Expert Opinion

Computational methods to predict the reactivity of nanoparticles through structure–property relationships

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Importance of the field: Innovative biomedical techniques operational at the nanoscale level are being developed in therapeutics, including advanced drug delivery systems and targeted nanotherapy. Given the large number of nanoparticles that are being developed for possible biomedical use, the use of computational methods in the assessment of their properties is of key importance.

Areas covered in this review: Among the *in silico* methods, quantum mechanics is still used rarely in the study of nanostructured particles. This review provides an overview of some of the main quantum mechanics methods that are already used in the assessment of chemicals. Furthermore, classical tools used in the chemistry field are described, to show their potential also in the pharmacological field.

What the reader will gain: The current status of computational methods in terms of availability and applicability to nanoparticles, and recommendations for further research are highlighted.

Take home message: The *in silico* modelling of nanoparticles can assist in targeting and filling gaps in knowledge on the effects of these particular particles. Computational models of the behaviour of nanoparticles in biological systems, including simulation models for predicting intermolecular interactions and harmful side effects, can be highly valuable in screening candidate particles for potential biomedical use in diagnostics, imaging and drug delivery.

Keywords: carbon nanoneedle, chemical hardness, computational modelling, conceptual density functional theory, electrophilicity, energy decomposition analysis, Fukui function, nanomedicine, structure–property relationship

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1. Introduction

The broad variety of applications in a wide range of fields of nanostructured materials has pushed nanoscience to be one of the most outstanding subjects in science in this new millennium. Nanomaterials (NMs) have plenty of applications, such as opacifiers, semiconductors, fillers, electronics and microelectronics, sporting goods, tyres, stain-resistant clothing, self-cleaning surfaces, sunscreens and cosmetics. In the medical field, NMs are potentially useful for the purposes of diagnosis, imaging and drug delivery. On the other hand, nanoparticles (NPs), which are a subset of NMs and have at least one dimension < 100 nm [1], usually have particular magnetic, electrical, optical, thermal and chemical properties [2] that make them very useful for commercial, technological and therapeutic applications. Special attention

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Article highlights.

- The importance of nanoparticles.
- A detailed overview of computational techniques to get insight into the study of NPs such as quantum mechanical calculations, conceptual DFT, chemical hardness and electrophilicity, Fukui functions, energy decomposition analysis and Mayer bond orders, and QSAR.
- The application of computational techniques to the study of a particular example of NPs, such as CNNs.
- The Expert opinion section includes what has been done and what else could be improved in the study of NPs through computational techniques.

This box summarises keypoints contained in the article.

is paid to the biomedical and biotechnology applications of nanotechnology to nanomedicine [3]; in particular, to medical diagnostics and imaging [4] and to nanoneurosurgery [5]. Innovative techniques operational at the nanoscale level are being developed in therapeutic modalities, including advanced selective drug delivery systems and targeted nanotherapy [6]. Some of these modalities include polymeric NPs [7], micelles [8], liposomes and dendrimers [4], fullerenes [9,10], hydrogels [11], nanoshells [12] and smart surfaces. Some of the key performance characteristics of these materials are the high loading capacity, release kinetics, circulation time, biodistribution, size distribution and stability [13].

The rational structure-based design of NPs is assisted by their increasing use in biomedicine for diagnostic and therapeutic applications. *In silico* modelling applications to understand receptor–ligand interactions, cell signalling pathways, simulated organ dysfunction, and human and environmental toxicity have an important role in addressing some of the main challenges with NPs. Furthermore, data are increasingly being generated by genomic and proteomic methods (e.g., in the US EPA Toxcast project), and interestingly, physiological modelling of the heart and lungs is being explored [14]. Nevertheless, NPs have a hard handicap related to the toxicity and negative impact in the environment. Their unique properties, such as their size, surface area and biopersistence, also need to be considered in assessments of human health and environmental risk. The occurrence of occupational lung disease demonstrates that particles such as asbestos, quartz and coalmine dust are associated with this disease. On the other hand, NPs derived from combustion also cause adverse effects in the cardiovascular and respiratory systems, such as lung cancer or exacerbations of asthma and chronic obstructive pulmonary disease (COPD).

Nanotechnologies are still at an early stage of development, however, and much research effort is being directed to understanding the properties and behaviour of NMs, including NPs. In particular, the current understanding of NP toxicity is still rather limited and data on their behaviour (e.g., mechanisms and pathways of toxicity, human exposure routes, physicochemical and biological properties relevant for modelling toxicity and adverse effects) are still relatively sparse. Some recent efforts have focused on theoretical modelling of NPs [15,16] and on the prediction of toxicological properties by using computational techniques [17,18] because it is difficult to establish toxicological data and determination of occupational exposure limits with existing methodologies [19]. On the other hand, recent theoretical studies indicate that these NPs might be good carriers in biological media [18,20].

An overview of the main computational methods that are already used in the assessment of chemicals has been given by Gallegos Saliner *et al.* [18,21]. It is anticipated that classical methodologies used in chemistry research will spread their uses in pharmacological fields, as shown recently by Zhang and co-workers, who applied mathematical methodologies to biological problems at the nanoscale [22].

This review provides an overview of some of the main quantum mechanics methods that are already used in the assessment of chemicals. Furthermore, classical tools in chemistry are described to show their applicability also in the pharmacological field.

2. Advances in predictive computational approaches for nanoparticles

Recently, NMs have become the focus of interest in computational studies. It is envisaged to obtain structural information and predict mechanical, chemical, electronic and optical properties of NPs through simulations based on various techniques, such as quantum mechanical calculations, force field-based methods, and classic and *ab initio* molecular dynamics (MD). The combination of these techniques and other computational predictive approaches such as read-across and grouping, and also (quantitative) structure–activity relationships, are key elements in reaching the aims of prediction in a synergistic way.

2.1 Quantum mechanical calculations

In the early 1930s, the advent of the new quantum concepts to the study of atomic and molecular systems initiated the field of computational and theoretical chemistry. Some semiempirical approximations were developed, such as the Hückel model, which calculates the orbital energies of conjugated organic molecules by making use of empirical parameters. *Ab initio* quantum mechanical methods are, on the other hand, aimed at solving the Schrödinger equation. Since the 1960s, with the introduction of computing machines, the development of more and more efficient algorithms for solving the equations involved in the motion of electrons allowed the first relevant results to be obtained [23-28].

The most characteristic quantum mechanical method for solving the Schrödinger equation is the Hartree-Fock approach [23-28]. In this method, the electronic correlation due to the Coulomb hole (two electrons with different spin can be at the same time in the same position in space, but with

reduced probability) is not introduced explicitly. Nevertheless, the Fermi hole (two electrons with the same spin cannot be at the same time in the same position in space) is well described, because the wave function is built from a Slater determinant. To improve the Hartree-Fock wave function it is necessary to introduce the electronic correlation due to the Coulomb hole by different methods, known as post-Hartree-Fock methods. The easiest way to achieve this is by using perturbation theory (Møller-Plesset [MP]), or by introducing extra determinants promoting occupied orbitals towards unoccupied ones (configuration interaction [CI]). However, these post-Hartree-Fock methods, such as MP2, MP3, MP4, CISD, CCSD, and CCSD(T), display an expensive computational cost.

The Hohenberg-Kohn theorem, the starting point of the density functional theory (DFT) [23-28], establishes that the wave function of the ground state of an electronic system is a functional of the electronic density. Therefore, it is necessary only to know the density to calculate all the properties of a system. The fact that DFT displays a relatively lower computational cost with respect to the conventional *ab initio* methods has allowed large organometallic and bioinorganic systems to be studied. Therefore, during recent years DFT has become the most widely used methodology in the study of the ground state of molecules with medium or large size.

The computational methodology is chosen depending on the number of atoms that are modelled, taking into account that it is not possible to obtain exact solutions, thus different approximations are adopted depending on the technique. Up to a maximum of several hundred atoms, *ab initio* simplified quantum mechanical-based methods, such as the density functional theory, are feasible. To reach larger systems, even several million atoms, methods based on classic statistical mechanics, such as the molecular dynamics simulation method, are used. Although still scarce, in the field of nanostructures different studies have used DFT as the computational technique [16,29,30]. An extensive computational modelling review collects data about thermomechanical and transport properties of carbon nanotubes [31]. On the other hand, classical molecular dynamics, in addition to calculating particular properties of the NPs, is able to describe these properties when proteins are adsorbed in their surfaces [32].

2.2 Conceptual density functional theory

An important branch derived from DFT theory useful for predictive computational approaches has been conceptual DFT [23,33,34]. This theory, created by Robert G Parr, is based on the idea that electronic density is the fundamental tool to describe the electronic states of atoms and molecules. Conceptual DFT has allowed mathematical definition to be given to a series of chemical concepts such as electronegativity and hardness.

A large part of the theoretical chemistry related to reactivity is based on the concept of the frontier molecular orbitals (FMO), introduced by Fukui and co-workers [35,36], especially the lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO). The interaction between these orbitals often allows a good description of the reactivity and the stereoselectivity of the reactions to be obtained. The FMO theory says that the attack of an electrophilic species will take place where there is more density of the HOMO, whereas the attack of a nucleophilic species will take place in a region with higher density of the LUMO. Parr and co-workers have demonstrated that nearly all the frontier molecular theory can be rationalised from the DFT [23].

In the conceptual DFT, the chemical reactivity is quantitatively studied by using a set of chemical reactivity indices (e.g., hardness, Fukui functions, electrophilicity). Furthermore, these indices have been useful to define and redefine other chemical reactivity principles such as the hard–soft acid–base principle (HSAB) [37], the electronegativity equalisation principle (EEP) by Sanderson [38,39], the maximum hardness principle (MHP) [40] and the minimum polarisability principle (MPP) [41].

2.2.1 *Chemical hardness and electrophilicity*

The chemical potential and molecular hardness for the *N*-electron system with total energy *E* and external potential $v(\vec{r})$ are defined as the following first and second derivatives of the energy with respect to *N*: [23,42-44]

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(\vec{r})} = -\chi \tag{1}$$

and

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{v(\vec{r})} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{v(\vec{r})} \tag{2}$$

where χ in Equation 1 is the electronegativity. In numerical applications, μ and η are calculated using the finite difference approximation.

$$\mu \approx -\frac{1}{2}(IP + EA) \tag{3}$$

$$\eta = \frac{1}{2}(IP - EA) \tag{4}$$

The vertical ionisation potential (*IP*) and the electron affinity (*EA*) can be obtained from the energy of the neutral, anionic, and the cationic species at the geometry of the corresponding *N*-electron neutral species, as follows.

$$IP = [E(N-1) - E(N)] \tag{5}$$

$$EA = [E(N) - E(N+1)] \tag{6}$$

Equations 3 and 4 can be simplified by using Koopmans' theorem [45], which approximates the electronic affinity and the ionisation potential to the negative of the LUMO energy (ε_L) and the HOMO energy (ε_H), respectively.

$$\mu \cong \frac{1}{2}(\varepsilon_L + \varepsilon_H) \tag{7}$$

and

$$\eta = \frac{1}{2}(\varepsilon_L - \varepsilon_H) \tag{8}$$

The electrophilicity index is defined as [46]:

$$\omega = \frac{\mu^2}{2\eta} \tag{9}$$

The conceptual DFT is a useful tool to obtain quantitative information about the chemical reactivity and it presents the extra advantage that in spite of the fact that the reactivity indices are developed from DFT, they can be used for DFT and non-DFT calculations (semiempirical, HF or post-HF).

2.2.2 Fukui functions

The Fukui function is a reactivity index that connects the concepts of the Fukui frontier molecular orbitals with DFT. It was defined by Yang and Parr as the partial derivative of the electron density with respect to the total number of electrons at a constant external potential or as the derivative of the chemical potential with respect to the external potential, keeping constant the total number of electrons of the system [47].

$$f(\vec{r}) = \left(\frac{\delta\mu}{\delta v(\vec{r})}\right)_N = \left(\frac{\partial\rho(\vec{r})}{\partial N}\right)_{v(\vec{r})} \tag{10}$$

The Fukui function describes the local changes in the electronic density of a system due to a perturbation in the total number of electrons. For a molecule or an atom, the right-hand derivative of Equation 10 is not continuous with the number of electrons and is difficult to evaluate [48,49]. Therefore, Parr and Yang [47] defined the Fukui functions $f^+(r)$, $f^-(r)$ and $f^0(r)$ corresponding to the reactivity index that describes the attack towards our system by a nucleophile, electrophile or a radical species.

$$f^+(\vec{r}) = \left(\frac{\partial\rho(\vec{r})}{\partial N}\right)^+_{v(\vec{r})} \tag{11}$$

$$f^-(\vec{r}) = \left(\frac{\partial\rho(\vec{r})}{\partial N}\right)^-_{v(\vec{r})} \tag{12}$$

$$f^0(\vec{r}) = \left(\frac{\partial\rho(\vec{r})}{\partial N}\right)^0_{v(\vec{r})} \tag{13}$$

where the superscripts '+', '-' and '0' refer to the right, left and central derivatives, respectively. If the same technique of the finite differences used in the chemical potential and the hardness is applied to Equations 11 – 13 it can be shown that the Fukui functions can be evaluated from the following density differences [50]:

$$f^+(\vec{r}) = \rho_{N+1}(\vec{r}) - \rho_N(\vec{r}) \tag{14}$$

$$f^-(\vec{r}) = \rho_N(\vec{r}) - \rho_{N-1}(\vec{r}) \tag{15}$$

$$f^0(\vec{r}) = \frac{1}{2}\left[\rho_{N+1}(\vec{r}) - \rho_{N-1}(\vec{r})\right] \tag{16}$$

If Equations 14 – 16 are integrated within specific regions of the molecular topology, the corresponding condensed Fukui functions are obtained.

$$\begin{aligned} f^+_x &= q_x(N+1) - q_x(N) \\ f^-_x &= q_x(N) - q_x(N-1) \\ f^0_x &= \frac{1}{2}\left[q_x(N+1) - q_x(N-1)\right] \end{aligned} \tag{17}$$

where the parameters q_x are the charges of the atom X calculated in the systems with N, N - 1 and N + 1 electrons at the optimised geometry of the molecule with N electrons. In the past few years, the condensed Fukui functions have been used to explain the regioselectivity in chemical reactions, especially in cycloaddition reactions [51]. It is a tool that allows the prediction of which atom or moiety of a molecule will display more or less nucleophilic or electrophilic character [52].

2.3 Energy decomposition analysis and Mayer bond orders

By the energy decomposition analysis (EDA) [53-57], the total binding energy (BE) between two fragments in a molecule is divided into deformation energy and interaction energy ($BE = \Delta E_{def} + \Delta E_{int}$). The deformation energy (ΔE_{def}) is

the energy needed to modify the geometry of the ground state free fragments to attain the geometry they have in the molecule. The interaction energy (ΔE_{int}) is the energy released when the two ground state deformed fragments are brought to the position that they have in the molecule, and it has been, in turn, split into electrostatic, Pauli repulsion and orbital interaction terms ($\Delta E_{int} = \Delta E_{elstat} + \Delta E_{Pauli} + \Delta E_{oi}$). The term ΔE_{elstat} corresponds to the classical electrostatic interaction between the unperturbed charge distributions of the prepared fragments, and is usually attractive [58]. The Pauli repulsion term, ΔE_{Pauli}, comprises the destabilising interactions between occupied orbitals and is responsible for the steric repulsion. This repulsion is caused by the fact that two electrons with the same spin cannot occupy the same region in space. The term comprises the four-electron destabilising interactions between occupied orbitals. The orbital interaction term, ΔE_{oi}, accounts for charge transfer (interaction between occupied orbitals on one moiety with unoccupied orbitals of the other, including the HOMO–LUMO interactions) and polarisation (empty occupied orbital mixing on one fragment owing to the presence of another fragment). The latter term can be partitioned further into contributions of the orbitals that belong to different irreducible representations of the point group of the interacting system. Owing to the fact that orbital interactions (ΔE_{oi}) can be associated to the covalent bond contributions and the electrostatic term (ΔE_{elstat}) to the ionic ones, the $\Delta E_{elstat}/(\Delta E_{elstat} + \Delta E_{oi})$ term provides a measure of the ratio of the ionic character of the bonds studied.

Finally, Mayer bond orders (MBO) were calculated through the expression [59-62]:

$$B_{AB} = 2\sum_{\mu\in A}\sum_{\upsilon\in B}\left[\left(P^{\alpha}S\right)_{\mu\upsilon}\left(P^{\alpha}S\right)_{\upsilon\mu} + \left(P^{\beta}S\right)_{\mu\upsilon}\left(P^{\beta}S\right)_{\upsilon\mu}\right] \quad (18)$$

where **S** is the atomic orbital overlap matrix and $\mathbf{P}^{\alpha}$ and $\mathbf{P}^{\beta}$ are the density matrices for the α and β electrons, respectively. Both the EDA and the MBO are methods to describe the interaction between two moieties [63-66]. In 2006, Poater *et al.* reproduced in detail the interaction of carbon clusters with CO through these two methodologies [52].

2.4 Quantitative structure–activity relationship

As predictive approaches, structure–activity relationship (SAR) and quantitative structure–activity relationship (QSAR) studies are theoretical models that relate the structure of chemicals to their properties [18]. These tools are useful to predict the physicochemical properties and biological effects of molecules based on structural parameters of the compounds.

SARs are qualitative relationships between a chemical moiety, frequently a molecular structure or substructure, that is, an atom or group of adjacently connected atoms, and the presence or absence of a biological activity. SARs can also be based on the ensemble of steric and electronic features of a molecule that are considered necessary to ensure an intermolecular interaction with a biological target molecule, resulting in the manifestation of a specific biological effect. In particle toxicology, SARs have been proposed in the study of asbestos. These chemical agents are toxic because of their ability to persist in the lungs [67]. On the other hand, QSARs are quantitative relationships between a biological activity and one or more descriptors that are used to predict the activity through current data analysis approaches such as multiple linear regression. The molecular descriptor can be the structural or physicochemical property of a whole or part of a molecule that specifies a particular characteristic of the molecule and is used as an independent variable in the model. Related to NPs the more relevant properties include size, shape, chemical composition, surface structure and properties, electronic properties, solubility, and state of aggregation and agglomeration. However, the main obstacle in the development of QSARs for NPs is the absence of high-quality and quantitative biological data for groups of similar NPs. Thus, more test data are required, especially *in vitro* data generated by targeted studies for defined groups of NPs. Another problem is the lack of descriptors that are optimised for representing the structural and chemical characteristics of NPs.

3. Application: carbon nanoneedles

Carbon nanotubes have emerged as potential drug carriers in the field of nanomedicine. Some recent studies have demonstrated that chemically modified carbon nanotubes can act as nanoneedles, easily crossing biological barriers and penetrating a variety of cell types [68-70]. This finding raises the potential of functionalised carbon nanotubes as a new form of direct drug delivery [71]. Functionalised nanotubes capable of acting as cell-penetrating materials can behave as nanoneedles that pierce plasma membranes and translocate directly into cytoplasm without causing cell damage, with the advantage of being quickly excreted. The nanotubes also offer a structural advantage in that they are extremely thin but very long, offering a large surface area on which the required drug can be bound. This allows the amount of drug loaded onto the nanotube to be regulated. However, the mechanisms of action are still unclear and the release of the chemically conjugated drug from the nanoneedle is not always possible. Current investigations are directed to studies of increased efficiency of drug delivery and drug targeting [72], as well as improved release profiles and reversible associations for the intracellular release of the drug [73]. On the other hand, similar structures, such as fullerenes [74], have been found to be good drug carriers but with the inconvenience of not being soluble in polar solvents, which reduces their application in medicinal chemistry.

Some recent studies have focused on ultrafine nanoneedles [75]. They provide a low invasive means for molecular delivery, manipulating cells and transferring genes in living cells by using atomic force microscopes [76]. DNA can be

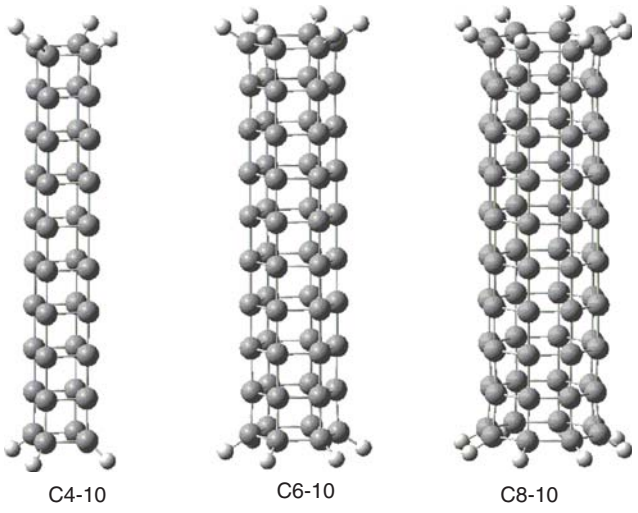

Figure 1. Structure of C4, C6 and C8 carbon nanoneedles with 4, 6 and 8 terminal units, respectively, and 10 layers.

immobilised on the surface of nanoneedles by covalent bonding and affinity binding. This technique enables accurate displacement and low invasiveness.

By contrast, synthetic nanoneedles have been applied in oncology therapy [4] as highly selective ion channels that control the molecular traffic across the cell membrane, targeting specific diseased cells [77]. Similarly, magnetic drug targeting using iron oxide NPs as carriers is a promising cancer treatment that avoids the side effects of conventional chemotherapy [78]. Once the drug is delivered, it can be easily eluted by simply changing either the ionic strength or the pH of C4, C6 and C8 carbon nanoneedles (CNNs) with 4, 6 and 8 terminal units, respectively, and 10 layers.

In a recent study by Mezey and co-workers, electronic and theoretical properties of ultrathin carbon [29] and nitrogen [30] needle-like and tube-like nanostructures, which are tighter than the smallest single wall nanotubes, have been studied by using quantum chemical calculations. Knowing that the synthesis of these structures is not straightforward [79], a more recent study aimed to investigate the geometry and stability of a family of packed CNNs by using quantum chemistry computational modelling methods [20]. A family of packed CNNs was investigated using various terminal units (C4, C6 and C8) and a different number of layers (from 1 to 10 layers, and punctual calculations with 15, 20 and 25 layers). **Figure 1** displays these highly symmetrical structures corresponding to 10 layers. The electronic properties and energetic stability of all these nanostructures were investigated.

The average C–C bond distance clearly reflects that when increasing the number of layers the strength between layers is lower. For C4, the study has been enlarged with punctual calculations for 15, 20 and 25 layers. The values are very similar with respect to C4-10, but they show a slight decrease of the C–C strength between layers. This confirms the validity of the extrapolation from simplified CNNs to explain the properties of real CNNs at the limit of infinite length.

Conceptual DFT turns out to be a useful tool to compare the similarity and relationships between structures. The calculated values of the HOMO–LUMO energy gap, chemical potential (μ), chemical hardness (η) and Parr electrophilicity (ω) for C4, C6 and C8 CNNs for the different number of layers (N layers) allow deep comprehension of their behaviour. The gap decreases when increasing the number of layers. For the C8-10 structure the gap is only 1.574 eV with respect to the 2.771 eV of the C4-10 structure. The C4-15, C4-20 and C4-25 CNNs give values of 2.482, 2.437 and 2.358 eV, respectively. The asymptotic value of the HOMO–LUMO gap might be too large to allow conductivity, thus agreeing with the paper of Wang and Mezey [29]. However, this asymptotic value is quite small at infinite length of the nanoneedle, pointing towards a certain semiconductor character when increasing the CNN size. Therefore, for very long layered structures the corresponding CNNs are likely to have semiconducting properties and could possibly be used as actual semiconductors as the (3, 0) structures described by Wang and Mezey [29]. From the frontier molecular orbital theory, it is confirmed that the possible conjugation between layers for the shortest CNNs (from one to four layers) decreases with increasing number of layers. The strong overlaps both between layers and within layers present, especially in C4-4, nearly disappear in C4-20. Therefore, at infinite length the CNN properties cannot be extrapolated from the shortest structures.

The chemical hardness for C8-1 with D_8h geometry is 1.820 eV, compared with the 1.022 for the S_4 geometry, thus reinforcing the idea of the instability of the planar minimum. When increasing the number of layers the CNN becomes less and less hard, and when going from C4 to C6 and C8 the CNN is even less hard. In the case of the less hard C8, these structures are more reactive with respect to other chemical species. The values for the C4 CNNs with 15, 20 and 25 layers are 1.052, 1.032 and 0.999 eV, showing the same decreasing trend, but not enough to predict very unstable species at an infinite length. This confirms the structural factor that describes a slightly lower binding strength between layers when increasing the number of layers of the CNN.

The Parr electrophilicity (ω) is higher when the number of layers is increased, and consequently C8 CNNs are much more electrophilic than the C4 and C6 CNNs for more than four layers. **Figure 2** illustrates that the expected asymptotic behaviour described by Wang and Mezey [29] that precludes conductivity for these CNNs at the infinite length is not completely true. Instead of this asymptotic behaviour a quite linear relationship between the electrophilicity and the increase of the number of layers is observed, although with a low slope. Therefore, it is plausible that at infinite length the synthesised species are quite electrophilic, as observed in **Figure 2**.

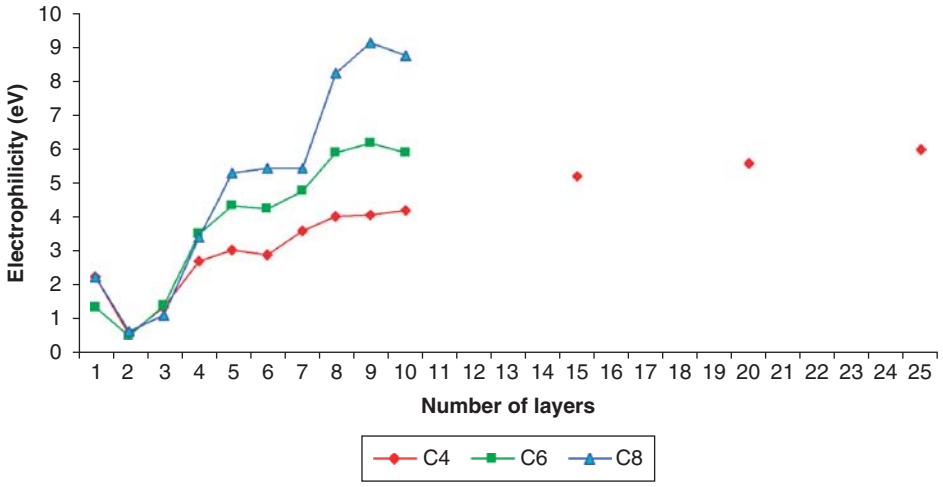

Figure 2. Electrophilicity versus number of layers for C4, C6 and C8 carbon nanoneedles.

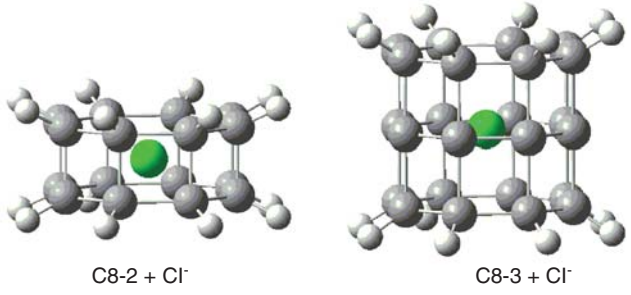

Figure 3. C8-2 and C8-3 structures as carriers of one chloride anion.

The particular properties of CNNs make them potentially suitable in the biological field as carriers. Taking advantage of the unexpected high electrophilicity for C8 structures, an attempt to simulate the application of CNNs has been made including charged ions inside their structure, thus accommodating ions in the middle of each layer and also between layers. The first approach reveals that including a chloride anion inside the C8-2 and C8-3 structures decreases the HOMO–LUMO gap from 7.265 to 5.438 and from 5.462 to 0.402 eV, respectively. **Figure 3** shows that the chloride in C8-2 is between the layers and for C8-3 in the middle of the central layer of the CNN. Therefore, it seems reasonable that CNNs including the carried ions could adopt the property of conductivity, which would have potential applications in facilitating ion exchange in cells. On the other hand, potassium cations have also provided a decrease of the HOMO–LUMO gap from 5.462 to 4.329 eV for the C8-3 structure, although the increase of conductivity is lower than for the chloride anion, because the electrophilicity of C8 structures favours the interaction with anionic species. More research is needed to tailor the use of CNNs to deliver drugs, to improve the release of the drugs, and to complement the theoretical studies with toxicity studies.

The versatility of CNNs as well as the possibility to control their length in terms of number of layers makes them potentially useful as specifically targeted drug delivery systems. Thus based on CNNs, different computational techniques have been applied to study theoretical physicochemical properties that can be directly related to reactivity, demonstrating how the different geometrical and reactivity measures build up a picture of how the properties of CNNs depend on length and diameter.

The studied families of CNNs can be considered as carbon nanostructures with unique structural and chemical properties. Owing to their unusual electronic properties, they have potential practical applications as NMs and nanostructure devices. In addition, infinite-length CNNs are likely to have semiconducting properties, allowing their use as semiconductors in nanostructure devices. The increase in the diameter of the needle makes it more conductive. However, the main property of these CNNs is the role as biological ion carriers. When the ring is made of at least eight atoms, it is possible to bind potassium, sodium, chloride, or iron ions, which would enlarge greatly this conductivity. More research is focused on this aspect, to explore the use of CNNs as a possible mechanism for the oral ingestion of ionically charged drugs embedded in the nonpolar CNNs, varying the width of the cavity of the CNNs by modifying the number of terminal units of the layers.

4. Expert opinion

By simulating CNNs with quantum mechanics it is possible to predict their properties at infinite length. Indeed, some studies reveal that the CNNs might act as semiconductors, especially when the number of terminal units is increased. CNNs are also potentially able to stabilise ions around their structure [16,29]. Therefore, owing to the apolar characteristics

of CNNs and their ability to carry ionic species, they are expected to be suitable to act as drug carriers through nonpolar biologic media.

The molecular modelling of NPs is useful for elucidating the mechanistic basis of their effects. Techniques such as quantum mechanical calculations, force field-based methods, and classical and *ab initio* molecular dynamics simulations are the means to reach this goal.

This review aims to raise awareness of typical computational tools such as conceptual DFT traditionally used in the chemistry field and in the healthcare and pharmaceutical field. These tools are often computationally undemanding and provide a high number of predicted properties that could avoid a lot of experiments in laboratories. The above overview highlights studies on CNNs that illustrate the possible application of computational tools; however, these tools may be also useful for any study related to NPs on the nanometric scale.

On the other hand, even though so far few computational studies have been published, QSAR methodology should increasingly provide a means to predict optical, mechanical, chemical and electronic properties of NPs. The synergistic combination of computational methods for property prediction includes multivariate statistical methods that relate structural descriptors to end points, molecular modelling approaches for simulating the interaction of the NPs with biological systems, and statistical probabilistic methods. To gain insight through QSAR methodology it will be necessary to use new quantitative studies. In particular, data on the characterisation of NPs, data on toxicological end points of interest, and physicochemical properties and calculated structural descriptors are needed. Future efforts should focus on identifying and developing new relevant descriptors, and on investigating and adapting quantum mechanical methods. Meanwhile, new biological studies aim to develop *in vitro* protocols that improve the structure–activity modelling, NP functionalisation, as well as the description of the interaction with biomolecules. The integration of all the useful techniques will help to understand better the role of NPs in nanomedicine.

Owing to the fact that ultrathin needles provide a minimally invasive and highly selective means of molecular delivery and cell manipulation, a study related to CNNs allowed a few descriptors to be identified based on different computational techniques. These theoretical physicochemical properties can be directly related to reactivity, illustrating how the different geometrical and reactivity measures build up a picture of how the properties of CNNs depend on length and diameter [20]. These CNNs may act as semiconductors, allowing such use in nanostructure devices, and are potentially active as ion carriers in biological fields. Thus, the combination of apolar CNNs and ionic species reveals that these species might develop the function of drug carriers through nonpolar biological media. A potential application could be the oral ingestion of ionically charged drugs embedded in the nonpolar CNNs, controlling the width of the cavity of the CNNs by modifying the number of terminal units of the layers. However, more research on the assessment of potentially adverse human health effects should be conducted. For example, the exposure to nanotube fibres has been associated with mesothelioma in a mouse model, pulmonary fibrosis and lung cancer.

To sum up, the *in silico* modelling of NPs can assist in targeting and filling gaps in knowledge on the effects of these particular particles. Computational models of the behaviour of NPs in biological systems, including simulation models for predicting intermolecular interactions and harmful side effects, can be highly valuable in screening candidate particles for potential biomedical use in diagnostics, imaging and drug delivery.

Declaration of interest

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