

# Ab initio study of oxygen atom transfer from hydrogen peroxide to trimethylamine†

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**Unlike what has been theoretically proposed for ammonia oxidation with hydrogen peroxide, trimethylamine oxidation occurs with a concerted mechanism, which is favored even when an explicit water molecule is added or continuum solvent (water) is simulated.**

Tertiary amines can be oxidised to their corresponding *N*-oxides using a large variety of oxidants, one of the most widely used of which is hydrogen peroxide. However, despite the simplicity of this reaction, there is a lack of published *ab initio* calculations of oxygen transfer from hydrogen peroxide to tertiary amines.

By means of such calculations, Bach *et al.* have extensively studied the transfer of an oxygen atom from organic and inorganic peroxy acids,<sup>1</sup> dioxiranes,<sup>2</sup> hydroperoxides<sup>3</sup> and hydrogen peroxide<sup>4</sup> to a broad array of substrates (reactions which involve the cleavage of an oxygen–oxygen  $\sigma$  bond), but the *N*-oxidation of tertiary amines by means of hydrogen peroxide is still not completely understood. Such an understanding would be extremely useful because this reaction can be considered a model for its biological counterpart, which involves the hydroperoxy-enzymes that are currently the subject of intense fundamental and applied research.<sup>5</sup>

Bach has also reported that the oxidation of ammonia by hydrogen peroxide is a 2-step process dominated by a 1,2-hydrogen shift, which is followed by a simple  $S_N2$ -like displacement to afford  $H_3NO$  and water: *i.e.* the transition state seems to be controlled by the formation of the water oxide ( $H_2OO$ ) during the reaction.<sup>4b</sup> Furthermore, investigation of the role of solvation showed that a molecule of water stabilised the transition state. This differs from the generally accepted mechanism,<sup>6</sup> which assumes that hydrogen peroxide is attacked by the substrate with a direct nucleophilic displacement of the  $\beta$ -peroxy oxygen. In this study, we investigated this last mechanism by means of *ab initio* calculations, using the model reaction of trimethylamine (TMA) oxidation to the corresponding *N*-oxide (TMAO).

Table 1 shows the optimised geometries and related energies of the reactant complex (TMA– $H_2O_2$ ), transition state (TS-1) and product complex (TMAO– $H_2O$ ) obtained using the 6-31+G\* basis set at different levels of theory.<sup>7</sup> The TMA– $H_2O_2$  complex was obtained through the hydrogen bond between the hydrogen of  $H_2O_2$  and the TMA nitrogen. Differences in geometry (mainly in the torsion angle  $\angle HOOH$ ) and energy can be found using HF, B3LYP or MP2 calculations. Significant differences in energy were also found in TS-1, which had only one negative eigenvalue in the Hessian matrix, and  $\Delta E$  values ranging from 72.24 kcal mol<sup>-1</sup> (HF) to 36.86 kcal mol<sup>-1</sup> (B3LYP). Initial TS-1 geometries were obtained from several relaxed PES scans and refined with the eigenvalue-following methodology. It has been reported that the activation energy involved in the oxidation of ammonia by means of water oxide is regulated by the formation of the water oxide itself (56 kcal mol<sup>-1</sup> MP4SDTQ/6-31G\*/MP2/6-31G\*),<sup>4a</sup> but our calcu-

lated activation barriers were in the range of 36–39 kcal mol<sup>-1</sup> for B3LYP and MP2 (without ZPE), and thus far below the energy of water oxide formation. This suggests a concerted mechanism for the oxidation of TMA by means of hydrogen peroxide. Another important aspect for all of the transition states (TS-1) is that the hydrogen is not partially shifted towards the distal oxygen as in the concerted transition state mechanism found by Bach in the case of the oxidation of ammonia.<sup>4a</sup>

In our calculations, the 1,2-hydrogen shift occurs with the transfer of oxygen by cleavage of the O–O bond after the activation barrier is crossed. This was also demonstrated by far-reaching intrinsic reaction coordinate (IRC) calculations along the reaction pathway.<sup>8</sup>

In the TMAO– $H_2O$  complex, the water was in staggered disposition to the methyl group in TMAO and had a strong hydrogen bond ( $\sim 10$  kcal mol<sup>-1</sup> for each case), as has already been shown for the TMAO– $H_2O$  complex.<sup>9</sup>

Oxidations with hydrogen peroxide are typically carried out in aqueous solution, and so specific solvent effects were calculated including one explicit water molecule. The transition state (TS-2) parameters (together with the TMA– $H_2O_2$ – $H_2O$  and TMAO– $H_2O$ – $H_2O$  complexes) are summarised in Table 2.

**Table 1** Optimized geometries and energies for the *N*-oxidation of TMA with  $H_2O_2$  (6-31+G\* basis set)

	HF	B3LYP	B3LYP <sup>a</sup>	MP2 <sup>b</sup>
TMA– $H_2O_2$				
<i>R</i> (OO) <sup>c</sup>	1.398	1.462	1.459	1.481
<i>R</i> (NO)	2.914	2.790	2.770	2.770
<i>R</i> (NH)	1.953	1.787	1.759	1.769
$\angle$ NOO <sup>d</sup>	100.3	98.0	100.4	92.8
$\angle$ HOOH	–116.9	–122.9	–105.6	–126.8
<i>E</i> <sup>e</sup>	–324.05650	–326.04573	–326.04815	–325.00570
<i>E</i> <sub>ZPE</sub> <sup>f</sup>	0.16123	0.14982	0.14984	0.15212
TS-1				
<i>R</i> (OO)	1.915	2.018	2.016	2.010
<i>R</i> (NO)	1.759	1.826	1.834	1.762
$\angle$ NOO	164.2	161.1	170.3	164.5
$\angle$ HOOH	–122.0	–120.2	–125.8	–123.0
Frequencies <sup>g</sup>	984i	775i	421i	1147i
<i>E</i>	–323.94138	–325.98699	–326.00338	–324.94305
<i>E</i> <sub>ZPE</sub>	0.15723	0.14982	0.14684	0.14801
$\Delta E$ <sup>h</sup>	72.24	36.86	28.10	39.31
$\Delta E$ <sub>IR</sub> <sup>i</sup>	64.42	26.65	18.03	26.23
TMAO– $H_2O$				
<i>R</i> (OO)	2.794	2.711	2.717	2.726
<i>R</i> (NO)	1.369	1.384	1.384	1.387
$\angle$ NOO	105.1	99.5	142.3	98.4
<i>E</i>	–324.09258	–326.08734	–326.08493	–325.04795
<i>E</i> <sub>ZPE</sub>	0.16225	0.15100	0.15031	0.15356

<sup>a</sup> In bulk solvent (water). <sup>b</sup> MP2 frozen core. <sup>c</sup> Bond lengths in Å. <sup>d</sup> Angles in deg. <sup>e</sup> Total energy in hartree with geometry optimized at the level indicated. <sup>f</sup> Zero-point energies in hartree. <sup>g</sup> Frequencies in cm<sup>-1</sup>. <sup>h</sup> Relative energy in kcal mol<sup>-1</sup>. <sup>i</sup> Energies relative to the isolated reactants in kcal mol<sup>-1</sup>.

† Electronic supplementary information (ESI) available: transition state structures and experimental data. See <http://www.rsc.org/suppdata/cc/b1/b104902j/>

**Table 2** Optimized geometries and energies for the *N*-oxidation of TMA with H<sub>2</sub>O<sub>2</sub> in the presence of one water molecule (6-31+G\* basis set)

	HF	B3LYP	MP2 <sup>a</sup>
TMA–H <sub>2</sub> O <sub>2</sub> –H <sub>2</sub> O			
<i>R</i> (OO) <sup>b</sup>	1.396	1.456	1.472
<i>R</i> (NH)	1.924	1.749	1.736
∠NOO <sup>c</sup>	104.8	106.0	103.9
∠HOOH	–109.3	–107.9	–126.8
<i>E</i> <sup>d</sup>	–400.08350	–402.48018	–401.22984
<i>E</i> <sub>ZPE</sub> <sup>e</sup>	0.18721	0.17457	0.17702
TS-2			
<i>R</i> (OO)	1.899	2.090	2.014
<i>R</i> (NO)	1.761	1.724	1.701
<i>R</i> (HB <sub>OH</sub> –water)	1.928	1.828	1.867
<i>R</i> (HB <sub>water</sub> –OH)	1.747	1.570	1.654
∠NOO	170.9	165.5	165.8
∠HOOH	–124.1	–114.8	–116.6
Frequencies <sup>f</sup>	883i	359i	623i
<i>E</i>	–399.98506	–402.43481	–401.18062
<i>E</i> <sub>ZPE</sub>	0.18597	0.17264	0.17533
Δ <i>E</i> <sup>g</sup>	61.77	28.47	30.89
Δ <i>E</i> <sub>IR</sub> <sup>h</sup>	48.18	10.81	8.79
TMAO–H <sub>2</sub> O–H <sub>2</sub> O			
<i>R</i> (OO)	2.760	2.671	2.692
<i>R</i> (NO)	1.367	1.385	1.387
∠NOO	122.7	118.9	118.4
<i>E</i>	–400.12549	–400.51944	–401.27841
<i>E</i> <sub>ZPE</sub>	0.18915	0.17619	0.17897

<sup>a</sup> MP2 frozen core. <sup>b</sup> Bond lengths in Å. <sup>c</sup> Angles in deg. <sup>d</sup> Total energy in hartree with geometry optimized at the level indicated. <sup>e</sup> Zero-point energies in hartree. <sup>f</sup> Frequencies in cm<sup>–1</sup>. <sup>g</sup> Relative energy in kcal mol<sup>–1</sup>. <sup>h</sup> Energies relative to the isolated reactants in kcal mol<sup>–1</sup>.

The geometric and energy parameters obtained from the optimised structures indicate the presence of hydrogen bonds.

Comparing the energies obtained from the optimised TMA–H<sub>2</sub>O<sub>2</sub> and TMA–H<sub>2</sub>O<sub>2</sub>–H<sub>2</sub>O complexes with those of the isolated reactants, the energy of the water-induced hydrogen bond stabilisation was 6–9 kcal mol<sup>–1</sup>, and further increased in the transition state: the Δ*E* values for TS-2 were 8–10 kcal mol<sup>–1</sup> below the TS-1 values. The overall barrier from the isolated reactants was also reduced by about 16–20 kcal mol<sup>–1</sup> (Δ*E*<sub>IR</sub> in Tables 1 and 2) by the action of one molecule of water.

TS-2 optimisation and IRC indicated that the water molecule did not act as a proton relay, but was involved in a relatively strong hydrogen bond linking the complex. This finding is very important because it excludes the alternative mechanism of the 1,4-hydrogen shift that has been proposed for ammonia oxidation *via* hydrated water oxide.<sup>4b</sup> The 1,4-shift barrier for hydrated water oxide at MP4SDTQ/6-31G\*//MP2/6-31G\* was 37.4 kcal mol<sup>–1</sup>,<sup>4b</sup> whereas we calculated a barrier of 30.89 kcal mol<sup>–1</sup> for TS-2 at MP2/6-31+G\*. These results suggest that the concerted mechanism is preferred even when one molecule of water is added.

We also studied the effect of a continuum bulk solvent, and analysed its consequences on the geometric and energetic characteristics of the reaction. Our attempts to calculate the bulk solvent effect using polarised continuum model (PCM) approaches were unsuccessful,<sup>10</sup> and so we adopted the Onsager model.<sup>11</sup> The results obtained at the B3LYP level (summarised in italics in Table 1) show that the solvent induced only small geometric changes. The main effect was a decrease in the imaginary frequency associated with the transition state, which indicates that this is significantly looser in aqueous solution than in the gas phase. Despite the small difference between some of the geometric parameters optimised in the gas phase

and solution, there was a significant difference in the implied energy. Comparison of the energy in the gas phase and solution clearly showed that the transition state was stabilized (8.62 kcal mol<sup>–1</sup>) as a result of the electrostatic effect of the solvent. On the other hand, the TMA–H<sub>2</sub>O<sub>2</sub> complex was destabilized by 0.15 kcal mol<sup>–1</sup> and the TMAO–H<sub>2</sub>O complex stabilized by 2.47 kcal mol<sup>–1</sup>.

Comparison of the optimised structures in bulk solvent and with one explicit water molecule revealed that the geometric differences were mainly localised to the transition state and, to a lesser extent, to the product complex: *e.g.* in the transition state, the N–O distance was lengthened in solution by 0.110 Å and the O–O bond simultaneously shortened by 0.07 Å.

In brief, unlike what has been proposed for ammonia, our results show that the 1,2-hydrogen shift follows the oxygen transfer in the case of TMA oxidation by means of hydrogen peroxide. The concerted mechanism was favoured at the studied theoretical levels even when an explicit water molecule was added or continuum water was simulated.

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