Self-aggregation as a source of chiral discrimination

Ibon Alkorta *, Krzysztof Zborowski 1, José Elguero

Instituto de Química Médica (C.S.I.C.), CIJuan de la Cierco, 3 28006, Madrid, Spain

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Abstract

A theoretical study of the hydrogen peroxide clusters, (HOOH),n, from 2 to 10 monomers, has been carried out using DFT/B3LYP and MP2 ab initio methods. The results show that for n = 2 and 3, the cluster with mixed chirality is preferred while for larger clusters, the homochiral cluster is favoured. The Optical Rotatory Power and Vibrational Circular Dichroism spectra of some of the systems have been calculated and analyzed.

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1. Introduction

Chirality is present in the two main building blocks of nature (aminoacids and sugars). The selection of a unique chiral form in those molecules, is a process which is not clearly understood and which has been recently considered by Science as one of the most important unsolved scientific problems [1]. The energy differences between enantiomeric structures (RR vs. SS for instance) are governed by the parity violation principle which is too small to be measured or calculated with the present scientific resources. Thus, in an achiral medium, only diasteromeric structures (RR vs. RS for instance) can be considered as energetically different [2].

Hydrogen peroxide is one of the smallest molecule that present chirality, in this case axial chirality. The corresponding enantiomers are named as Ra and Sa. Even though the racemization barrier is very small, hydrogen peroxide is a suitable model for computational studies. Thus, the homo and heterochiral dimers have been studied, theoretically, in vacuum and in solvent models [3,4]. A detailed analysis of many body contributions to interaction energies of two configurations of the dimer, and one of the trimer and tetramer have been carried out using Møller–Plesset (MP) perturbation theory [5]. The effect of complexation on the racemization process has been studied using DFT/B3LYP and ab initio methods [6,7]. The experimental infrared spectrum of the hydrogen peroxide dimer in argon matrices at 17 K, show a cyclic structure with both molecules acting as hydrogen bond donors and as hydrogen bond acceptors [8].

Gas phase clusters with more than two monomers have been described for serine and lactic acid derivatives. In the first case, serine, the protonated octamer has been found to be unusually stable, being the homochiral structure the preferred one [9]. For the lactate derivatives, several molecular stretchings have been characterized by ragout-jet FTIR-spectroscopy and in the case of the tetramer an alternant chirality cluster have been found to be the more stable one [10,11].

Computationally, clusters of tetrahydroimidazo[4,5-d]imidazole with 2–7 monomers have been studied using DFT/B3LYP methods. In all the cases, the more stable cluster presents alternant chiral molecules [12].

In this Letter the effect of the cluster size on the chiral discrimination is studied for hydrogen peroxide. DFT/B3LYP and MP2 have been applied to clusters from 2 to 10 monomers of hydrogen peroxide.

2. Methods

The geometry of the complexes has been optimized with the B3LYP/6-31+G** [13–15] and MP2/6-31+G** [16] computational methods as implemented in the Gaussian-03
package [17]. The minimum nature of the structures has been confirmed by frequency calculations at both computational levels. The interaction energy has been corrected by the inherent Basis Set Superposition Error (BSSE) using the ‘Counterpoise’ keyword included in the GAUSSIAN-03.

The IR, Raman and Vibrational Circular Dichroism (VCD) spectra [18] have been obtained at the B3LYP/6-31+G** computational level without scaling. The Optical Rotatory Power (ORP) [19] has been calculated at the B3LYP/6-311++G(2d,2p) computational level using the B3LYP/6-31+G** geometries. This level of calculation has been considered as the minimum adequate to obtain reliable results [19].

3. Results and discussion

Previous studies have shown that the most favourable disposition of the dimers is that where each molecule forms two HB and act as HB acceptor and donor with different OH groups [3,4,20]. Based on these results we have initially explored the potential structures for the cluster formed by monomers of the same chirality (homochiral) and those where the chirality of the monomers is alternant along the chain, Ra and Sa. Two generic structures have been found for the homochiral cluster, the double helix and the double ring, while for the ‘alternant racemic’ only the zig-zag one is obtained (Fig. 1, illustrated the results for the hexamer). The symmetry of the complexes is C₂ and Dₙ for the homochiral helix and ring, respectively and C₂/C₁ for the alternant chiral clusters with odd/even number of monomers. The smallest homochiral structure that present 2n HBs, where n is the number of monomers, is the tetramer since in the cyclic trimer only three HBs are formed.

The energetic results obtained are shown in Table 1. The two methods considered here, B3LYP/6-31+G** and MP2/6-31+G**, provide very similar numerical results and in all the cases the same trend is observed. In all of them, the most stable non-cyclic structure corresponds to that with the alternant chiral monomers. Regarding the most stable structure of the three considered for each cluster size, in the dimer and trimer, it is the one with the alternant monomers. For the tetramer and larger structures, the possibility of formation of additional HBs in the case of the homochiral cyclic structures, result in these cyclic clusters being the most stable ones for a given number of monomers.

The analysis of the average interaction energy per HB (Fig. 2), shows that in all cases, the HBs are stronger in the alternant chiral structures than in the non-cyclic homochiral ones. In both cases, a clear effect of the HB cooperativity is observed and thus, the interaction energy per HB becomes larger as the cluster size increases. The behaviour observed for the cyclic structures is different to that previously discussed, the hexamer presenting the strongest HBs, which corresponds to the larger energetic difference between the homochiral cyclic structure and the linear alt-

![Fig. 1. Optimized geometries of the non-cyclic homochiral, cyclic homochiral and non-cyclic alternant chiral hexamers.](image)
Table 1
Energetic results (kJ/mol)

<table>
<thead>
<tr>
<th>No. of monomers (disposition)</th>
<th>Chirality</th>
<th>No. of HBs</th>
<th>B3LYP/631+G**</th>
<th>MP2/631+G**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$E_{I+BSSE}$</td>
<td>$E_{rel}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>$RR$</td>
<td>2</td>
<td>$-30.74$</td>
<td>$0.00$</td>
</tr>
<tr>
<td>2</td>
<td>$RS$</td>
<td>2</td>
<td>$-32.24$</td>
<td>$-1.73$</td>
</tr>
<tr>
<td>3</td>
<td>$RRR$</td>
<td>4</td>
<td>$-64.71$</td>
<td>$0.00$</td>
</tr>
<tr>
<td>3</td>
<td>$RSR$</td>
<td>4</td>
<td>$-67.25$</td>
<td>$-2.89$</td>
</tr>
<tr>
<td>4</td>
<td>$RRRR$</td>
<td>6</td>
<td>$-98.95$</td>
<td>$0.00$</td>
</tr>
<tr>
<td>4-Cyclic</td>
<td>$RRRR$</td>
<td>8</td>
<td>$-113.53$</td>
<td>$-16.91$</td>
</tr>
<tr>
<td>5</td>
<td>$RRRS$</td>
<td>6</td>
<td>$-102.91$</td>
<td>$-4.49$</td>
</tr>
<tr>
<td>5</td>
<td>$R(RR)_1$</td>
<td>8</td>
<td>$-133.26$</td>
<td>$0.00$</td>
</tr>
<tr>
<td>5-Cyclic</td>
<td>$R(RR)_1$</td>
<td>10</td>
<td>$-161.72$</td>
<td>$-32.80$</td>
</tr>
<tr>
<td>6</td>
<td>$R(SR)_3$</td>
<td>8</td>
<td>$-138.51$</td>
<td>$-5.60$</td>
</tr>
<tr>
<td>6</td>
<td>$R(RR)_2 R$</td>
<td>10</td>
<td>$-168.19$</td>
<td>$0.00$</td>
</tr>
<tr>
<td>6-Cyclic</td>
<td>$R(RR)_2 R$</td>
<td>12</td>
<td>$-205.89$</td>
<td>$-37.70$</td>
</tr>
<tr>
<td>7</td>
<td>$R(SR)_3$</td>
<td>12</td>
<td>$-209.78$</td>
<td>$-7.09$</td>
</tr>
<tr>
<td>7</td>
<td>$R(RR)_1 R$</td>
<td>14</td>
<td>$-237.46$</td>
<td>$0.00$</td>
</tr>
<tr>
<td>8</td>
<td>$R(RR)_2 R$</td>
<td>16</td>
<td>$-267.85$</td>
<td>$-33.50$</td>
</tr>
<tr>
<td>8-Cyclic</td>
<td>$R(RR)_2 R$</td>
<td>14</td>
<td>$-245.41$</td>
<td>$-8.26$</td>
</tr>
<tr>
<td>9</td>
<td>$R(RR)_1 R$</td>
<td>16</td>
<td>$-271.90$</td>
<td>$0.00$</td>
</tr>
<tr>
<td>9-Cyclic</td>
<td>$R(RR)_1 R$</td>
<td>18</td>
<td>$-297.84$</td>
<td>$-27.95$</td>
</tr>
<tr>
<td>10</td>
<td>$R(SR)_3$</td>
<td>16</td>
<td>$-280.99$</td>
<td>$-9.44$</td>
</tr>
<tr>
<td>10-Cyclic</td>
<td>$R(RR)_1 R$</td>
<td>18</td>
<td>$-306.32$</td>
<td>$0.00$</td>
</tr>
<tr>
<td>10</td>
<td>$R(SR)_3$</td>
<td>18</td>
<td>$-316.64$</td>
<td>$-10.66$</td>
</tr>
</tbody>
</table>

The interatomic distances obtained in the HB range between 1.83 and 1.93 Å. The HB angle (O·H···O) shows small variations being its range between 151° and 157° (the Cartesian coordinates of the complexes have been included in the supporting information material to allow a complete analysis of the geometries). In the case of the homochiral cyclic clusters, a shortening of the intermolecular distances is observed up to the heptamer. In the non-cyclic structures, each additional monomer produces a shortening of the HB distances for the same position. The shortest HB distance is always found in the second HB and the longest is the last one for each chain (see Fig. 3). A comparison of the HB distances of the homochiral and alternant chiral structures shows that the former have larger interatomic distances in all the positions, except for the last one, that, in general, is shorter.

Fig. 2. Interaction energy per HB (kJ/mol) as a function of the number of monomers in the cluster. Triangles, squares and stars represent the alternant chiral, non-cyclic homochiral and cyclic homochiral clusters, respectively.

Fig. 3. Evolution of the HB distances (Å) in the non-cyclic hexamers and heptamer along the chain (the numbering is specified in Fig. 1). Square and triangles represent the alternant chiral and homochiral complexes, respectively. Empty and full symbols correspond to the hexamer and heptamer structures, respectively.
3.1. Other structures

In order to confirm that the clusters studied so far are representative of all the possible ones, calculations in two directions have been carried out:

(i) Inclusion of a monomer of opposite chirality in the cyclic structures of the homochiral tetramer, pentamer and hexamer.

(ii) The remaining possible combinations of chiral monomers have been considered for the trimer and tetramer.

In the first case, the calculations have been carried out in two steps, initially the dihedral angle of the monomer with opposite chirality has been fixed while the rest of the geometrical parameters have been optimized to avoid the racemization and, in a second step, all the system has been optimized. Only in the case of the cyclic tetramer, the system presents one of the monomers with the opposite chirality to the rest but forming only two HBs with the surrounding monomers, instead of four. The relative energy of this structure is 1.79 kJ/mol less stable than the non-cyclic homochiral tetramer. For the pentamer and hexamer cases, the systems revert at the end of the optimization to the homochiral cyclic structures described previously.

The energetic results obtained for the remaining possibilities of the trimer and tetramer clusters are shown in Table 2. It should be noted that due to the C\(_2\) symmetry of the hydrogen peroxide monomer, the total number of configurations is reduced since for instance the RSRR tetramer is identical to the RRRS. All the new structures are more stable than the corresponding non-cyclic homochiral structures but less stable than the ones with the alternate chirality along the cluster chain. The interaction energy values included in Tables 1 and 2 for the non-cyclic structures have been correlated with the number of HB and the number of heterochiral interactions (Eq. (2)). The cyclic clusters show a different trend to the one observed for the non-cyclic ones probably due to the fact that the overall shape of the cluster is not chiral while in the latter case it is.

\[
\alpha_0 = 84 \times (\text{no. of monomers}) - 164 \times (\text{no. of homochiral interactions}), \quad r^2 = 0.92 
\]

3.2. ORP and VCD spectra

The calculated Optical Rotatory Power (ORP) of the homochiral complexes are listed in Table 3. The effect of the complexation is very important in the ORP, reversing its sign in the non-cyclic clusters. For these cases, a linear correlation can be found between the ORP and the number of monomers and homochiral contacts (Eq. (2)). The cyclic clusters show a different trend to the one observed for the non-cyclic ones probably due to the fact that the overall shape of the cluster is not chiral while in the latter case it is.

A similar equation has been found for the case of the clusters of tetrahydroimidazo[4,5-d]imidazole [12].

\[
E_{1+\text{BSSE}} = -16.91 \times (\text{no. of HB}) - 1.16 \times (\text{no. of } R:S\text{ interactions}), \\
n = 22, \quad r^2 = 0.9996
\]

Table 2

<table>
<thead>
<tr>
<th>No. of monomers</th>
<th>Chirality</th>
<th>No. of HB</th>
<th>E(_{1+\text{BSSE}})</th>
<th>E(_{\text{rel}}) (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>RRS</td>
<td>4</td>
<td>-67.15</td>
<td>-2.73</td>
</tr>
<tr>
<td>4</td>
<td>RSRR</td>
<td>6</td>
<td>-102.52</td>
<td>-3.98</td>
</tr>
<tr>
<td>4</td>
<td>SSRR</td>
<td>6</td>
<td>-102.48</td>
<td>-3.87</td>
</tr>
<tr>
<td>4</td>
<td>SRRR</td>
<td>6</td>
<td>-102.37</td>
<td>-3.93</td>
</tr>
</tbody>
</table>

\(^a\) E\(_{\text{rel}}\) with respect to the corresponding non-cyclic homochiral structure (see Table 1).
ones found in the present Letter but without considering its implications in the chiral recognition processes [22].

Acknowledgements

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Appendix A. Supplementary data

Coordinates of the complexes calculated at the B3LYP/6-31+G(d,p) computational level. IR and Raman spectra of (HOOH)$_n$, $n = 1$–4 complexes. Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.cplett.2006.06.104.

Fig. 4. VCD spectra of the homochiral (HOOH)$_n$, for $n = 1$–4, with $R_a$ chirality. Graphics b–d show detailed shape of the spectra in selected regions and have been rescaled.

References