Evaluation of the Molecular Polarizability Using the IPPP−CLOPPA−INDO/S Method. Application to Molecules of Biological Interest

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The IPPP−CLOPPA−INDO/S method is introduced to investigate the static molecular polarizability in macromolecules. As an example of application, the polarizability of phospholipidic compounds, with and without the presence of water molecules has been estimated. The IPPP technique was employed to calculate the polarizability of the polar head and the hydrocarbon chains separately to analyze the feasibility of evaluating the total polarizability of the molecule by addition of these two projected results. INDO/S dipole moments of different fragments of the complex molecule were obtained by means of localized molecular orbitals in order to evaluate the charge transfer in the system.

1. Introduction

The response of molecules to externally applied electric fields is a topic of fundamental interest for many phenomena such as nonlinear optics or molecular interactions. In particular, the static molecular polarizability tensor $\overset{\leftrightarrow}{\alpha}$ gives information of the electronic distribution in molecules and, for example, it is a fundamental parameter in the theory of light dispersion by macromolecule suspensions.[1] Hence, theoretical methods designed to unravel the mechanisms involved in such interactions may be of great importance. However, up to now, the theoretical estimation of the static polarizability of large molecules usually involves the addition of polarizabilities of the functional groups arranged in the complex system.[2] This method depends, in many cases, on the validity of crude approximations, such as (a) the partial or complete neglect of environmental electronic effects on each functional groups and (b) the assumption of a total additivity of the polarizabilities of the different functional groups. On the other hand, accurate *ab initio* calculations of the polarizability tensor of such macromolecules based on quantum mechanical grounds turn out to be completely unfeasible, due to the large requirements of computer resources. Therefore, the possibility of obtaining calculated polarizabilities of the whole system from rigorous methods based on quantum mechanics using less time-consuming semiempirical wave functions may become a more attractive and reliable alternative.

Although the molecular polarizability characterizes the response of the whole molecule to a uniform external field, further information on the electronic system distortion in the presence of an electrostatic perturbation can be provided by specifying the polarizability associated with each suitable fragment within the molecule. Moreover, this “local” polarization effects description can be most useful to characterize the influence of a particular molecular fragment on the others. A method intended to carry out this type of analysis of the molecular polarizability has been implemented some years ago in an *ab initio* level of approximation.[3] This method is based on “contributions from localized orbitals within the polarization propagator approach (CLOPPA)[4]—inner projections of the polarization propagator (IPPP),[5] which makes use of the polarization propagator formalism, together with localized molecular orbitals (LMOs). This method provides a decomposition of the molecular polarizability tensor into contributions arising from different molecular fragments, described in terms of usual chemical concepts. Furthermore, direct as well as indirect influences of each molecular fragment can be determined by means of the inner projection technique.[6] This is particularly useful for identifying the underlying mechanisms which define the polarization of the electronic cloud.

In this work, the IPPP−CLOPPA approach is implemented at an INDO/S[7] level for the study of the polarizability tensor in large molecules, within a local modified version of ZINDO package.[8] IPPP−CLOPPA−INDO/S was already implemented for the calculation of nuclear spin−spin coupling constants.[9] The versatility of ZINDO allows the calculation of the semiempirical molecular wave function by manually introducing polarization orbitals over the different atoms of the molecule. This additional capability in the evaluation of the molecular polarizability also employing such polarization functions appear as an appealing tool that has been also implemented in the IPPP−CLOPPA−INDO/S method. A series of test calculations (unpublished results) of molecular polarizabilities using this approximation on small systems reveal its prospective applicability[10] to larger systems where the molecular polarizability represents a fundamental parameter. Moreover, INDO/S approximation has also very recently demonstrated[11] a very good performance in the description of circular dichroism of helical

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systems, showing its usefulness to treat response properties in large molecular systems.

In order to show the potentialities of this approach, the method is applied in this work to investigate the polarizability of phospholipidic compounds, isolated and in the presence of water molecules. In particular, the crucial issue of the lack of additivity of fragment polarizabilities is discussed.

Phospholipids (PLs) are the basic constituent units of cell membranes. They present a highly polar hydrophilic head and a nonpolar hydrophobic tail that creates a barrier in cellular membranes, forming phospholipidic bilayers or polymeric nanoparticles called liposomes. Due to their properties, PL vesicles can be used as a drug delivery device,[12] or biomimetic materials can be developed from self-assembled monolayers of PLs.[13] The molecular design of layers containing phospholipid units with specific dielectric properties[14] is continuously investigated, as well as their interactions with different types of drugs such as PRODAN[15] or valproic acid.[16] In theoretical studies of such phenomena, electrostatic interactions of the phospholipid and its surroundings must be taken into account, i.e., the presence of water, an essential component of biomembranes, due to its functional and structural roles at the environment of PL molecules. For this reason, it becomes critical to study the interaction of PL with water,[17–22] which has been extensively analyzed in experimental and theoretical works.[23–28] Such interactions with the environment may be described by the polarity of different fragments of the molecule and by the response of a given fragment to an electrostatic interaction. Therefore, the IPPP−CLOPPA−INDO/S approach is presented as a suitable method for analyzing this kind of interactions.

Finally, as an accessory subject, the analysis of dipole moments of different molecular fragments is also accomplished, to get a complementary overview of the different effects that take place. To this end, two different criteria of evaluating the dipole moment of a molecular fragment are proposed, which give additional information about the charge distribution in the fragment. To our knowledge, this approach constitutes an original quantum mechanical method to analyze the polarizability of macromolecules of biological interest.

2. Method of Calculation

IPPP−CLOPPA−INDO/S Method. Since the IPPP−CLOPPA method applied to the analysis of the static molecular polarizability tensor was fully described previously,[3] only its main concepts are presented here, for the sake of comprehension. The central idea is to represent the electronic structure of a molecular fragment in terms of LMOs which closely resemble the chemical functions of bonds, lone pairs and the corresponding antibonding orbitals ("antibonds"), providing a framework for defining "local polarizabilities", i.e., the polarizability of the local fragment. This approach consists of the following steps. First, the electronic ground-state of the system is obtained as a unideterminantal wave function, calculated in this work with the INDO/S approximation. Then, adequate unitary transformations are separately applied to the occupied and vacant canonical molecular orbitals (MOs) to get localized molecular orbitals, which represent the chemical functions mentioned above. Finally, "local" polarizabilities are calculated within the polarization propagator formalism at the random phase approximation (RPA)[29] level, by means of the inner projections technique[6] onto the LMOs that define the fragment.

Within the PP formalism, the polarizability tensor can be written as[29]

$$\overleftrightarrow{\alpha} = -2 \sum_{ia \leq jb} {}^{1}P_{iajb}(\langle a|\vec{r}|i\rangle\langle b|\vec{r}|j\rangle + \langle b|\vec{r}|j\rangle\langle a|\vec{r}|i\rangle) \qquad (1)$$

where ${}^{1}P$ is the singlet part of the PP matrix and i,j (a,b) stands for occupied (vacant) canonical MOs. $\langle a|\vec{r}|i\rangle$ is the matrix element of the dipole operator $\vec{r}$ for a given vacant a and occupied i canonical MOs.

The contribution of a molecular fragment to the rs Cartesian component ($r,s = x,y,z$) of the polarizability tensor is defined by rewriting (1) in the LMOs basis

$$\begin{aligned} \alpha^{L,rs} &= -2 \sum_{ia \leq jb}^{\text{local}} W_{iajb}(\langle a|r|i\rangle\langle b|s|j\rangle + \langle b|r|j\rangle\langle a|s|i\rangle \\ &= \sum_{ia \leq jb}^{\text{local}} \alpha_{iajb}^{L,rs} \end{aligned} \qquad (2)$$

where now $a,b(i,j)$ are vacant(occupied) LMOs. The sum in eq 2 is restricted to the subset of LMOs, which define the chosen molecular fragment. W_{iajb} is the element of the singlet PP matrix "inner-projected" onto the subset of LMOs that define the chosen fragment.

Each term $\alpha_{iajb}^{L,rs}$ of the sum in eq (2) involves at most two occupied and two vacant LMOs and indicates to what extent the a vacant LMO contributes to the polarization induced in the i occupied LMO by the effect of intramolecular interactions, when the j occupied LMO is coupled with the b vacant LMO by the external field. Therefore, each term gives a measure of the efficiency of such involved LMOs in transmitting the polarization of the electronic cloud induced by the external perturbation. However, it must be noted that W_{iajb} depends on all LMOs belonging to the local fragment and, thus, each $\alpha_{iajb}^{L,rs}$ term contains the influence of the whole fragment under consideration. Similarly, if in eq 2 the total PP matrix ${}^{1}\mathrm{P}_{iajb}$ instead of the projected one W_{iajb} is used, the resulting $\alpha_{iajb}^{L,rs}$ terms contain the indirect influence of all LMOs of the whole molecule. This indirect influence can be quantified as:

$$\alpha^{\text{ind},rs} = \sum_{iajb}^{\text{local}} \alpha_{iajb}^{\text{ind},rs} = \sum_{iajb}^{\text{local}} (\alpha_{iajb}^{rs} - \alpha_{iajb}^{L,rs}) \equiv \alpha_{\text{CLOPPA}}^{rs} - \alpha_{\text{IPPP}}^{rs} \qquad (3)$$

where the sums run over all virtual excitations of the chosen fragment. $\alpha^{\text{ind},rs}$ shows to what extent the rest of the molecule contributes indirectly to the polarization of the fragment. This constitutes the difference between the IPPP and the CLOPPA approach, when the polarizability of a molecular fragment is sought. While in the IPPP method the "local polarizability" is calculated as in eq 2, in the CLOPPA approach, the same equation is used but using the whole PP matrix instead of the projected one. In that sense, the first sum of eq 3 is calculated by means of the CLOPPA method, while the second one is performed by means of the IPPP approach. Therefore, the CLOPPA method provides the polarizability of the considered fragment, but also including the indirect influence of the rest of the molecule.

Although CLOPPA calculation could be more appropriate if the influence of the whole system on the polarizability of the fragment is significant, an IPPP calculation can be useful and reliable if this influence can be neglected, or the polarizability strictly originated in the chosen fragment is looked for. Moreover, if the influence between fragments is not considerable, the polarizability of the whole compound could be considered as the sum of the IPPP calculations of the different molecular fragments. Consequently, the rs component of the polarizability tensor can be written as:

$$\alpha^{rs} = \sum_{X} [\alpha^{X,rs}_{\mathrm{IPPP}} + (\alpha^{X,rs}_{\mathrm{CLOPPA}} - \alpha^{X,rs}_{\mathrm{IPPP}})] + \sum_{XX'} \alpha^{XX',rs} \quad (4)$$

where $\alpha^{X,rs}_{\mathrm{IPPP}}$ represents the *rs* component of the polarizability tensor of fragment X, strictly originated in such fragment, calculated with the IPPP approach, whereas $\alpha^{X,rs}_{\mathrm{CLOPPA}}$ is the *rs* component originating in fragment *X* that contains the indirect influence of other fragments. Hence, $\Delta\alpha^{X,rs} = (\alpha^{X,rs}_{\mathrm{CLOPPA}} - \alpha^{X,rs}_{\mathrm{IPPP}})$ gives the indirect influence of other fragments on the polarizability of fragment *X*, and $\alpha^{XX',rs}$ represents the sum of CLOPPA terms that mix virtual excitations of different fragments *X* and *X′*. This last term can be dubbed "mutual polarizability between fragments". From eq 4, it can be seen that additivity of fragment polarizabilities only holds, if and only if, the three last terms of eq 4 can be neglected. However, it must be taken into account that, although the IPPP value can be considered as strictly belonging to a certain fragment, it depends on the molecule to which the fragment belongs.

Calculation of the Dipole Moment of a Fragment. The procedure used to perform the calculation of the dipole moment of a fragment with LMOs involves the nuclear contribution of the nuclei of the fragment and the occupied LMOs belonging to the fragment to evaluate the electronic contribution. Thus, the calculation of a component *r* (*r* = *x, y, z*) of dipole moment of the fragment *X* using a semiempirical method is read as:

$$\vec{m}^{X}_{r}(\vec{r}) = \sum_{N\in X} Z_N\vec{r} - [\sum_{N\in X} Z'_N\vec{r} + 2\sum_{i} \langle i|\vec{r}|i\rangle] \quad (5)$$

where terms inside the square brackets describe contributions of core electrons (Z′ is their charge) and valence electrons. For this last term

$$\sum_{i} \langle i|\vec{r}|i\rangle = \sum_{i\neq k_n} \langle i|\vec{r}|i\rangle + \sum_{k_n\in \mathrm{boundary}} \langle k_n|\vec{r}|k_n\rangle/2 \quad (6)$$

where k_n denote the LMOs of the fragment boundary. It is obvious that LMOs "in this boundary" belong to the fragment as well as they also belong to the rest of the system. It appears reasonable that the total electronic contribution includes the internal LMOs plus half the contribution of LMOs of the boundary. With this criterion the contribution of these LMOs are assigned in equal parts to the fragment of interest and to the rest of the system.

Another alternative to this calculation is the summation over the atomic basis of the fragment:

$$\vec{m}^{X}_{r}(\vec{r}) = \sum_{N\in X} Z_N\vec{r} - \left[\sum_{N\in X} Z'_N\vec{r} + 2\sum_{i}\sum_{\mu,\nu\in X} C_{\mu i}C_{\nu i}\langle\mu|\vec{r}|\nu\rangle\right] \quad (7)$$

This kind of calculation takes account of the fraction of charge transferred between both fragments and the dipole moment of the fragment of interest can be evaluated with the net charge, which stayed inside the "limits of the fragment" after such transfer.

3. Results and Discussion

Numerical results of the IPPP−CLOPPA−INDO/S analysis of the molecular polarizability tensor and dipole moments of phospholipidic compounds are presented as a suitable example to show the potentialities of the method. Calculations were carried out for a model phospholipid (PL) with two hydrocarbon chains (HCs) of five C atoms, isolated and in the presence of water molecules, and dimyristoylphosphatidylcholine (DMPC), which is similar to PL but contains two HCs of fourteen C atoms each (see Figure 1). Geometric structures of both compounds were obtained with the AM1[30] method, following these steps. First, the polar head (PHd) of PL without HCs was optimized. Then, the structure of the HCs was optimized separately from the polar head, and added to the optimized PHd, with the restriction of keeping the chains nearly parallel to each other. Such restriction was applied in order to mimic the actual structure of PL when it is immersed into the biomembrane surrounded with other neighboring PLs. The addition of three water molecules (WMs), W1, W2, W3, (PL+WMs in Figure 1), was performed keeping fixed the structure of PL and just optimizing the WMs after having placed two of them near the nonsterical oxygen atoms and the other one near the choline group (NMe_3). Coordinates axes *x* and *z* for the model compounds are shown in Figure 1; the *x* axis is nearly the direction of phosphocholine (PC) dipole, and *z* corresponds approximately to the direction along the HCs. All over this work, a minimal atomic valence basis set was used to calculate the INDO/S wave functions and properties, except when other basis sets were explicitly mentioned. The different molecular fragments were defined by the corresponding subset of LMOs (bonds, lone pairs and their antibonding orbitals) within the fragment, from the set of LMOs obtained after a full localization of the molecule. Molecular fragments will be denoted as X(Y) where X represents a fragment of compound Y. For example, PHd(PL + WMs) represents the PHd fragment from the whole (PL + WMs). In order to compare with results obtained for fragments within the molecules, two additional model compounds which mimic the phospholipidic polar head are taken into account. These compounds are dubbed PHd and PHd1, the latter being a simplified portion of the former, as it lacks the polarizable $O{=}C{-}O_2{-}C{=}O$ group, which is present in PHd (see Figure 1).

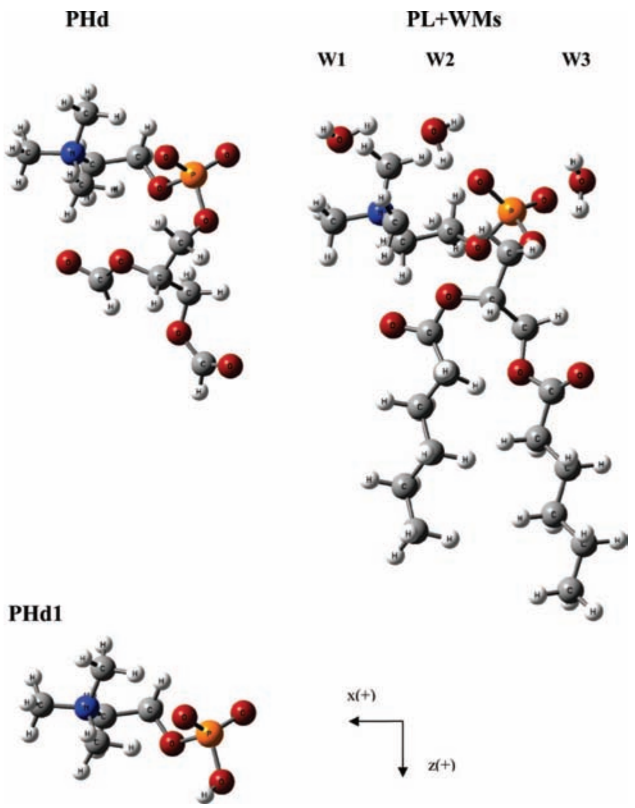

Figure 1. Model compounds used for the calculation of dipole moment and static molecular polarizability.

Analysis of Dipole Moments and Charge Transfer. Table 1 displays the dipole moments calculated following eq 7, for PHd, PL, and PL + WMs with INDO/S approximation, taking

TABLE 1: Electric Dipole Moment (in au) of Compounds Calculated with INDO/S and Other Levels of Theory X(Y) Corresponding to a Fragment X of system Y[b]

fragments		*X*	*Y*	*Z*	norm
PHd1	INDO/S	1.87	3.75	−6.21	7.49
	B3LYP/6-31G**	2.00	3.23	−4.74	6.07
	B3LYP/aug-cc-pVDZ	2.02	3.20	−4.76	6.08
	HF/6-31G**	2.13	3.42	−5.00	6.42
	HF/aug-cc-pVDZ	2.07	3.35	−4.97	6.34
PHd	INDO/S	5.43	−0.08	2.81	6.12
	HF/6-31G**	4.50	−0.38	2.16	5.00
	HF/aug-cc-pVDZ	4.45	−0.41	2.11	4.95
PL	INDO/S	4.84	0.15	2.90	5.64
	B3LYP/6-31G**	4.02	−0.22	2.32	4.65
	INDO/S				
PHd(PL)		5.12	0.06	2.73	5.80
HCs(PL)		−0.29	0.10	0.16	0.34
PL+WMs		4.26	−0.34	3.26	5.37
PHd(PL+WMs)		5.23	−0.00	2.82	5.94
HCs(PL+WMs)		−0.28	0.095	0.17	0.34
PL/PL+WMs[a]		4.95	0.09	3.00	5.79
PL+WMs/PL[a]		5.14	0.15	3.34	6.13
PL/PL[a]		5.33	0.07	3.19	6.21

[a] The notation stands for LMOs/AOs. It denotes the subspace of LMOs and AOs used in the calculation. [b] See Figure 1 for identification of molecular systems.

into account the contributions from several molecular fragments. Other *ab initio* and DFT calculations are also included for PHd1, PHd, and PL. A qualitative, and almost quantitative, good agreement of these calculations with INDO/S results is observed, demonstrating a reliable description of INDO/S approximation. It can be observed from the table that the calculated dipole moments of fragments PHd(PL) and PHd(PL + WMs) yield a similar result to the dipole moment of the isolated polar head PHd. The HCs have a small dipole moment as it can be assessed from the results of HCs(PL) and HCs(PL + WMs) projections. The presence of such chains slightly diminishes the polar head dipole moment; the largest difference corresponds to the *x* direction where the chains present a major charge asymmetry (direction of the PC dipole moment).

Concerning the addition of WMs, three different projection schemes denoted [LMOs/AOs] are employed in this section when projecting over the PL subspace, which involve different subsets of LMOs and atomic orbitals (AOs). Thus, (a) PL/PL + WMs corresponds to the subspace of LMOs localized over the PL fragment and considering the contribution of the whole atomic basis set, (b) PL + WMs/PL involves a subspace defined by all LMOs of the system PL + WMs and AOs of the chosen fragment (PL), and (c) PL/PL contains only LMOs and AOs of the PL. The physical interpretation of results obtained from each of these three cases can be figured out in the following way. PL/PL + WMs yields a charge distribution where LMOs of the fragment are extended to the region of WMs and thus, it includes a fraction of the charge transferred from the PL to such region. PL + WMs/PL takes into account the spreading out of LMOs belonging to the WMs subspace onto the region of the PL, i.e., the fraction of the charge transferred in the opposite sense from the first case. Meanwhile, the case PL/PL involves the charge distribution of LMOs of the fragment that stays within the “region of the PL”. When the PL valence charge is calculated taking the fragment described by this last case, a charge of 177.96 electrons is obtained while the total valence charge of compound PL (without the WMs) corresponds to 178 electrons. The missing fraction of charge is the net charge transferred to the WMs because of their interaction with the PL. It involves charge going to opposite senses, depending on the WMs location related to the PL functional groups.

TABLE 2: Charge of WMs, W1, W2 and W3 When Interacting with the PL, and Charge Transfers between WMs and PL (See Figure 1) with All Values in au

	AOs[a]	LMOs[a]	W1	W2	W3
1	PL+WMs	WMs	8.0000	8.0000	8.0000
2	WMs	PL+WMs	7.9980	7.9960	8.0160
3	WMs	WMs	7.9966	7.9770	7.9982
4	WMs	PL	0.0014	0.0190	0.0178
5	PL	WMs	0.0034	0.0230	0.0018

[a] Subspace of AOs and LMOs included in the calculation.

Table 2 displays the calculated charges of the WMs W1, W2, and W3 (see Figure 1). There are four occupied LMOs per WM, i.e., 8.00 electrons, as indicated in line 1 of Table 2. However, due to interaction with PL, there is a small charge redistribution, which can be analyzed as follows. In line 2, values correspond to the total electronic charge on each WM; i.e. they take into account the contribution of the PL LMOs to the charge of each WM when interaction occurs. Subtraction of line 2 from line 1 results in the net charge transferred between the fragments. Third and fourth lines of Table 2 display the projection of the LMOs of WMs and PL, respectively, over WMs AOs subspace. From line 3, it is seen that there is electronic transfer from WMs to PL, and the largest value is found for W2. Line 4 shows the contribution of WMs AOs to PL LMOs; i.e., these values represent the amount of electronic transfer from PL to the WMs region. Similar values are found for W2 and W3, but for W1 it is much smaller. Finally, line 5 is obtained when line 3 is subtracted from line 1 and it corresponds to the charge transferred from the WMs to PL.

In the optimization of WMs in the vicinity of the PL system, W1 and W2 have stayed close to each other so that W2 appears to be interacting through two hydrogen bonds: one with PL and the other with W1. W1 acts as an electron donor with PL, while W2 acts as an electron donor in its interaction with W1, but as an electron acceptor in its interaction with PL. W3 acts as an electron acceptor and interacts exclusively with PL. Within the perturbation molecular orbital (PMO) approach, the charge transfer is directly related to the strength of the interaction between fragments.[31] Thus, interaction with W1 is the weakest according to this scheme.

Analysis of Polarizabilities. In a first step the static polarizabilities of the two model compounds PHd1 and PHd are investigated (see Figure 1). Due to the absence of the polarizable $O{=}C{-}O_2{-}C{=}O$ group, it is expected to obtain a considerably lesser polarizability for the former than for the latter, as it can be assessed in Table 3. Indeed, the decrease of α_{xx} in PHd1 can attain half the value in PHd.

Table 3 presents the results obtained by means of the INDO/S approximation, compared with those obtained by other theoretical approaches. The diagonal components of the polarizability as well as their isotropic values are displayed for the B3LYP hybrid DFT functional and HF at *ab initio* and semiempirical levels (AM1 and INDO/S wave functions). Concerning the DFT and *ab initio* results, different basis sets are employed and the most refined *ab initio* calculation reported is at CCSD/6-31+G* level. More sophisticated calculations, as for instance with larger basis sets, imply consuming too many computational resources. This is the reason why a compromise has been sought by employing the 6-31+G* basis set, which contains diffuse and polarization functions offering a sufficient accuracy for the calculation of static polarizabilities (see for example ref 32). It

TABLE 3: Comparison of the Diagonal Elements of the Static Polarizability Tensor and Its Isotropic Value $\langle\alpha\rangle = {}^1/_3 tr\tilde{\alpha}$ Using Different Methods and Basis Sets for the Compounds PHd1 (a) and PHd (b) (See Figure 1) with All Values in au[a]

(a) PHd1

PHd1	α^{xx}	α^{yy}	α^{zz}	$\langle\alpha\rangle$
B3LYP/6-31G	86.21	90.28	87.53	88.01
B3LYP/6-31G**	88.82	92.29	91.62	90.91
B3LYP/cc-pVDZ	91.41	94.19	93.52	93.04
B3LYP/aug-cc-pVDZ	107.11	110.20	112.66	109.99
CCSD/6-31+G*	94.99	99.12	98.88	97.66
HF/6-31G**	77.51	79.90	92.97	83.46
HF/SADLEJ	91.54	93.98	111.02	98.85
HF/aug-cc-pVDZ	96.04	99.25	100.05	98.45
HF/AM1	66.74	71.57	66.13	68.15
HF/INDO/S	46.89	50.26	54.07	50.41
HF/INDO/S*	97.37	99.54	101.51	99.47

(b) PHd

PHd	α^{xx}	α^{yy}	α^{zz}	$\langle\alpha\rangle$
B3LYP/6-31G**	288.66	231.44	285.70	268.60
HF/6-31G**	164.40	124.33	139.90	142.88
HF/aug-cc-pVDZ	187.97	144.62	163.29	165.29
HF/AM1	151.55	102.02	119.95	124.51
HF/INDO/S	109.13	73.54	81.36	88.01
HF/INDO/S*	183.91	149.51	160.00	164.47

[a] INDO/S* using s and p orbitals for all the atoms (H inclusive).

can be observed that B3LYP predicts larger responses than HF for PHd, and PHd1, although the difference is much larger in the former than in the latter. This enhancement could suggest that correlation effects are important. Nevertheless, as it is well-known that singlet properties are quite insensible to this kind of effects, the functional also possibly overestimates the response due to the well-known self-interaction error in delocalized systems.[33] Indeed, a larger delocalization could be reinforced in PHd by the presence of the $O{=}C{-}O_2{-}C{=}O$ group. The HF/INDO/S approximation yields values that attain half the values of the *ab initio* and DFT values, whereas the addition of polarization atomic "p" functions over the hydrogen atoms (HF/INDO/S* values in Table 3) enhance the polarizability to values definitely closer to the other methods. In particular, there is an exceptional good agreement with values obtained with the largest basis set used, namely aug-cc-pVDZ, at the HF level, in both PHd1 and PHd, and a quite good agreement with CCSD/6-31+G* in PHd1. This fact suggests that B3LYP values could be indeed overestimated for PHd. It is also noteworthy that INDO/S values, although underestimated, follows similar trends to *ab initio* and INDO/S* values. Thus, it can be concluded that INDO/S results are adequate for performing a qualitative analysis of the polarizability of the phospholipidic compounds. It is expected that for larger systems, the employment of standard valence basis sets with INDO/S wave function should be enough to account for the principal features of linear response properties, as was claimed by Zerner two decades ago.[34]

IPPP−CLOPPA Results. The contributions to the polarizability from different fragments, and the influence of the environment were analyzed for PL and DMPC (Figure 1) by means of the IPPP−CLOPPA method. This method was used to obtain the response from different fragments of the studied systems to the perturbation of an external electric field. It is interesting to compare results using the IPPP method instead of the CLOPPA one, as the former does not take into account the indirect influence of the rest of the system on the chosen fragment.

Following eq 4, the polarizability components of the model compound PL can be decomposed into two fragments, the polar head PHd(PL) (Figure 1) and the hydrocarbon chain HCs(PL):

$$\alpha^{rs} = \alpha^{\mathrm{PHd},rs} + \alpha^{\mathrm{HCs},rs} + \Delta\alpha^{\mathrm{PHd},rs} + \Delta\alpha^{\mathrm{HCs},rs} + \alpha^{\mathrm{PHd/HCs},rs} \quad (8)$$

where symbols were defined in eq 4. The considered fragments are denoted in a similar way as in Table 1, but taking into account the fact that, since the polarizability is a second order property, vacant orbitals are also involved in the calculation. As it was explained in the preceding section, the polarizability of the whole compound could be considered as the sum of the fragment polarizabilities if and only if the last three terms of eq 8 can be neglected.

Table 4 displays the different terms of such equation for the three diagonal components of the tensor and the isotropic value. The reported results deserve several comments. There is a non-negligible anisotropy of $\tilde{\alpha}$ in PL, with the largest value corresponding to the PC dipole axis; however, the fragment corresponding to the HCs(PL) presents nearly isotropic polarizabilities. The IPPP and CLOPPA contributions from PHd(PL) and HCs(PL) to the total value can be compared with the polarizability of the isolated PHd molecule. It is seen that in both cases small but non-negligible differences are found between the IPPP and CLOPPA calculated fragments. For PL, the indirect influence of the HCs fragment on the PHd polarizability, $\Delta\alpha^{\mathrm{PHd},rs}$, is rather small, showing that the response of the polar head is hardly modified via interactions with the HCs and, therefore, it is almost originated in the fragment. The same comment holds for the indirect influence of the PHd fragment on the polarizability of HCs, $\Delta\alpha^{\mathrm{HCs},rs}$. The mutual polarizability $\alpha^{\mathrm{PHd/Cs},rs}$ carries information about interactions between the electronic distribution of both fragments PHd and HCs of PL. Its magnitude depends on to what extent both fragments involved are polarizable: on one hand, a more polarizable X′ fragment produces an internal field of larger magnitude; on the other hand, a more polarizable X fragment is more affected by this field, and therefore, its induced dipole is larger. In this case, the mutual polarizability is rather small, as it corresponds to groups that are not quite polarizable. Furthermore, the polarizability of the two HCs results to increase nearly linearly with the number of HC units. This fact shows again that groups with a moderate polarizability could be nearly additive.

The present analysis allows assessing quantitatively the limits of the addition of the polarizability fragments in defining the total value. Although all the "nonadditive" effects have small values in this case, the sum of effects represents a non-negligible amount. Thus, when comparing the polarizability diagonal components of the whole system PL calculated using the IPPP technique: 170.29 au, 134.02 au and 136.29 au with total values 185.69 au, 141.26 au, 154.38 au, respectively, the nonadditive terms amount to about 10% of the total value of PL. It is noteworthy that nonadditive terms provide a large fraction of the total anisotropy of $\tilde{\alpha}$ in PL. This fact is not taken into account if fragment polarizabilities are added. Concerning the calculations of DMPC, Table 4 reports on the IPPP PHd(DMPC) and HCs(DMPC) values. In this case the polarizability of PHd(DMPC) is considerably smaller by about one-third of the isolated PHd, denoting that the interaction between PHd(DMPC) and the HCs(DMPC) is stronger than between similar fragments of PL. Bearing in mind that the phospholipids may possess HCs

TABLE 4: IPPP and CLOPPA INDO/S Values of Diagonal Elements of the Static Polarizability Tensor and Its Isotropic Value $\langle \alpha \rangle = {}^{1}/_{3} tr \tilde{\tilde{\alpha}}$ for PL and Several Fragments of PL and DMPC[a]

		α^{xx}	α^{yy}	α^{zz}	$\langle \alpha \rangle$
isolated PHd		109.13	73.54	81.36	88.01
PHd(PL+WMs)	IPPP	91.71	61.69	69.31	74.24
PHd(PL+5WMs)	IPPP	79.12	58.13	69.47	68.91
PHd(PL+8WMs)	IPPP	86.55	60.52	67.96	71.68
PHd(PL)	IPPP	107.27	72.61	80.00	86.63
	CLOPPA	108.66	73.34	80.76	87.59
HCs(PL)	IPPP	63.02	61.41	56.29	60.24
	CLOPPA	64.14	62.61	57.44	61.40
	$\Delta\alpha^{\mathrm{PHd},rs}$	1.39	0.73	0.76	0.96
	$\Delta\alpha^{HCs,rs}$	1.12	1.2	1.15	1.16
	$\alpha^{\mathrm{PHd/HCs},rs}$	12.89	5.31	16.18	9.43
	$\Delta\alpha^{\mathrm{PHd},rs}+\Delta\alpha^{\mathrm{HC}s,rs}+\alpha^{\mathrm{PHd/HCs},rs}$	15.40	7.24	18.09	11.55
PHd(PL)+HCs(PL)	IPPP	170.29	134.02	136.29	146.87
PHd(PL+WMs)+HCs(PL)	IPPP	154.73	123.10	125.60	134.48
PHd(PL+5WMs)+HCs(PL)	IPPP	142.14	119.54	125.76	129.15
PL		185.69	141.26	154.38	160.44
PHd(DMPC)	IPPP	72.96	73.00	66.62	70.86
HCs(DMPC)	IPPP	177.23	169.52	194.43	180.39
PHd(DMPC)+HCs(DMPC)	IPPP	250.19	242.52	261.05	251.25

[a] X(Y) corresponds to a fragment X of system Y. See Figure 1. All values are in au.

of a size up to 24 units, this effect could be significantly enhanced for longer tails.

Another important point to take into account is the influence of the environment. In Table 4, the IPPP components of the polarizability of the PHd fragment are displayed when the PL compound is surrounded by three water molecules (fragment PHd(PL + WMs)). It is observed that, for example, the *xx* component (i.e., the component in the same direction of the main permanent dipole of the polar head) is decreased by the presence of the water molecules. This effect can be due to the specific interactions that hold between the polar head and water, which make electrons in hydrogen bonds to be more bound and, consequently, less amenable to be polarized. There is also a conspicuous difference between values calculated for the PHd(PL) fragment and those calculated for the polar head PHd when taken as a separate compound. These differences can be considered as a direct influence of the rest of the molecule, since they are due to changes in its own electronic distribution when the polar head is embedded in a certain electronic environment. It must be pointed out that IPPP values account for this direct influence. In this case, the effect of the surrounding WMs is extremely important. The calculated values of the polarizability components for PHd(PL + WMs), when merging three WMs, are about 14% smaller than the results of PHd(PL). As in the former case, this effect is due to the specific interactions between the polar head and the water molecules because electrons in hydrogen bonds are more bound than for the isolated PHd. This effect of the environment on the polarizability is larger if more water molecules are added to the system. Table 4 shows the IPPP results corresponding to the polar head subspace surrounded by five and eight WMs, respectively. In these cases, the method predicts a polarizability still a bit smaller (20% and 17%, respectively). Note, however, that the polarizability considering the inclusion of eight WMs increases slightly from that of the system with five WMs. This effect can be due to specific interactions between the WMs themselves and with the fragment PHd.

4. Conclusions and Outlook

A new approach, based on rigorous quantum mechanical grounds, has been implemented to deal with molecular polarizabilities of large organic systems: the IPPP−CLOPPA−INDO/S method. The approach has been compared with *ab initio* and DFT benchmark results to assess its quantum chemical applicability, exhibiting an efficient performance to describe polarizabilities and dipole moments of model phospholipids. At this semiempirical level of theory, this method appears as a useful tool to identify electronic effects taking place in macromolecules and their surroundings. In order to show its potentialities, the method was applied to the fundamental units of membranes, the phospholipids. The explicit application of the IPPP method restricted to different fragments of the system to calculate the polarizability tensor allows the study of larger molecules, with the important improvement of taking into account the direct influence of the rest of the molecule and its environment as well. The fact of restricting the calculation to separate fragments spanned by the own occupied and vacant LMOs of the molecule under consideration, together with the use a semiempirical wave function saves computational resources.

The specific interactions between PL and WMs denote a more realistic situation where the polarizability is diminished by up to 20% by means of charge stabilization. This reduction is very important and must be taken into account for the final result.

It is interesting to observe that the calculations of the IPPP polarizability of HC isolated chains are nearly additive, due to the absence of highly polarizable groups in these fragments. However, the interaction of the PHd fragment with different sizes of these entities appears to have a strong impact on the polarizability of the former.

It must be stressed that still other aspects, out of the scope of the present work, should be considered in the calculations of phospholipid compounds, as a detailed treatment of different conformations of the phospholipids units and their interaction with water molecules. Moreover, the present model investigations might also be extended to more complex models formed by several PL units and WMs in their environments for which a more efficient version of the code is being written.

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