

# Effect of Double Bonds on the Conducting Properties of Ciguatoxin 3C and Tetrahydropyran-Based Polymers: A Theoretical Study

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The electronic structure of the ciguatoxin 3C is analyzed through the Kohn–Sham model by using two different kinds of basis sets: localized basis set (Gaussian functions) and nonlocalized basis set (plane wave functions). With the localized basis functions, two approximations are used for the exchange–correlation functional: the local density approximation and the generalized gradient approximation. With the nonlocalized basis set, just the local density approximation is used. The energy gap, obtained from the frontier molecular orbitals, for this molecule predicts that this system is a semiconductor, even when the number of double bonds is increased inside the structure. However, as large molecules built with the basic unit—the tetrahydropyran—of the ciguatoxin 3C are found in nature, it suggests studying the gap in polymeric systems built with the basic unit of this molecule. It is demonstrated that the presence of double bonds reduces considerably the gap, indicating the possibility of forming conducting materials by introducing double bonds in this kind of molecular systems. Thus, molecules strongly linked with biological systems can be used as precursor to build electric conducting systems.

## 1. Introduction

Marine toxins are the largest natural products after polypeptides, nucleic acids, and polysaccharides. They are produced by different microalgae, and they are the cause of several types of intoxication produced by the ingestion of seafood contaminated by red tide, such as ciguatera, which produces gastrointestinal and neurological symptoms.<sup>1</sup>

The principal toxin that causes ciguatera is known as ciguatoxin (CTX). It was first isolated in 1967 from the moray eel (*Gymnothorax javanicus*),<sup>2</sup> but it was not until 1977 that the epiphytic dinoflagellate, *Gambierdiscus toxicus*, was identified as the producer of such a toxin.<sup>3</sup>

Because of their biological interest, several congeners of the CTX have been structurally elucidated<sup>4</sup> since the late 80s. Their toxicity is considerably dangerous, and it is known that they behave as selective activators of voltage-sensitive sodium channels (VSSC) in nerves, heart, and muscle.<sup>5</sup> From all the CTX congeners, ciguatoxin 3C (CTX3C), shown in Figure 1, is one of the most representatives; it was isolated in 1993,<sup>6</sup> but the principal reason that differentiates it from the rest of the congeners is that, after many efforts,<sup>7</sup> it was the first synthesized toxin of the CTXs group.<sup>8</sup>

From the theoretical point of view, the electronic structure for some CTX congeners (CTX-1, CTX-2, and CTX-3)<sup>9</sup> has been reported at the semiempirical MNDO<sup>10</sup> level of theory; that study focuses in the chemical reactivity based on charge distribution and structural analysis. To our knowledge, there

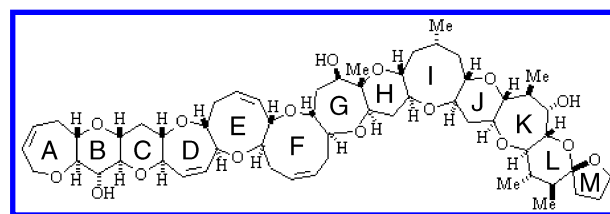


Figure 1. Complete structure for the CTX3C molecule ( $C_{57}H_{82}O_{16}$ ).

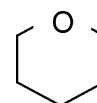


Figure 2. Tetrahydropyran: basic structural unit of some marine toxins.

are no further reports of the electronic structure of these molecules with another quantum chemistry method.

Additionally to the biological interest given by the CTXs systems, their basic structural unit, the tetrahydropyran (Figure 2), defines them as polycyclic ethers. Red tide micro-organisms synthesize long and rigid structures of these basic units; in nature, the longest chains are present in another toxin, also related to ciguatera, known as maitotoxin.<sup>11</sup> Besides nature, organic chemists have synthesized chains of these basic units through different paths to obtain polycyclic ethers of marine origins.<sup>8,12</sup> In this context, it is possible to think that the tetrahydropyran can be used to build a certain kind of polymers, which, in turn, could be modified in order to obtain materials with specific properties, in particular, their electrical properties.

For many years the scientists have been interested in organic molecules with electric conducting properties. The electric conducting organic polymers have been widely studied, since the late 70s; these studies go from extended linear chains, such as polyacetylene,<sup>13</sup> to heterocycles.<sup>14</sup> Their applications are

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mainly related to electronics<sup>15</sup> and their conducting properties.<sup>13,16</sup> In addition to the organic polymers, the molecular wires<sup>17</sup> and some other organic systems,<sup>18</sup> most of them conjugated systems, have demonstrated that can also be employed as conducting systems.

The energy gap, i.e., the difference between the highest-occupied molecular orbital (HOMO) and the lowest-unoccupied molecular orbital (LUMO), is one factor that provides a measure of the conductance. It has been said that a material is an insulator if it shows a gap bigger than 6 eV, while that if its gap is between 2 and 4 eV, it is a semiconductor.<sup>17g</sup> The material is an electric conductor if it shows a small or zero gap. Although some semiconductor systems show a small gap (0.4–0.7 eV),<sup>19</sup> it is well recognized that the gap gives a good idea about the electric conducting properties of materials.

The present work has several aims. In the first one, the energy gap and the electronic structure of the CTX3C is analyzed by using two different kinds of basis sets, localized and nonlocalized, principally focusing on the energy-gap behavior as a function of the size of the basis set used. The main reason to perform such a study is to compare the gap obtained with two different methodologies, one based on Gaussian functions, localized functions, and the other based on plane-wave functions, nonlocalized functions. In the second aim, we inserted double bonds in the CTX3C molecule such that the gap is modified due to the electron conjugation. We want to make this simulation since these new molecules represent a way to build molecules with a different gap just by modifying the number of double bonds. Finally, we explore the gap behavior in different polymers built from the tetrahydropyrene, which is the basic unit of the marine toxins, and the fact that it can be found in nature or can be obtained in the laboratory. The main difference between these proposed polymers is that the basic unit differs in its double bonds. In summary, we explore the possibility to produce conducting materials through the theoretical manipulation of the number of double bonds in a marine toxin and in its basic units to build polymers. It is important to notice that the synthesis of this kind of polyethers is already known by the experimental research groups.<sup>8</sup>

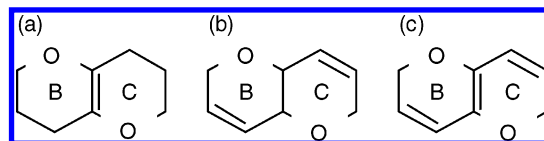
Details about the computational methods are given in the next section as well as a description of the analyzed systems. In section 3, we present the results followed by a discussion, and the conclusions of this work are presented in section 4.

## 2. Computational Methods

The electronic structure of the systems considered in this work was obtained with the Kohn–Sham model. The local density approximation, LDA,<sup>20</sup> and the generalized gradient approximation with the exchange correlation functional BLYP<sup>21</sup> were used with localized basis sets and the NWChem program.<sup>22</sup> The nonlocalized basis sets, plane waves, were used with LDA as this is implemented in the DFT++ code.<sup>23</sup> The GAUSSIAN98 package program<sup>24</sup> was used to perform semiempirical MNDO calculations.

The CTX3C geometry optimization was achieved by using the MNDO method. This geometry was the starting point for the full geometry optimization with localized basis functions and the LDA/DZVP/A1 level of calculation. Only for this molecule was the geometry optimized with localized basis functions and the BLYP/TZVP/A2 level of calculation.

On the optimized geometries, the electronic structure analysis was made with the following basis sets: 4-31G,<sup>25</sup> DZVP/A1,<sup>26</sup> TZVP/A2,<sup>26</sup> and plane waves.<sup>27</sup> It must be pointed out that A1 and A2 are auxiliary basis sets which were specifically designed



**Figure 3.** Increasing insertion of double bonds in the B and C cycles of the CTX3C structure: (a) with one double bond; (b) with two double bonds; (c) with three double bonds.

for DZVP and TZVP, respectively, and they were used just to approximate the coulomb contribution.<sup>26</sup>

The plane-waves method that we employed applies the supercell approximation to treat isolated molecules;<sup>27</sup> therefore, a 5 Å vacuum distance was used to avoid the interaction effects caused by the neighbor supercells. As a result, a 38.12 Å × 15.71 Å × 9.08 Å orthorhombic cell was built for the CTX3C. The pseudopotential approximation<sup>27</sup> was also applied together with plane waves; the pseudopotentials used are nonlocal Kleinman and Bylander types;<sup>28</sup> they were obtained by Ireta and Galván<sup>29</sup> through the Rappe et al. procedure.<sup>30</sup> The kinetic energy cutoff employed was 40 Ry, and a single **k** point, the  $\Gamma$ -point (0,0,0), was used to describe the electronic structure inside the Brillouin zone.<sup>27</sup>

The double-bond insertion in the CTX3C structure was performed in the B and C cycles of Figure 1, as described in Figure 3.

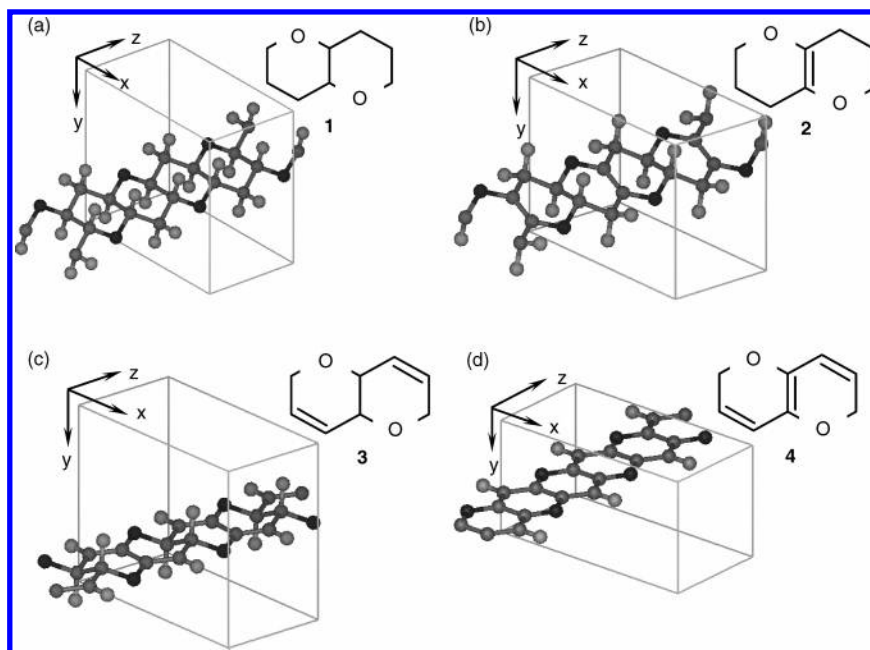
The geometry was optimized with localized basis functions and the LDA/DZVP/A1 level of calculation, and the analysis of the gap behavior was carried out by localized basis functions and the BLYP/TZVP/A2 level. To obtain information of the possible excited states of these molecular systems, time-dependent density functional theory<sup>31</sup> (TDDFT) was applied at the BLYP/TZVP/A2 level.

The periodic systems were built from the tetrahydropyrene with zero, one, two, and three added double bonds. These systems were studied imposing periodic boundary conditions with plane-waves expansions having a kinetic energy cutoff of 40 Ry; the geometry optimizations were carried out with four **k** points, obtained through the Monkhorst–Pack method.<sup>32</sup> The dimensions of the unit cells were 8.80 Å × 7.61 Å × 4.75 Å, 9.19 Å × 6.69 Å × 4.71 Å, 9.29 Å × 7.61 Å × 4.69 Å, and 9.44 Å × 5.00 Å × 4.73 Å for the periodic systems with zero, one, two, and three double bonds, respectively (structures 1 to 4 in Figure 4). All the cells are orthorhombic, and the polymeric regime is achieved along the *z* direction. The optimization procedure includes the relaxation of the lattice parameter along the *z* axis and the positions of all the atoms in the unit cell. In contrast, a fixed 5 Å vacuum distance was used on the *x* and *y* coordinates. The density of states (DOS) for each polymer was obtained from 50 **k**-points calculation in the ground-state geometry.

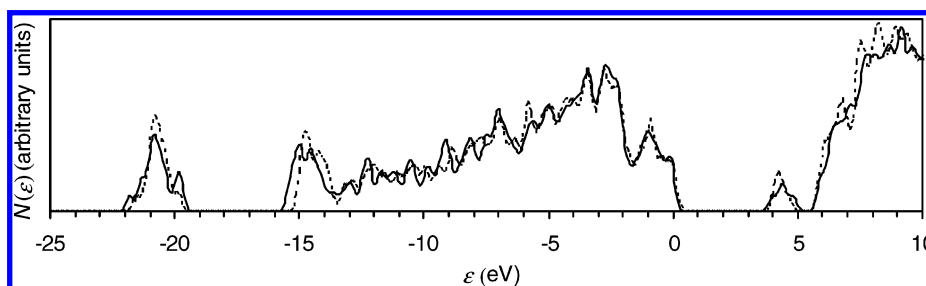
## 3. Results and Discussion

**3a. DOS for the CTX3C.** To see the effect of the geometry on the DOS of the CTX3C, in Figure 5, we are depicting this quantity on the full optimized geometries at the LDA/DZVP/A1 and MNDO levels of calculation. On these geometries the DOS,  $N(\epsilon)$ , was obtained at the LDA/DZVP/A1 level.

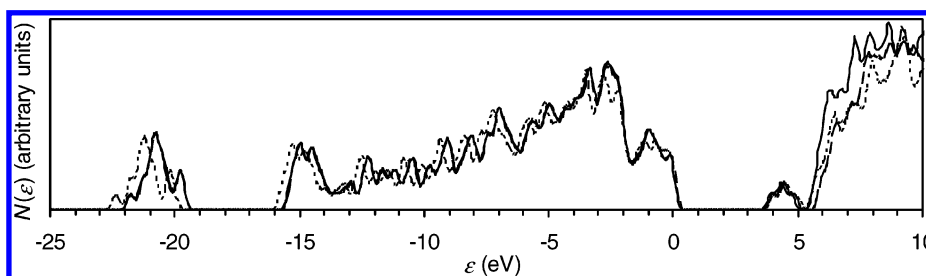
From Figure 5, it can be seen that the DOS obtained from both geometries, with the same basis set, is similar for the occupied states. We found appreciable differences with the virtual states for high energies. In particular, the four LUMOs (LUMO to LUMO+3) compose a separated band (LUMO band) for these geometries, which resides between 3.5 and 5.0 eV. It must be noticed that, in the geometry optimized by MNDO,



**Figure 4.** Unit cells for the different periodic systems: (a) without double bonds, structure 1; (b) with one double bond, structure 2; (c) with two double bonds, structure 3; (d) with three double bonds, structure 4. The inset beside every figure shows the structure inside the unit cell.



**Figure 5.** Density of states obtained from different CTX3C geometries and the LDA/DZVP/A1 method. The dotted line belongs to the geometry obtained by MNDO and the solid line, to that obtained by LDA/DZVP/A1. The Fermi level is aligned to zero.



**Figure 6.** Density of states for the CTX3C obtained from different basis sets on the geometry obtained with the LDA/DZVP/A1 method. The dotted line belongs to the LDA/4-31G calculation, the dashed line, to the LDA/DZVP/A1, and the solid line, to the LDA/TZVP/A2 calculation. The Fermi level is aligned to zero.

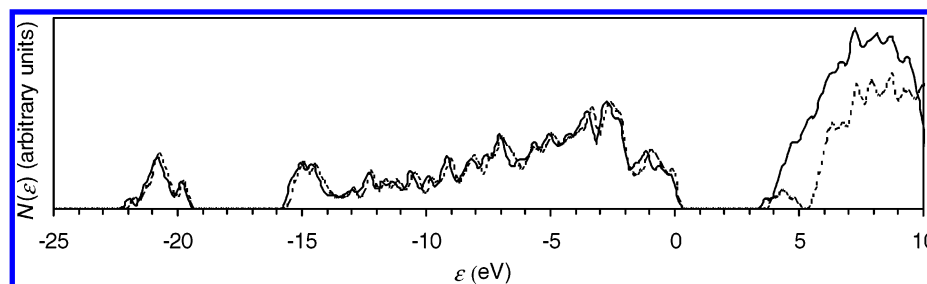
the LUMO band is a slightly narrow peak; this behavior for the LUMO band is also followed for the rest of the virtual states. Thus, it can be seen from Figure 5 that the difference between the geometries optimized at MNDO and LDA/DZVP/A1 levels for the CTX3C molecule does not imply large changes in the description of the DOS; changes are rather small (less than 0.1 eV).

The DOS behavior obtained with the LDA method and with the basis sets 4-31G, DZVP/A1, and TZVP/A2, at a fixed geometry (in this case, the one obtained by LDA/DZVP/A1), is depicted in Figure 6.

From Figure 6, we can see that the LUMO band is clearly separated from the rest of the virtual space for the three basis sets. It must be noticed that, for the DZVP/A1 and TZVP/A2 basis sets, the DOS of the occupied states is almost the same.

The principal difference between these basis sets is localized in the virtual states description, right after the LUMO band; in this region, when the basis set size increases, the DOS indicates that some virtual state energies are shifted in the direction of the LUMO band. It is worth noting that the 4-31G basis set differs with respect to the others basis sets for deep and high energies, but at the Fermi level and in the LUMO band it gives similar results.

From the previous paragraph, we conclude that if we increase the basis set the DOS for the virtual states is changed. It is well known that the methods based in plane waves use a large number of basis set functions. Thus to obtain a comparison between localized and nonlocalized basis sets, the DOS obtained with TZVP/A2 and with plane waves, at the geometry optimized by the LDA/DZVP/A1 level, is shown in Figure 7.



**Figure 7.** Density of states for the CTX3C obtained by the TZVP/A2 basis set (dotted line) and by plane waves (solid line) on the geometry optimized by the LDA/DZVP/A1 method. The Fermi level is aligned to zero.

**TABLE 1: Gap Values for the CTX3C Molecule Obtained by Different Levels of Calculation (All Values are in eV)**

level of calculation in which the gap was obtained	level of calculation of the optimized geometry	
	MNDO	LDA/DZVP/A1
LDA/4-31G	4.01	4.00
LDA/DZVP/A1	4.06	3.97
LDA/TZVP/A2	3.99	3.92
BLYP/DZVP/A1	4.20	4.07
BLYP/TZVP/A2	4.14	4.02
LDA/plane waves	3.95	3.70

We see from Figure 7 that for the case of plane waves the DOS of the virtual states shows just one band and the LUMO band is not separated from the rest of the unoccupied states.

It is important to mention that the impact on the DOS description of the virtual states is more significant for different basis set sizes (Figures 6 and 7) than for different levels of calculation of the geometry optimization (Figure 5). This observation suggests that one can use geometries obtained from semiempirical methods to perform a subsequent electronic structure analysis in this kind of rigid macromolecules.

**3b. Energy Gap for the CTX3C.** In Table 1, we are reporting the energy gap as a function of the basis set size on two different geometries.

As it is shown in Table 1, for the geometry obtained by LDA/DZVP/A1, it is accomplished that the gap diminishes as the basis set size is increased. However, such a direct comparison is actually more reliable for DZVP/A1 and TZVP/A2, since these basis sets belong to the same type; one must remember that 4-31G belongs to the Pople basis sets and plane waves are a kind of nonlocalized basis sets. Therefore, the most appropriate comparison can be found for the values obtained with DZVP/A1 and TZVP/A2. In general, it can be said that the size of the basis set reduces the gap. The most notorious changes correspond to the plane-waves description where, in accordance with Table 1, the gap is the smallest obtained. When comparing methods, LDA slightly underestimates the results with respect to those for BLYP.

It also must be observed the behavior of these basis sets with different geometries. Smaller gap values are found for the geometry optimized by LDA/DZVP/A1 than by MNDO, and this result is valid for all the employed basis sets.

Just as a comparison, the CTX3C molecule was optimized at the BLYP/TZVP/A2 level, and we found a gap of 4.08 eV, which differs by 0.06 eV with respect to the gap obtained with the same exchange-correlation functional on the geometry at the LDA/DZVP/A1 level. For this reason, no further optimizations were carried out with the BLYP/TZVP/A2.

From a previous study, applied to ethylene and butadiene,<sup>33</sup> we know that the gap obtained with a large basis set is 5.74 eV for ethylene and 3.13 eV for butadiene. With the TZVP/A2 and the LDA method we found a gap of 5.76 eV for ethylene and

3.95 for butadiene. We see that the TZVP/A2 basis set gives an overestimation of 0.02 eV; thus, we expect a gap of about 0.02 eV smaller for the LDA/TZVP/A2/LDA/DZVP/A1 level, if a larger basis is used. For plane waves, it is known as well that, when the vacuum used to isolate the molecule inside the supercell is increased, the gap is also increased. For ethylene, we have: 5.52 eV at 5 Å and 5.77 eV at 10 Å (although changes are almost neglected at higher vacuum values). Therefore, an increase of  $\sim 0.25$  eV could be also expected when the vacuum of the supercell rises to reach a converged value for the gap. Thus, localized and nonlocalized basis functions methods give similar results for the occupied states of the DOS and the gap.

**3c. Orbital Densities of the HOMO and LUMO Bands for the CTX3C.** The orbital densities corresponding to the HOMO band, defined from HOMO to HOMO-5, are depicted in Figure 8a.

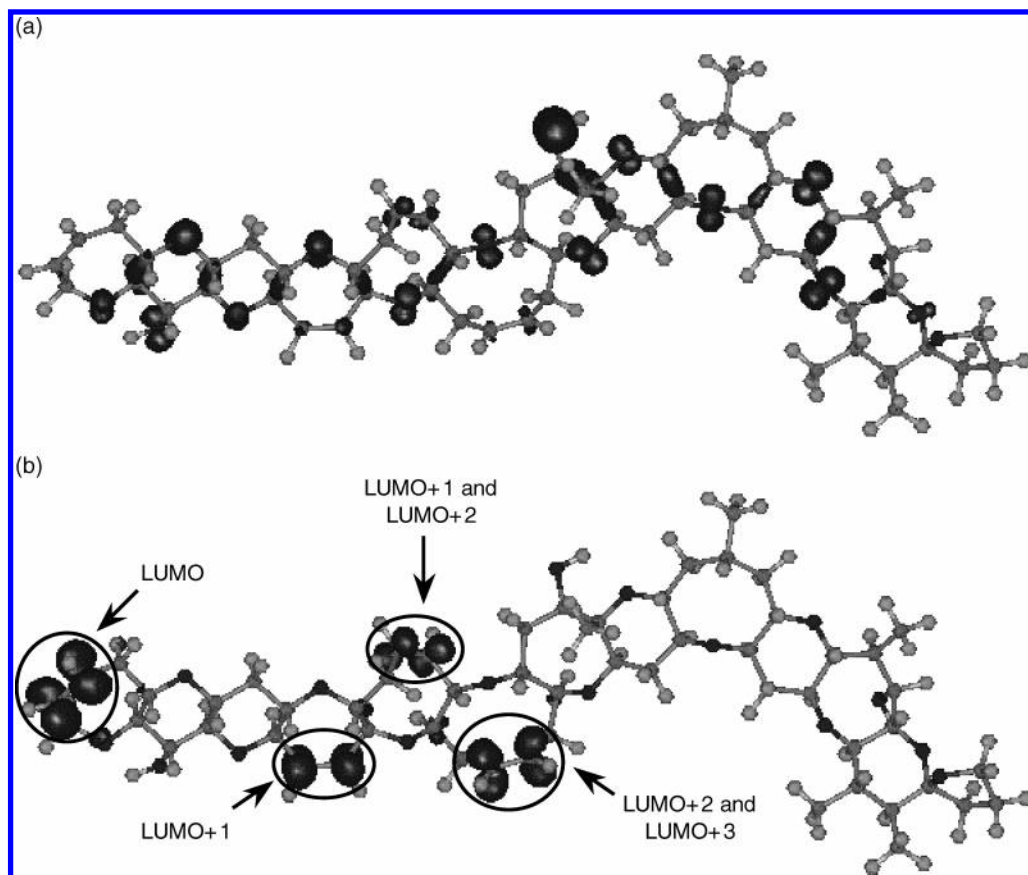
We can see that these states are principally localized on the electron lone pairs of almost all oxygen atoms (excepting those that belonged to the M cycle in Figure 1). And, in a smaller proportion, on some single bonds in the border of two fused cycles. These states are nonlocalized. In contrast, the states of the LUMO band are localized on the double bonds of the molecule, as indicated in Figure 8b, and they are clearly of antibonding nature. It is interesting to observe that the LUMO state corresponds to the double bond in one end of the CTX3C structure, while the rest of the states of the LUMO band (LUMO+1 to LUMO+3) are placed inside the structure.

It is worth mentioning that the occupied states below the HOMO band (HOMO-6 and lower states) also reside on the double bonds of the molecule.

By combination of the local behavior of the LUMO band and the structure of the DOS around the Fermi level, one may say that the presence of double bonds in the structure of CTX3C introduces states in the gap reducing it by at least 1 eV. In the next sections, this fact is explored in more detail.

**3d. Energy Gap as a Function of the Number of Double Bonds inside the CTX3C Structure.** As we mentioned in section 1, one aim of this work is to explore the impact of the number of double bonds of the CTX3C molecule on the gap. In Table 2 we are reporting the behavior of this property as a function of the number of double bonds in the CTX3C molecule which were increased according to Figure 3. As it is expected when the number of double bonds is increased the gap shows a reduction. However the reduction is nonmonotonic. Thus, these molecules, even when the double bonds are increased, present a semiconductor behavior. In addition, we estimate the effect of the double bonds in the first excited singlet state of CTX3C by using TDDFT (see Table 2). As one could expect, the reduction of the gap goes along with the values of such excitation energy; it is striking the agreement for the case with no double bonds in the B-C region, but this concordance is lost for three double bonds. It is important to remark that a





**Figure 8.** (a) HOMO band, from HOMO-5 to HOMO, and (b) LUMO band, from LUMO to LUMO+3, for the CTX3C. Isosurface = 0.005 au.

**TABLE 2: Comparison of Gap Values for the Increasing Number of Double Bonds Inside the CTX3C Structure<sup>a</sup>**

no. of double bonds inside the CTX3C structure	gap
0	4.02 [4.02]
1	3.20
2	3.42
3	2.06 [2.38]

<sup>a</sup> Geometry was obtained by LDA/DZVP/A1 and gap values obtained by BLYP/TZVP/A2. The first singlet excitation energy obtained by TDDFT is in square brackets. All values are in eV.

calculation of the gap at the BLYP/TZVP/A2//LDA/DZVP/A1 level of theory contains similar trends than that obtained by the TDDFT procedure.

**3e. Density of States and Energy Gap for Infinite Periodic Systems Built from Tetrahydropyrane and Its Derivatives.** The selection of the position of the double bonds in the CTX3C molecule, in the previous section, is related with the full periodic models that we are interested since we want to build acceptable unit cells for linear polymers, based on the fused rings B–C of the CTX3C molecule; the possibilities are reduced to those of Figure 4. Thus to study the effect of having an infinite periodic system, as well as the effect of the presence of double bonds, four different periodic systems were constructed and analyzed.

The first periodical system is based on tetrahydropyrane (Figure 2), which has no double bonds (structure 1 in Figure 4). In the second, a double bond was inserted in the middle of the structure (structure 2 in Figure 4); for the third, there are two double bonds symmetrically placed inside the structure (structure 3 in Figure 4). And finally, the fourth system contains three double bonds arranged in such order that the system can be described as infinitely conjugated (structure 4 in Figure 4).

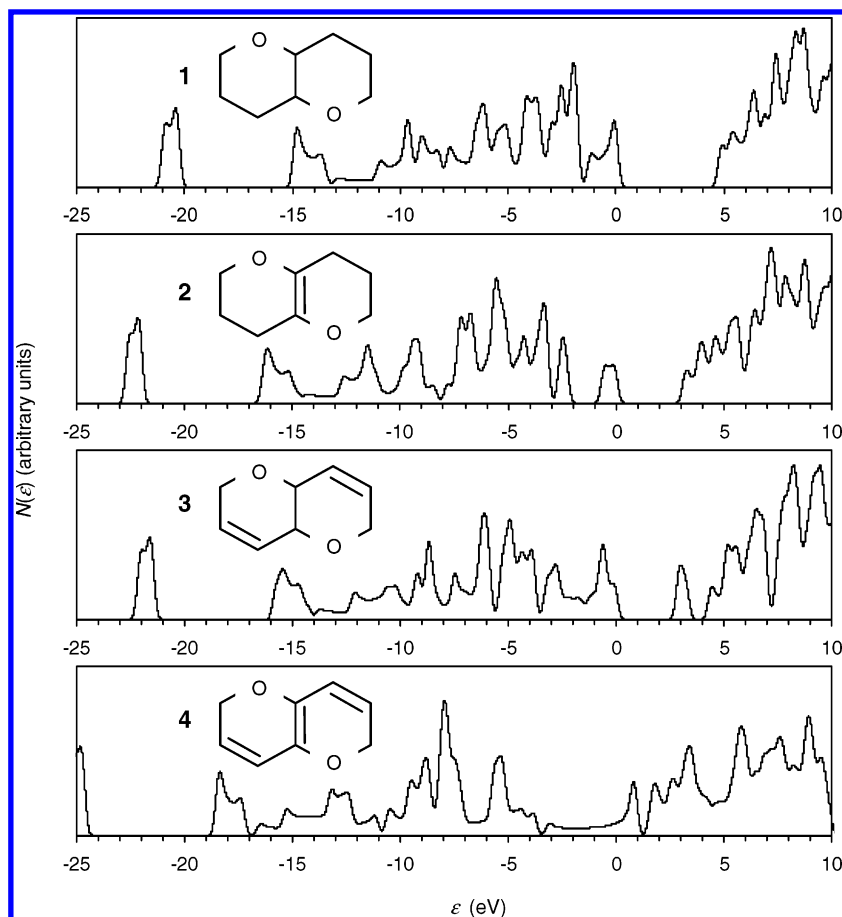
It is important to recall that the selection of these model systems depends on the possibility of building an acceptable linear polymer.

The DOS for the periodical systems are displayed in Figure 9. From this figure it is evident that the gap is reduced considerably when the number of double bonds is increased. This fact is more pronounced when the polymer is closer to a full delocalized system (that is, for the 2 and 3 double-bond cases), in fact, when the periodic system contains three double bonds, it can be seen that there is no visible gap with the Gaussian width employed to calculate the DOS.

A quantitative description of the behavior of the gap with respect to the number of double bonds inside the unit cell structure is shown in Table 3. It can be seen that, when no double bonds are present, the periodic system can be considered as a semiconductor (gap, 4.81 eV). This semiconducting behavior may also be applied to the periodic systems with one and two double bonds (gap, ~3.00 eV). However, it must be noticed that, when three double bonds are present, the gap drastically diminishes (0.10 eV) and the possibility of having a conducting polymer must be seriously considered. This sudden reduction of the gap, when one is changing from two double bonds into three, is the result of having an almost full conjugated system.

#### 4. Conclusions

For the DOS of the CTX3C, at different geometries, it can be said that it has just slight effects on the virtual states description. A well-defined LUMO band is present when localized basis sets are employed; at a fixed geometry, when the basis set is increased the distance between the LUMO band and the rest of the virtual states is reduced. This observation is corroborated when a large basis set, such as plane waves, is



**Figure 9.** Comparison among densities of states for the different periodic systems, the inset in every figure shows the structure inside the unit cell. The Fermi level is aligned to zero.

**TABLE 3: Comparison of Gap Values for the Different Periodical Systems. All Values are in eV**

no. of double bonds in the unit cell of the periodical system	gap
0 (structure 1)	4.81
1 (structure 2)	3.16
2 (structure 3)	2.88
3 (structure 4)	0.10

used since it does not only vanish this distance but it also compresses the virtual states. In general, the occupied states descriptions are quite similar for every analyzed DOS when localized or nonlocalized basis are used. More significant changes can be observed at different basis set sizes regardless if geometries optimized by MNDO or Kohn–Sham are used.

The gap shown by the CTX3C ( $\sim 4.00$  eV) is similar to a semiconductor. An important reduction of the gap is observed when the basis set size is increased, particularly when plane waves are used.

The LUMO band is well localized in the double bonds of the CTX3C structure; in contrast, the HOMO band is spread out in different sites, which principally correspond to the oxygen lone pairs of the molecule.

It was demonstrated that, when the number of double bonds is increased in the CTX3C structure, the gap could be reduced, especially when double bonds are conjugated.

Although many conducting systems have been discovered through the past decades, we think that it is worth to try on new materials which could be easier to elaborate and taking into account the previous results and the different synthesis methods applied nowadays by several experimental research

groups, for this kind of molecules, it could be interesting to observe the behavior of polymeric systems such as those studied in this work. Our findings indicate that a polymer, constructed from a monomer containing two tetrahydropyrane rings fused as it is found in marine toxins, can be transformed from a semiconductor wire into a conductor when three double bonds are appropriately added. A substantial reduction in the gap of the real toxin is also achieved by the same procedure.

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