chloropiperidine (**5-Cl**), but 8 kJ mol^{-1} less favorable than the elimination in **6** (at B2PLYP level). Similar to **6**, intramolecular processes, in which the C3-hydroxymethyl group is involved in elimination of β-hydrogen atom, are more favorable than intermolecular dehydrochlorination. The most important



Scheme 7 Conformational (ring inversion), configurational (nitrogen inversion), two elimination and two cyclization processes (intramolecular addition and S_N2 reactions) considered for paroxetine metabolite **4**.

Table 3 Relative energies ΔH (in kJ mol^{-1}; at 298.15 K) for stationary points in rearrangement processes of **4**, calculated at different levels of theory[a]

Structure[b]	B3LYP/6-31+G(d) $+\Delta G_{solv}$[c]	MP4/6-31+G(d) $+\Delta G_{solv}$[c]	B2PLYP/aug-def2-TZVPP $+\Delta G_{solv}$[c]
$\mathbf{4}_{eee}$	0[d]	0[d]	0[d]
$\mathbf{4}_{aee}$	+12.0	+10.5	+11.0
$\mathbf{4}_{aaa}$	+32.1	+34.4	+30.4
$\mathbf{4}_{ni}$	+54.7	+65.5	+58.1
$\mathbf{4}_{ri}$	+53.2	+57.0	+56.4
4-TS$_{A1}$	+53.6	+62.0	+78.9
4-TS$_{B1}$	+86.0	+92.3	+109.0
4-TS$_{A2}$	+55.2	+62.8	+79.2
4-TS$_{B2}$	+56.2	+58.0	+80.6
4-TS$_{A3}$	+79.6	+77.1	+99.0
4-TS$_{B3}$	+79.4	+79.0	+99.7
4A	−245.7	−223.7	−234.7
4B	−251.2	−231.1	−239.9
7-TS	+72.9	+67.2	+94.5
7	−108.7	−88.0	−94.2
8-TS	+99.0[e]	+69.5[e]	+93.1[e]
8	−241.8	−227.9	−228.0

[a] All energies have been calculated for B3LYP/6-31+G(d) geometries. [b] Only lower energy isomers were included. [c] Solvation energies calculated with CPCM/B3LYP/6-31+G(d) method. Single point energy calculation with continuum model have been performed in the model solvent $\varepsilon = 78.4$ (water). [d] Sum of energies for $\mathbf{4}_{eee}$ and $OH^-(H_2O)$ set to zero. [e] Relative to sum of energies for reactants **4B** and $OH^-(H_2O)$.

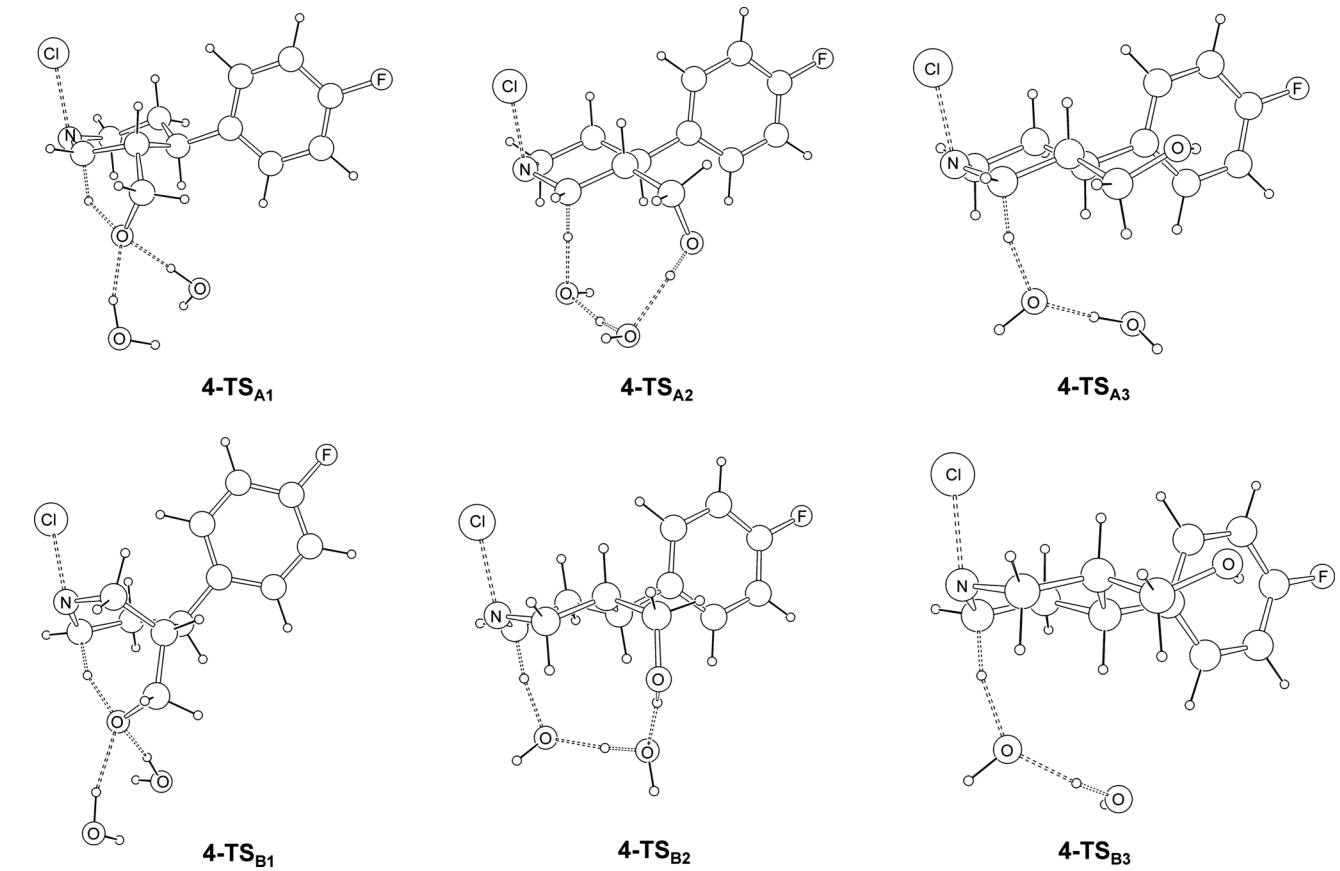


Fig. 3 B3LYP/6-31+G(d) optimized transition state structures for intramolecular (**4-TS$_{A1}$** and **4-TS$_{B1}$**), "bridging" (**4-TS$_{A2}$** and **4-TS$_{B2}$**), and intermolecular mechanism (**4-TS$_{A3}$** and **4-TS$_{B3}$**), for dehydrochlorination of **4**.

reaction channel for intramolecular *anti*-elimination $\mathbf{4}_{aee}$ -> **4TS$_{A1}$** -> **4A** was calculated to be 20 kJ mol^{-1} kinetically more favorable than intermolecular processes $\mathbf{4}_{aee}$ -> **4TS$_{A3}$** -> **4A** or $\mathbf{4}_{aee}$ -> **4TS$_{B3}$** -> **4B**. Formation of imines **4A** and **4B** is exothermic, with the latter imine being slightly more stable (Table 3).

It is well-known that imines undergo fast reaction with water, resulting in a number of different hydrolysis products.[8] Therefore, it is expected that both imines **4A** and **4B** undergo hydrolysis to give the expected products with free amino and aldehyde functionality. It is also known that imines can undergo trimerization process

resulting in cyclic products,[56] and in the protic solvent the equilibrium between trimers and monomers is promoted.[57,58]

In addition, two rearrangement pathways were considered (Scheme 7): isoxazolidine **7** formation directly from $\mathbf{4}_{eee}$, and oxazinane **8** formation from $\mathbf{4}_{aee}$ (*via* imine **4B**). The first reaction is an intramolecular S_N2 reaction, in which cyclized product **7** is formed. The second reaction starts with an intramolecular attack of the hydroxyl group on imine **4B** resulting in oxazinane product **8** (similar in energy of imines **4A** and **4B**, see Table 3). The cyclization **4B** -> **8** is accompanied by proton transfer from the hydroxyl group to the nitrogen atom. At the B2PLYP level the formation of oxazinane **8** is endothermic by 12 kJ mol^{-1} (Table 3). It has recently been shown than this type of oxazinane product is also relevant in cytochrome P450-catalazyed transformations of imine metabolites of some pharmaceuticals.[59]

Our preliminary results on base-catalyzed rearrangements of radicals derived from paroxetine metabolite **4** suggest that some reactions of open-shell systems are less likely, at least under basic conditions.[60] For example, the calculated energy barriers for hydrogen migrations, analogous to those we have described earlier,[16] are *ca*. 20 kJ mol^{-1} higher than the barriers for elimination processes studied here. It is in agreement with findings that neutral piperidine radical, which exists in basic medium, is kinetically more stable than its protonated form (becomes dominant at lower pH). Therefore, the protonation of neutral aminyl radicals can strongly affect its reactivity.[61] In order to explore the reactivity of open-shell systems in acidic media, the rearrangements of paroxetine-derived radical cations should be considered as well.

In conclusion, four different degradation products of paroxetine metabolite **4** are predicted by the current theoretical studies: imines **4A** and **4B**, and two cyclized products isoxazolidine **7** and oxazinane **8**. It is likely that formation of these products can be expected in aqueous environment as well. We are not aware that these products have been considered in earlier environmental risk assessments of paroxetine. The fruitful interplay between theory and experiment supports the idea that reaction mechanisms, which are important for the chemical fate of environmentally relevant chloramines such as **4**, could be successfully modeled by computational techniques. We believe that computational results on possible reaction pathways in *N*-chlorinated metabolites **4** and **6** could be relevant for studies of the chemical/environmental fate of the vast array of nitrogen-containing pharmaceuticals, which have been frequently detected in municipal wastewaters as potent toxicants.

Computational details

All geometries have been optimized at B3LYP/6-31+G(d) level[62] of theory with Gaussian 03, Revision D.01.[63] Thermochemical corrections to enthalpies at 298.15 K have been calculated at the same level of theory using the rigid rotor/harmonic oscillator model. Improved energetics have been calculated using a modified G3B3 scheme, termed here as G3B3(+), where we used geometry optimization at the B3LYP/6-31+G(d) level instead of the standard protocol at the B3LYP/6-31g(d). The general expression of the total G3B3 energy has not been changed from its original form.[64,65] Single point energies at the B2PLYP/aug-def2-TZVPP level[66] have been calculated using the program package ORCA.[67] Solvation free energies have been determined at CPCM/B3LYP/6-31+G(d) level.[68,69]

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