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COMPARATIVE ANALYSIS OF COMPLEXATION OF PESTICIDES (FENITROTHION, METHYLPARATHION, PARATHION) AND THEIR CARBOXYLIC ESTER ANALOGUES BY β-CYCLODEXTRIN. THEORETICAL SEMIEMPIRICAL CALCULATIONS

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The complexation by β-cyclodextrin (β-CD) of three organophosphorus pesticides, fenitrothion, parathion and methylparathion, and of their carboxylic ester analogues was analyzed using PM3 and molecular mechanics methods. The objective was to elucidate structural features and energy changes that accompany the complexation and could possibly affect the hydrolysis process, which is catalyzed by β-CD in the case of carboxylic esters but inhibited for the pesticides, in alkaline medium. The complexation of fenitrothion was further explored, since experiments proved its hydrolysis is relatively less inhibited and progresses mainly through a different pathway than that usually accepted. The results of this study show that complex structures involving esters enable effective interactions between the guest carbonyl and the rim of the host; methylparathion and parathion, however, appear to be deeply included in the cavity of β-CD. Therefore the conditions for a nucleophilic attack by the β-CD are favorable for the carboxylic esters but not for the two pesticides. Different complex geometries resulted for fenitrothion depending on its mode of inclusion in the cavity, none apparently being prone to an attack by the β-CD, but favoring instead the approach of an external OH^- group, in agreement with the experiment.

K e y w o r d s: supramolecular complexes, β-cyclodextrin, inclusion compounds, semiempirical calculations, pesticides.

INTRODUCTION

Cyclodextrins (CDs) are cyclic molecules, built by glucopyranose units, that form host-guest inclusion complexes [1—4]. The most widely used β-cyclodextrin is formed by seven such units and adopts, like other members of the family, the shape of a truncated cone. Glucopyranose secondary hydroxyls are situated on the wider rim of the cone, whereas the primary hydroxyls are located on the narrower rim. The interior of the cavity is lined with two rows of CH groups (*i.e.* the C-3 and C-5 groups) and, in between, by a row of glycosidic oxygen atoms. Thus the exterior of the CD is fairly polar, the interior relatively nonpolar and the cavity becomes attractive to molecules capable of entering it and forming inclusion complexes.

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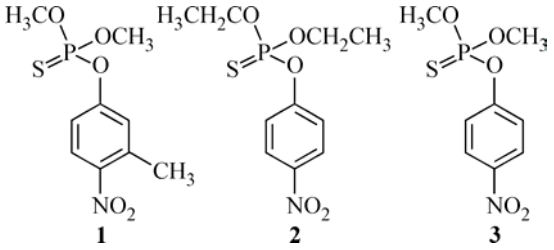

Fig. 1. Pesticides fenitrothion (**1**), parathion (**2**) and methylparathion (**3**)

CD complexation protects the guest molecule against atmospheric oxidation of easily oxidizable substances, enhances solubility of poorly soluble ones, and reduces the loss of those that are highly volatile. Also, synthetic pesticides that can be complexed with CDs frequently show modifications of properties [5—8] such as: enhanced bioavailability, selective toxicity as regards insects, reduced phytotoxicity and long lasting effects in soil due to controlled release properties. The dose of environmental polluting synthetic agrochemicals could thus be significantly reduced and their effectiveness could be improved, if CDs were used in pesticide solution formulations [9].

The application of CD to pesticide formulation was, until recent years, rather modest [10], but the situation has now significantly changed since the cost of technical quality β-CD, entirely acceptable for the pesticide formulation industry, has declined. So potential use of β-CD could be of great interest to enhance biological activity of these chemicals [11—13]. Three organophosphorus pesticides, fenitrothion, parathion and methylparathion (Fig. 1), have been (and some still are) widely used; therefore, their chemical behavior is of interest. Their alkaline hydrolysis, for example, appears to be inhibited by β-CD [14, 15], this effect, ascribed to a shallower inclusion of guest in the cavity, being lower in the case of fenitrothion [16]. Induced circular dichroism analysis [17] revealed that the inclusion of the pesticides occurs by the nitro group entering first. The same happens with the analogous carboxylic esters, whose hydrolysis is, contrarily, catalyzed by β-CD [1, 18].

The effects of CDs on organic reactions are classified in two main groups, depending on whether covalent bonds are involved or not [19]: (a) the CD and reactant bind and form a reaction intermediate that involves a covalent bond and then leads to a product; (b) the hydrophobic CD cavity provides the reactant with a new reaction environment changing reactivity, *i.e.* selectivity and/or rate.

Alkaline hydrolysis reactions that are CD-mediated proceed in general according to the first model: a CD′s secondary alkoxide ion performs a nucleophilic attack on the included reactant, forming a tetrahedral intermediate by means of a covalent bond, then acyl transfer to the CD takes place [20] and finally the hydrolysis products are released.

Tee *et al.* have widely analyzed the cleavage of esters in basic medium and in the presence of CDs (see [21] and refs. therein). They explored several possible binding modes in the initial and the transition states during the process. According to their results, cleavage in *meta*-substituted phenylacetate appears to be more efficient than in *para* isomers. Explanation would be that the insertion of the former in the cavity leads to a geometry that is more favorable for a nucleophilic attack on the part of the CD. Moreover, the *para*-substituted phenyl would be obliged to emerge partially or completely from the cavity during the acyl transference [22].

The purpose of this work was to compare, from a theoretical viewpoint, the complexation and possibly CD mediated hydrolysis of the three pesticides mentioned above with the corresponding carboxylic ester analogues (having OCOR instead of $OPS(OR)_2$). This collection of molecules consists of: (a) two *para*-substituted pesticides and their carboxylic ester analogues; (b) fenitrothion and its carboxylic ester analogue. The latter are both *meta*- and *para*-substituted at the same time, the substituents exerting opposite trends on the included moieties during the hydrolysis process, as mentioned above. So it was interesting to elucidate how these two trends compromise. Moreover, for fenitrothion some of the authors have reported [15] that the attack of the substrate complexed with ionized β-CD by an external OH^- group seems to be the main pathway for basic hydrolysis, with no major nucleophilic attack by an alkoxide ion of β-CD. The rate constant of the process still four times lower than the constant corresponding to hydrolysis of the free substrate. Therefore some further complexation modes, of this compound particularly, were explored and the results are described here.

METHOD AND RESULTS

The accepted mode of complexation of the three organophosphorothioate pesticides [14], fenitrothion, methylparathion and parathion (Fig. 1), and of their corresponding carboxylic ester analogues was studied theoretically. The carboxylic ester analogues are those structures obtained by replacing the thiophosphate-based residues by either acetate (for fenitrothion and methylparathion) or propanoate (for parathion), correspondingly. Carboxylic ester analogues were further labeled according to the pesticide that each of them correlates with: FNth-ester with fenitrothion; MPth-ester with methylparathion; Pth-ester with parathion.

All molecular structures were optimized firstly by MM+ molecular mechanics method contained in the HyperChem-6 program and then by PM3 semiempirical method contained in the same package [23]. We used, as starting β-CD coordinates, the same coordinates as in our previous works [24, 25], with five interglycosidic hydrogen bonds (H-bonds) involving the secondary hydroxyl groups (OH) of the cycle. These coordinates were unloaded from http://www.lists.ic.ac.uk/hypermail/chemweb, as an extracted file from the 1DMB.pdb file available at http://www.rcsb.org/pdb.

Complexation was simulated *in vacuo* by locating each substrate molecule at a distance of ~3 Å from the center of the circle determined by the secondary rim of the β-CD. On the basis of the experimental data [17], the substrate or guest was oriented so that its vertical insertion into the cavity would take place with the nitro group entering first. Eleven different orientations were tried, each resulting from the rotation performed about the longitudinal axis of the guest. This procedure was due to the C1 symmetry of the β-CD that was employed, which is more frequent and probable in the reaction medium than the C7 symmetry structure [26].

The sequence followed was: (i) submission of the system to an MM+ process until convergence, which led the guest to dock into the β-CD molecule, and (ii) submission to a PM3 optimization. Convergence criteria were rms grad = 0.005 kcal·Å^{-1}·mol^{-1} for MM+ calculations (exception made for the β-CD whose structure would thus become too distorted; the value ~0.05 was adopted) and 0.05 kcal·Å^{-1}·mol^{-1} for PM3.

The most stable complexes were chosen, though some less stable structures were also considered because, being quite close in energy, they presented some feature of interest. The additional insertion modes explored for fenitrothion were performed according to the methodology just described and the results are commented apart.

T a b l e 1

MM and PM3 energies (kcal·mol^{-1}) *of molecules in free state, and selected atomic charges and bond orders in the substrates*

Molecule	E_{free} (MM)	E_{free} (PM3)	Atomic charge		Bond order	
			q(—O— [a])	q(P/C [b])	P(C_A—O— [c])	P(—O—P/C)
Fenitrothion	31.74	–2863	–0.563	1.835	1.033	0.630
Methylparathion	30.26	–2580	–0.535	1.840	1.029	0.671
Parathion	30.67	–3140	–0.535	1.849	1.030	0.669
FNth-ester	5.60	–2431	–0.231	0.379	0.992	0.967
MPth-ester	3.45	–2150	–0.231	0.380	0.994	0.964
Pth-ester	4.71	–2429	–0.234	0.377	0.995	0.961
Cyclodextrin	80.73	–14362				

[a] Oxygen bonding aromatic fragment with either thiophosphate in pesticides or alkanoate in esters.
[b] Atom bound to —O—, *i.e.* either P in pesticides or C in esters.
[c] Bond between aromatic carbon and —O—.

Table 1 shows the energy values obtained by both methods, MM+ and PM3, for the free substrates. This Table also includes net charges on the following atoms of the guests: (a) the O connecting either the thiophosphate-based residue or the acetate/propanoate fragment to the aromatic ring and symbolized here by —O—; (b) correspondingly, either the P or C atom belonging to the mentioned fragments and bound to —O—. The bond orders refer to the $C_{aromatic}$—O— (symbol CA—O), and either the —O—P or —O—C bonds, according to the case considered. Two features can be further noticed from Table 1:

(i) the larger charge on the —O— of thiophosphate residues as compared to the carboxylic esters (and correspondingly, the positive counterparts, P and C, as well);

(ii) the difference between the CA—O and —O—P bond orders, as compared to the mutually similar values of the CA—O and —O—C bonds.

These properties reveal a larger polarization of the —O—P bond in pesticides than the —O—C bond in the carboxylic esters. It was also observed that, in the pesticide structures, the two remaining oxygen atoms in the thiophosphate residue present net charges ranging from –0.540 to –0.600.

Results for Complexes Yielded by PM3 method

Table 2 shows the results obtained with PM3 calculations. Two complexes, at least, are reported for each guest. Complexes labeled ″1″ correspond to the lowest energy structure. One or two additional less stable complexes follow, differing in energy less than 0.1 % from the lowest: they present some interesting characteristic as, for example, H-bonds involving either the S atom or the carbonyl O and/or the —O— atom of the substrates. Such features are specified in the second column of the Table, while PM3 binding energies appear in the third column.

Figures 2 to 4 show selected pairs of complexes, one involving a pesticide and the other, the corresponding ester.

Table 2

Intermolecular H-bonding; *binding and formation PM3 energies* (kcal·mol^{-1}) *of complexes*; *selected atomic charges and bond orders of substrates and their corresponding changes relative to the free state*

Substrate	Intermolecular H-bond/s of β-CD with…	E_{cmplx}	$E_{formation}$	Atomic charge		change %		Bond order		change %	
				q(—O— *)	q(P/C *)	Δq(—O—)	Δq(P/C)	P(C_A—O *)	P(O—P/C)	ΔP(C_A—O)	ΔP(O—P/C)
Fenitrothion1	S, —O—	–17241	–16	–0.571	1.868	1	2	1.029	0.631	0	0
Fenitrothion2	S	–17236	–11	–0.555	1.867	–1	2	1.039	0.641	1	2
Methylparathion1	—	–16954	–12	–0.534	1.849	0	1	1.027	0.691	0	3
Methylparathion2	S	–16953	–11	–0.567	1.848	6	0	1.041	0.630	1	–6
Parathion1	S	–17515	–13	–0.566	1.864	6	1	1.032	0.636	0	–5
Parathion2	—	–17511	–9	–0.542	1.866	1	1	1.042	0.661	1	–1
FNth-ester1	—	–16804	–11	–0.226	0.385	–2	2	0.991	0.973	0	1
FNth-ester2	Carbonyl O	–16802	–9	–0.226	0.391	–2	3	0.989	0.975	0	1
FNth-ester3	—O—	–16801	–8	–0.235	0.386	2	2	0.999	0.961	1	–1
MPth-ester1	—	–16525	–13	–0.223	0.385	–4	1	1.006	0.961	1	0
MPth-ester2	Carbonyl O	–16520	–8	–0.222	0.393	–4	3	0.995	0.976	0	1
Pth-ester1	—	–16804	–13	–0.227	0.376	–3	0	0.994	0.964	0	0
Pth-ester2	Carbonyl O	–16799	–8	–0.229	0.390	–2	4	0.988	0.972	–1	1

* See footnotes to Table 1.

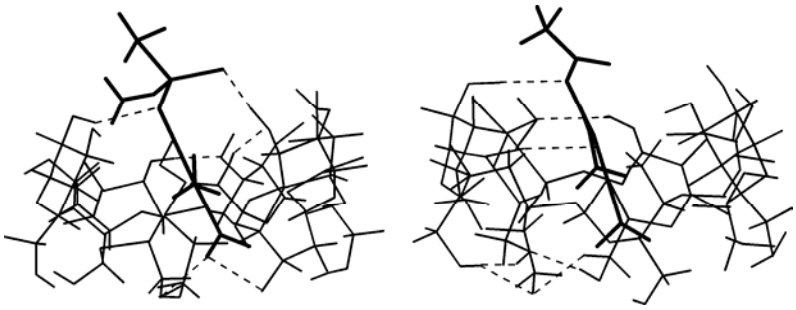

Fig. 2. Complexes of Fenitrothion1 (*left*) and of FNth-ester3 (*right*) with β-cyclodextrin. Intermolecular H-bonds with secondary β-CD hydroxyls: (*left*) S···HO, 2.51 Å; —O—···HO, 2.62 Å; (*right*) —O—···HO, 2.52 Å

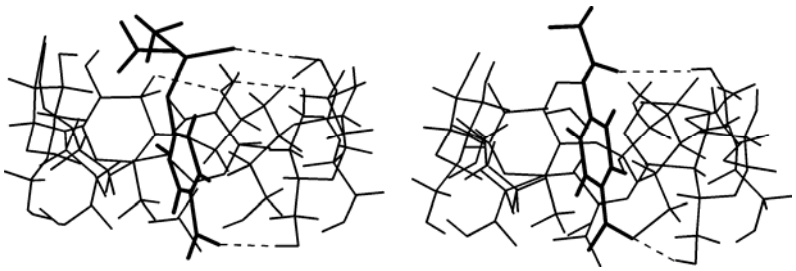

Fig. 3. Complexes of Methylparathion2 (*left*) and of MPth-ester2 (*right*) with β-cyclodextrin. Intermolecular H-bonds with secondary β-CD hydroxyls: (*left*) S···HO, 3.07 Å; (*right*) carbonyl-O···HO, 2.70 Å

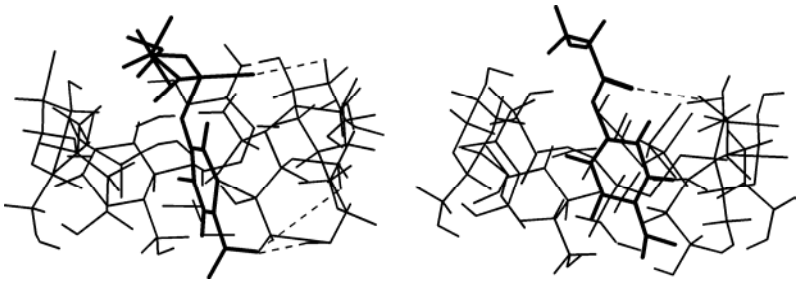

Fig. 4. Complexes of Parathion1 (*left*) and of Pth-ester2 (*right*) with β-cyclodextrin. Intermolecular H-bonds with secondary β-CD hydroxyls: (*left*) S···HO, 2.61 Å; (*right*) carbonyl-O···HO, 2.58 Å

It is worth mentioning that in all complexes, the nitro group of the guest appears to be H-bonded to primary OH′s of the macrocycle.

Table 2 also shows the formation energies obtained using eq. (1), in which the last two terms correspond to the free species.

$$E_{\text{formation}} = E_{\text{complex}} - E_{\text{substrate}} - E_{\text{CD}}. \quad (1)$$

Net atomic charges on —O— and P or C (after complexation) are also reported, as well as the percent change relative to the corresponding values in the free substrates, eq. (2). Analogous procedure, eq. (3), was accomplished with the bond orders of CA—O and —O—P/C bonds.

$$\Delta q_i = \frac{q_i(\text{in complex}) - q_i(\text{free})}{q_i(\text{free})} \times 100, \quad (2)$$

$$\Delta P_{ij} = \frac{P_{ij}(\text{in complex}) - P_{ij}(\text{free})}{P_{ij}(\text{free})} \times 100. \quad (3)$$

Further Treatment of Fenitrothion

Given that hydrolysis of this compound appears to be less inhibited by β-CD than the hydrolysis of the other two pesticides [16], and that the usual reaction pathway for catalysis of carboxylic ester hydrolysis seems not to occur appreciably with this phosphate ester [15], the idea of a somehow differently protected thiophosphate group was suggested. Therefore, additional ways of approaching the cycle on the part of fenitrothion were also considered, and the guest was thus oriented such as (a) the thiophosphate group enters first through the secondary rim of β-CD and (b) both the aryl group and the thiophosphate group successively enter through the primary rim.

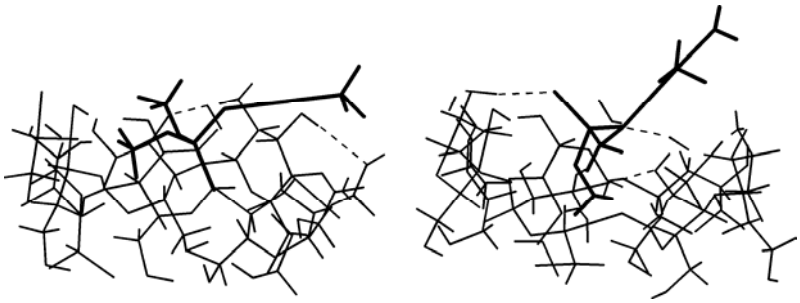

Fig. 5. Fenitrothion inserted by the thiophosphate moiety through the wide (secondary) rim of β-CD: (*left*) the S atom is centered in the cavity; (*right*) the S atom interacts with a rim hydroxyl (S···HO, 2.70 Å)

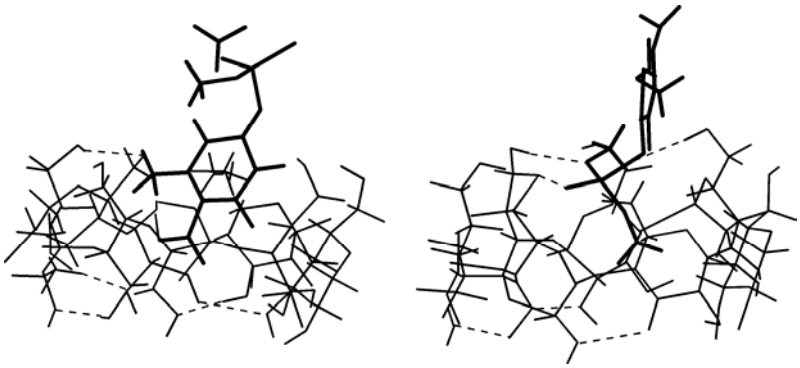

Fig. 6. Fenitrothion inserted by the —NO_2 (*left*) or the thiophosphate (*right*) groups through the narrow (primary) rim of β-CD. Intermolecular H-bonds with the primary β-CD hydroxyls: (*left*) (N)O···HO, 2.83 Å; (*right*) S···HO, 2.64 Å; (P)O···HO, 2.65 Å; (P)O′···HO, 2.73 Å

As for (a), Fig. 5 shows two complexes with the same lowest energy obtained (–17234 kcal·mol^{-1}): one with the S atom pointing to the center of the cavity and the other with the S oriented towards the secondary rim of the β-CD, interacting with it.

Regarding (b), that is the insertion through the narrow rim of β-CD, the interaction of either the —NO_2 group or the thiophosphate moiety with the primary OH′s of the cycle, made the entry of the guest into the cavity rather difficult during the docking process. Considering the cases where the entry was successful, the most stable complexes are shown in Fig. 6, with their energies being –17238 kcal·mol^{-1} for the complex with the guest introduced by the —NO_2 group, and –17237 kcal·mol^{-1} for the complex with the guest inserted by the thiophosphate moiety.

DISCUSSION

Taking into account that the hydrolysis of the pesticides was conducted under basic conditions, we should consider that some O^- belonging to the β-CD might be responsible for the nucleophilic attack.

Table 2 shows that the driving force towards the formation of complexes ($E_{formation}$) is, in average, scarcely larger for pesticides than for carboxylic esters. It is interesting to note that fenitrothion introduced by the —NO_2 group through the secondary rim of the β-CD, although appears less deeply included into the cavity, presents the highest complex formation energy. Two intermolecular H-bonds with S and —O—, respectively, contribute to the stability of the lowest energy complex.

Regarding reorganization of charges after the complexation, in carboxylic esters it generally occurs by increasing positive charge on C and decreasing negative charge on —O— in —O—C bonds, thus improving conditions for a nucleophilic attack on C. A different behavior is shown by FNthester3, whose negative charge over —O— increases, and the same happens with Fenitrothion1. In both cases, the corresponding —O— atoms appear involved in intermolecular H-bonds. Such interactions are facilitated by the shallower insertion of these substrates into the cavity, leaving the bridging —O— at the secondary OHs′ level, therefore, accessible. The other fenitrothion complex reported in Table 2 (Fenitrothion 2) reorganizes charges on the —O— and P in the way that carboxylic esters generally do, favoring (in this regard, at least) conditions for a nucleophilic attack on P.

The two remaining pesticides appear to be well included in the cavity and, in the two cases that they show formation of intermolecular H-bonds between S and some secondary OH, —O— happens

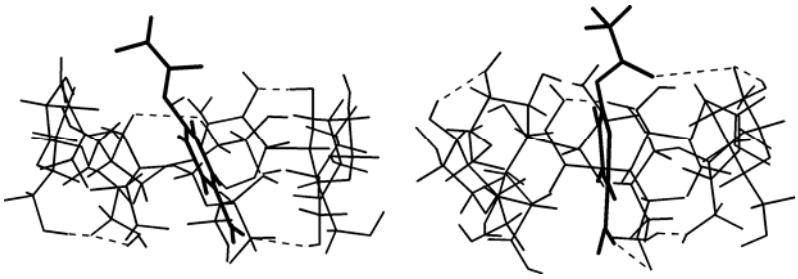

Fig. 7: Complexes of MPth-ester1 and MPth-ester2 with β-cyclodextrin showing different leaning degrees of the substrate *inside* β-*Cyclodextrin*. Intermolecular distances: (*left*) —O—···*closest*-rim-C, 3.89 Å; (*right*) —O—···*closest*-rim-C, 4.13 Å

to increase its charge by ~6 % while the —O—P bond order decreases simultaneously by ~5 %. In both cases all three thiophosphate oxygen atoms reorganize uniformly their charges to ~–0.565, whereas in the other pesticide complexes, oxygen charges do not differ much from the values initially obtained in the free state, whose range was mentioned in the preceding section.

Table 2 also shows that the most stable carboxylic ester complexes do not present intermolecular H-bonding involving carbonyl O. Another feature common to them is that the guests appear particularly leaned on the secondary rim (example in Fig. 7, left), approaching the host by the carbonyl, in the trend of the geometry previously inferred [21, 22] for *p*-nitrophenyl alkanoates during acyl transfer. On the other hand, the interaction of the carbonyl O with the rim through H-bonds (Fig. 7, right) leads to slightly less stable carboxylic ester complexes (2 to 5 kcal·mol^{-1}).

The observation of fenitrothion and its corresponding carboxylic ester in Fig. 2 reveals that, as a result of their relatively shallow inclusion in the cavity, thiophosphate and acetate substituents are quite exposed. The existence of the methyl group in *meta* position seems to restrict a deeper penetration of the substrate within the macrocycle (in spite of the presence of the —NO_2 group otherwise interacting with the primary OH′s of the cycle) and induces β-CD to adopt an almost oblong shape. In both complexes there are H-bonds generated between the secondary OH′s and the guest, involving either S or the carbonyl O, according to the case considered, but sometimes also involving —O— (as shown in the Figure). In the latter situation, both the pesticide and the carboxylic ester adopt a leaned position towards the secondary rim, differing in that the carbonyl C of the carboxylic ester appears unprotected, whereas the presence of two methyls in the thiophosphate residue (whose orientations are mutually influenced), makes the approach to P more difficult.

Methylparathion and its corresponding carboxylic ester, Fig. 3, penetrated more deeply into the CD cavity due to the absence of the *meta* methyl group in the aromatic ring. Here the thiophosphate group stays level with the wider rim, but in the center of the CD, forced by the two methyls that hamper its approach to the cavity wall. Contrarily, the carboxylic ester shows its methyl oriented outwards the cavity, and it is leaned enough towards the rim so that the carbonyl oxygen interacts with secondary OH′s.

Parathion in Fig. 4 appears more deeply introduced than the corresponding carboxylic ester (probably due to the stronger interactions of the carbonyl group with the CD rim), though both show their ethyls emerging from the cavity. In the carboxylic ester, the access to C appears thus to be facilitated, with respect to a nucleophilic attack in basic medium. Moreover, in the resulting complex there are two secondary OH′s of the cycle that appear closer to the carbonyl group of the guest than the other secondary OH′s and they are located in the right angle for nucleophilic attack, suggesting that, in basic medium, the necessary conformation for the intramolecular reaction would be attainable.

Figures 5 and 6 show complexes between β-CD and fenitrothion whose energies differ less than 0.1 % relative to the value of the most stable complex obtained for this compound reported in Table 2. When inserted by the aryl group, the guest appears to be rather protruding, so that a nucleophilic attack on the part of the β-CD appears difficult to be achieved. This would not be the case for the attack on the part of an external OH^-, as inferred from experiment [15], except for the electrostatic barrier created by the charged rim.

If the guest appears introduced by the thiophosphate group, the moiety stays leveled with the β-CD rim but the methyls hinder a nucleophilic attack by some alkoxy group of the rim, unless the

cycle undergoes a considerable distortion. As for the action of an external OH^- group, the most favorable conformation is the one with the S atom pointing towards the center of the cavity, while the P atom, though bare exposed, is quite deeply introduced in the β-CD cavity.

CONCLUSION

The complexation by β-cyclodextrin with three organophosphorus pesticides, fenitrothion, parathion and methylparathion, and of their carboxylic ester analogues was theoretically simulated in gaseous state and the host-guest interactions were compared.

Complexes involving MPth-ester and Pth-ester show substrates slightly less deeply included than the corresponding pesticides, which is consistent with the stronger interactions of the carbonyl O atom with the secondary rim of β-CD, than those of the phosphoryl S atom. These esters adopt leaned orientations and reveal such net charge changes that a nucleophilic attack on the carbonyl C, by some O^- of the β-CD, appears favored. In methylparathion and parathion complexes, substrates stay deeply inserted in the cavity, since weaker interactions of S with the secondary rim of the host come together with the effect of the $—NO_2$ group interacting with the primary rim of the β-CD. A nucleophilic attack seems to be sterically hindered, as the P is located in the center of the secondary rim, and the accessibility of the atom is obstructed by the methyl or ethyl components of each substituent. Another hampering factor to be considered is the oxygens that are present on guests restricting both mobility and conformational freedom of the guest in the cavity. They determine a potential barrier that would disfavor a nucleophilic attack in these conditions.

The FNth-ester complex shows a similar trend with the other carboxylic esters, with the difference in that the substrate appears less introduced due to the sterical characteristics of the aryloxy fragment. As for fenitrothion after complexation, when the substrate is inserted by the $—NO_2$ group, the thiophosphate moiety either emerges from the cavity and the access to P becomes difficult due to its remoteness to the rim alkoxides, or it is leaned towards the rim but to a limited degree due to its methyls. When the substrate approaches by its thiophosphate moiety the cycle, attractive interactions of the moiety with the rim prevent a significant entry of the substrate into the cavity and the P atom is kept in the center of the rim circle. Alkoxide attack would require an important straining on the part of the cycle because of the thiophosphate methyls hindrance. Therefore the stereochemical characteristics of the fenitrothion complexes would not give an easy way to hydrolysis mediated by an alkoxy group of the β-CD rim. Instead, geometries rather seem to favor the approach of an external OH^- group, which would still have to surmount the repulsion barrier exerted by the charged rim. This might explain why, though less inhibited than for the other two pesticides, mediated hydrolysis of fenitrothion is however slower than that of the free substrate.

Finally, it should be mentioned that interactions with the solvent could change, in general, the relative energies. Given, however, that the theoretical results here reported are in agreement with the experimental ones, it appears reasonable to consider these systems as approximately equally affected by such interactions.

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