Counterion Effects and Dynamics of Parathion in Anionic Lyomesophases

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Ingestion of parathion produces catastrophic effects on mammals. Transformed into paraoxon, it inhibits acetylcholinesterase, producing acetylcholine accumulation. The distribution, orientation, and dynamics of parathion in different hydrophobic bilayer environments is interesting from both ecological and biological perspectives. A study of parathion-d₄ dissolved in two nematic discotic lyotropic liquid crystals made of sodium and cesium decylsulfate (CsDS and NaDS)/decanol (10% 1,1-dideuterodecanol)/water ($0.1\% D_2O$)/M₂SO₄ (M = Na⁺, Cs⁺), is presented. Deuterium quadrupole splittings and relaxation times of all deuteriated species were measured. Parathion is strongly attached to both aggregates, increasing the alignment of CsDS and decreasing the alignment of NaDS. Molecular dynamics trajectories were calculated for both mesophases. CsDS appears more neutralized than NaDS. Despite the surface charge, parathion is associated to both aggregates, located near the interface, with the nitro group oriented to the headgroups and the ethoxy chains toward the hydrophobic core. When included in the CsDS interface, it stabilizes the system by shielding repulsive electrostatic interactions among headgroups. Included in NaDS, parathion induces an increase in the distance among counterions and sulfate headgroups, thus decreasing the degree of order.

Manuscript received: 1 August 2009. Manuscript accepted: 16 September 2009.

Introduction

Parathion, (diethoxy-(4-nitrophenoxy)sulfanilidene phosphorane), a well known organophosphorous pesticide (see Fig. 1), presents serious hazards for life and the environment. Intoxication with parathion involves accumulation of acetylcholine, and severe poisoning may cause serious damage, even death.^[1-5] A study on the dynamics and distribution of parathion in cationic and anionic bilayer environments is therefore of both ecological and biological interest. Recently, we published a paper concerning the dynamics and orientation of parathion-d₄ dissolved in a cationic Nematic Discotic Lyotropic Liquid Crystal (NDLLC) using ²H NMR and molecular dynamics (MD) simulations.^[6] These NDLLC are aqueous solutions of aggregates made of amphiphilic molecules assembled like bilayers, similar to a flat micelle, with average oblate symmetry. In the presence of magnetic fields, they spontaneously orient with the symmetry-axis of the oblate perpendicular to the field direction, generating an anisotropic medium, and allowing the measurement of residual quadrupole splittings. In that paper, the cationic NDLLC was prepared from tetradecyltrimethylammonium chloride, decanol, NaCl, and water. The results showed that parathion is completely incorporated inside the hydrophobic core, in agreement with previous experimental evidence.^[7] At equilibrium, it is located near the interface, with the nitro group interacting with the



Fig. 1. Schematic representation of parathion parathion-d₄.

ammonium headgroups of the aggregate, and the ethoxy chains pointing toward the interior. The addition of parathion increases the degree of order of all components of the cationic aggregate. This ordering effect has been observed before.^[8,9]

To study counterion effects on the dynamics, distribution, and average orientation of parathion dissolved in hydrophobic bilayers with an anionic interface, an NMR investigation of parathion-d₄ dissolved in two anionic NDLLC was made. The liquid crystal solutions consisted of sodium and cesium decylsulfate (NaDS and CsDS), decanol (DeOH), including 10% 1,1-dideuterodecanol, sodium or cesium sulfate and water (0.1% D₂O). Deuterium quadrupole splittings ($\Delta \nu_Q$) and longitudinal relaxation times (T_1) were measured for all deuterium-enriched



Fig. 2. 2 H NMR spectrum of parathion-d₄ dissolved in the CsDS mesophase.

components. The width of the broad signal observed in the ¹H NMR spectra of NDLLC (Δv_D) was also measured. To assist with the interpretation of the experimental observations, several simulations of the CsDS and NaDS mesophases were performed, with and without parathion. All systems were represented as bilayer fragments. Trajectories and further analyses were calculated using the software package *Gromacs* version 3.3.^[10]

Results

A total of four samples were prepared for the present study, two samples of NaDS, sample A without parathion and sample B with parathion, and two samples of CsDS, sample C without parathion, and sample D with parathion. Fig. 2 shows the ²H-NMR spectrum of parathion-d₄ dissolved in the CsDS mesophase. All other spectra are provided in the Accessory Publication. $\Delta v_{\rm O}$ of all deuterium labelled molecules were measured directly from the spectrum. The largest splitting arises from 1,1dideuterodecanol, the two intermediate splittings correspond to positions ortho and meta of parathion, and the smallest splitting is from monodeuteriated water (DHO). In contrast with our previous study of parathion in cationic NDLLC, where only one splitting from parathion was observed; in this case, both splittings were resolved. Estimated errors in the measured splittings are ± 1 Hz for DHO, ± 5 Hz for parathion-d₄, and ± 15 Hz for decanol-d₂. Integrals of the right hand peak of each splitting were employed to measure T_1 of all deuteriated molecules, except for DHO; in this case both peaks were used. The estimated errors in the measured T_1 are ± 10 ms for decanol, ± 3 ms for water, and ± 5 ms for parathion. The broad signal observed in the ¹H NMR spectra arises from the residual dipolar couplings among the protons of the magnetic field oriented chains that form the aggregate. The width of this signal (Δv_D) is a measurement of the degree of alignment with the magnetic field and was also measured. All measured properties are displayed in Table 1.

To understand these experimental results on a molecular level, several MD trajectories were calculated. A snapshot of the Cs3P simulation after 10 ns of trajectory is shown in Fig. 3. For a coloured edition of this figure the reader is referred to the online version of this article, where decylsulfate ion is orange, decanol is grey, cesium is violet, sulfur is yellow, oxygen is red, and hydrogen white. Parathion is represented using van der Waals spheres with carbon light blue, phosphorous brown, and deuterium green.

All simulations represent the aggregates as bilayer fragments enclosed in rectangular boxes with periodic boundary conditions. The CsDS mesophase simulation contained 48 decylsulfate ions, 24 decanol, 13 sulfate ions, 74 cesium ions, and 1781 simple point charge (SPC) water molecules, in a box of dimensions $29 \text{ nm} \times 36 \text{ nm} \times 75 \text{ nm}$. The NaDS simulation box, having the same dimensions, contained 48 decylsulfate ions, 24 decanol, 19 sulfate ions, 86 sodium ions, and 1769 SPC water molecules. These two boxes were allowed to equilibrate for 5 ns and replicated four times each. At this point, parathion molecules were added and all trajectories calculated for another 20 ns. All further analysis was performed in the last 17 ns of trajectory. A total of 10 simulation boxes were set up, according to the following conditions: two correspond to the pure mesophases, named NaP0 and CsP0. To investigate the preferential location of parathion three trajectories were calculated for each mesophase: one with one parathion initially located in the bulk water (P1); the second with one parathion at the interface (P2); and the third with one parathion in the middle of the bilayer (P3), named NaP1, NaP2, NaP3, CsP1, CsP2, CsP3. Equilibrium properties were obtained from simulations Na3P and Cs3P, which contained three parathion molecules each. Fig. 4 shows the z coordinate trajectory of the centre of mass of parathion in simulations CsP1, CsP2, CsP3, NaP1, NaP2, and NaP3. Despite the time it takes to reach equilibrium, all molecules are finally located at the interface. Therefore, to calculate equilibrium properties from simulations Na3P and Cs3P, one parathion molecule was positioned in the lower interface and two in the upper interface.

Mass density distributions of all species, along the z axis of the box, were calculated from simulations Na3P and Cs3P, and they appear in Fig. 5. For a better visualization of this plot, both amphiphiles that form the aggregate have been divided into three fragments: for decylsulfate ions, the first fragment includes the sulfate headgroup and the first two methylene groups and is called NaDS1 or CsDS1 (black solid trace); the second fragment is called NaDS2 or CsDS2 and it includes the next four methylene groups (black dashed trace); and the last fragment contains the last four methylene groups (black dotted trace). Similarly, decanol is also divided into three fragments: the first (DeOH1) contains the hydroxyl fragment and the first two methylene groups (grey solid trace); the second (DeOH2) includes the next four methylenes (grey dashed trace); and the last fragment (DeOH3) includes the last four methylene groups (grey dotted trace). Parathion densities appear in the right axis scale and are represented using a black trace with $+, \times,$ and \circ signs, to indicate molecules 1, 2, and 3, respectively. Vertical dashed lines denote the limits of the interface, according to a previous definition.^[11] A coloured version of Fig. 4 is provided in the online version of this article. Similar density plots from simulations NaP0 and CsP0 are included in the Accessory Publication.

Fig. 6 shows the radial distribution function (RDF) of solvent molecules surrounding the Na⁺ and Cs⁺ ions from simulations NaP0 and CsP0. RDF of counterions around the sulfate headgroup were also calculated for simulations NaP0 and CsP0 and they are displayed in Fig. 7. To estimate the orientation of parathion in the bilayer, mass density profiles of N and P atoms from parathion, along the *z* axis of the box, were calculated from simulations Na3P and Cs3P; they appear in Fig. 8.

	Α			C		
	Δv_{quad} [Hz]	NaDS $\Delta v_{\rm dip} [\rm Hz]$	<i>T</i> ₁ [ms]	Δv_{quad} [Hz]	CsDS Δv_{dip} [Hz]	<i>T</i> ₁ [ms]
DeOH	16659	-	62	15096	-	57
C10-	-	5780	-	-	5250	_
HDO	470	-	222	247	-	341
	В			D		
	NaDS/parathion			CsDS/parathion		
	Δv_{quad} [Hz]	$\Delta v_{\rm dip}$ [Hz]	T_1 [ms]	Δv_{quad} [Hz]	$\Delta v_{\rm dip}$ [Hz]	T_1 [ms]
DeOH	15805	_	75	17183	_	69
C10-	_	5600	_	_	7000	_
HDO	418	_	232	279	-	285
Para1	10865	_	21	11846	-	21
Para2	10481	-	20	11529	-	20

 Table 1.
 ²H NMR quadruple splittings and relaxation times of all deuterated species in samples A, B, C, and D The width of the broad band observed in the ¹H NMR spectra is also listed



Fig. 3. Snapshot of simulation Cs3P 10 ns after the addition of three parathion molecules. For a coloured edition of this figure the reader is referred to the online version of this article, where the TTA ion is orange, decanol is grey, cesium is violet, sulfur is yellow, oxygen is red, and hydrogen white. Parathion is represented using van der Waals spheres with carbon light blue, phosphorous brown, and deuterium green.

Discussion

The quadrupole splitting from the deuterium atoms attached to carbon 1 of decanol provides information about the mobility of the interface. The quadrupole splitting of DHO depends on

factors such as the width of the interface, the size of the aggregate, and the re-orientational dynamics experienced by DHO. The first two variables determine the amount of anisotropic water in the sample, in fast exchange with isotropic water, and they are responsible for the observed splitting. The dynamics experienced by DHO determine the average orientation, and the amplitude of fluctuations. Comparison of SDS and CsDS, samples A and C in Table 1, reveal that Δv_0 of decanol-d₂ and DHO are both smaller in sample C. To test if this difference is attributable to a difference in the size of the aggregate, a preliminary estimation of the aggregation number, N, of both mesophases without parathion, using the static fluorescence quenching of added pyrene by added hexadecylpyridinium chloride, was made.^[12] N is the number of amphiphiles that form the aggregate. It is well known that this methodology underestimates the aggregation number;^[13] however, for a qualitative comparison should be sufficient. In effect, the aggregation numbers obtained for NaDS and CsDS are 114 and 95, respectively. Table 1 shows that $\Delta v_{\rm D}$ for sample A is greater than for sample C, consistent with a smaller CsDS aggregate. Longitudinal NMR relaxation of deuterium is dominated by orientational fluctuations of the electric field gradient surrounding the quadrupolar nuclei in the magnetic field. Accepting that water is in an extreme narrowing regime, the value of T_1 should be proportional to the inverse of the rotational correlation time of the O-D bond. Because solvent molecules at the interface are less mobile than in the aqueous phase, and isotropic water molecules are more retained by Na⁺ than by Cs⁺, the observed values of T_1 for DHO in NaDS should be shorter, in agreement with the experimental observations. Finally, a crude estimation of viscosities of samples A and C reveals that viscosity of A is several times greater than viscosity of C, in agreement with a bigger NaDS aggregate. All the experimental evidence strongly suggests that the NaDS aggregate should be bigger.

The magnitude of the quadrupole splittings of parathion in both mesophases reveals that the pesticide is strongly attached to both aggregates. A comparison among the values in Table 1 shows an interesting phenomenon: the addition of parathion to the CsDS mesophase increases the values of all Δv_Q and also Δv_D , indicating an increase in the degree of alignment of all components with the magnetic field. Besides, the incorporation of the pesticide in the NaDS solution decreases the values of all



Fig. 4. Time evolution of the *z*-coordinate of the centre of mass of all parathion molecules in simulations Cs3P and Na3P. At equilibrium all molecules are located in the interface.

 Δv_Q and Δv_D , showing that the degree of order of the mesophase components has decreased. As far as we know, this is the first time that the disordering effect of parathion in bilayers has been observed.

Because the main difference between NaDS and CsDS mesophases is the counterion, most observations should be explained based on their properties. The main difference between Na⁺ and Cs⁺ is the ionic radius; the ratio r_{Cs+}/r_{Na^+} is ~1.78. Both ions posses the same charge; however, in sodium it is distributed in a much smaller sphere, generating a stronger electrostatic potential. As a consequence, sodium is able to retain water molecules in the solvation shell more strongly than cesium, with a more significant effect on the structure of water. Therefore, sodium ions should be more distributed in the bulk water phase rather than near the interface. However, cesium is unable to retain the solvation shell, and should be preferentially located closer to the interface, due to electrostatic interactions with sulfate headgroups. Therefore, NaDS and CsDS interfaces show a different behaviour when parathion is included, and should be related to differences in the distribution of counterions.

Mass density profiles of both mesophases, from MD trajectory calculations with and without parathion (see Fig. 5), reveal that all simulations possess a bilayer structure made of decyl sulfate ions and decanol, however, some differences can be observed. According to a previous definition,^[11] the width of the interface of pure CsDS and NaDS mesophases, obtained from simulations CsP0 and NaP0, are 9.2 Å and 7.7 Å, respectively. These values decrease ~1 Å with the addition of three parathion molecules to both systems (Cs3P and Na3P). The distance from the maximum value of the Na⁺ and Cs⁺ mass densities to the centre of the bilayer is 13.6 Å for Cs⁺ and 14.0 Å for Na⁺. Considering the difference in ionic radius, cesium appears to be significantly closer to the interface than sodium. From the radial distribution of solvent molecules around the counterions, shown in Fig. 6, it can be observed that Na⁺ in NaP0 has four solvation spheres, located at 2.3 Å, 2.9 Å, 4.8 Å, and 7.5 Å, whereas Cs⁺ in CsP0 shows only three, at 3.2 Å, 3.5 Å, and 5.9 Å. Clearly, Na⁺ is more effective than Cs⁺ perturbing the structure of water, in accordance with the Hofmeister series. The addition of three parathion molecules to the simulation box does not modify these values.

All the previous evidence seems to indicate that the value of the NaDS dissociation degree should be greater than that for CsDS. This is supported by the values of critical micelle concentration (CMC) of spherical micelles of CsDS and NaDS, 6.2 mM and 8.3 mM, respectively.^[14] To corroborate this hypothesis the short range Coulomb energy among sulfate headgroups was calculated; this destabilizing interaction is 215.7 kJ for CsDS (CsP0) and 224.4 kJ for NaDS (NaP0). Repulsions among the NaDS headgroups are greater than repulsions among CsDS headgroups, despite the fact that there is more Na⁺ in NaDS simulations than Cs⁺ in CsDS simulations. Another piece of evidence pointing in the same direction is the short range stabilizing electrostatic interaction energy among the counterions and the sulfate headgroups. The values obtained are -1765 kJfor CsDS in the absence of parathion (CsP0) and increases to -1813 kJ with the addition of three parathion molecules (Cs3P). The same interaction in NaDS is -1242 kJ without parathion (NaP0) and decreases to -1194 kJ after adding three parathion molecules (Na3P). This result strongly suggest that the observed difference in the degree of order between NaDS and CsDS interfaces after the addition of parathion, is closely related to electrostatic interactions between the pesticide and the interface components. To investigate the origin of this observation, the average distances between counterions and sulfate headgroups were calculated from the simulations with and without parathion. The average RSO_4^- -Cs⁺ distance increases from 2.2 ± 0.9 Å to 2.6 ± 1.2 Å with the inclusion of parathion in CsDS (18%);



Fig. 5. Mass density distributions of all species in simulations (a) Na3P and (b) Cs3P, along the z axis of the box. The limits of the interface are indicated by vertical black dashed lines. To improve visualization of this plot, the amphiphiles that form the aggregates have been divided into three fragments each: for decylsulfate ions the first fragment includes the sulfate headgroup and the first two methylene groups (NaDS1 and CsDS1, black solid trace); the second fragment includes the next four methylene groups (NaDS2 and CsDS2, black dashed trace); the last fragment contains the last four methylene groups (NaDS3 and CsDS3, black dotted trace). Similarly, decanol is also divided into three fragments: the first (DeOH1) contains the hydroxyl fragment and the first two methylene groups (grey solid trace); the second (DeOH2) includes the next four methylenes (grey dashed trace); and the last fragment (DeOH3) includes the last four methylene groups (grey dotted trace). Parathion densities appear in the right axis scale and are represented using a black trace with $+, \times,$ and \circ signs to indicate molecules 1, 2, and 3, respectively.

besides, inclusion of parathion in NaDS increases the average RSO_4^- -Na⁺ distance from 2.1 ± 0.8 Å to 3.6 ± 1.3 Å (71%).

RDF of counterions surrounding the sulfate headgroups in both mesophases was also calculated and the results corroborate all the previous observations. In effect, the maximum density for the first and second coordination sphere of Cs^+ surrounding the sulfur atom of the headgroup in CsDS are located at 4.2 Å and 6.1 Å; these values increase to 5.0 Å and 7.7 Å for Na⁺ in NaDS, showing that counterions in CsDS are closer to the headgroups of the interface. Therefore, all the evidence strongly suggests that the CsDS interface should be more neutralized by counterions than the NaDS interface.

Mass density distributions of the N and P atoms of parathion were calculated from simulations Na3P and Cs3P, and they are



Fig. 6. Radial distribution functions of water molecules surrounding Na^+ (solid trace) and Cs^+ (dotted trace).



Fig. 7. Radial distribution functions of counterions surrounding the sulfur atom of the decylsulfate headgroup. Na^+ corresponds to the solid trace and Cs^+ to the dashed trace.

shown in Figs 8a and 8b. These plots show that the N atom is closer to the interface than the P atom, which is pointing to the hydrophobic core, for all parathion molecules. This result allows us to conclude that parathion is positioned inside the interface, with the nitro moiety pointing toward the sulfate headgroups and the ethoxy chains oriented toward the hydrophobic core, similar to the location and orientation observed in a cationic mesophase.^[6]

All the experimental observations can be rationalized in terms of the difference in counterion distribution between both interfaces. According to the NMR and MD results, parathion is strongly attached to the aggregate and positioned at the interface. Sodium is more distributed in the bulk water, whereas Cs^+ is located closer to the interface. Therefore, the solubilization of parathion has different consequences in each case. In CsDS, the incorporation of parathion helps to stabilize the interface, possibly shielding electrostatic interactions among sulfate headgroups, without significantly modifying the distribution of counterions. However, in NaDS the counterions are partitioned more into the bulk water, at a longer average distance from the sulfate headgroups, even in the absence of added parathion. The



Fig. 8. Mass density distribution of N and S atoms of parathion molecules along the z axis of the box, in simulations (a) Cs3P and (b) Na3P.

inclusion of parathion in the NaDS interface increases the average distance among counterions and headgroups, decreasing the stabilization interaction and increasing mobility.

Conclusions

NMR spectroscopy and MD simulations have again proved to constitute a powerful set of complementary tools in the study of NDLLC and dissolved guest molecules.

The differences observed between the CsDS and NaDS mesophases can be understood in terms of the differences in size and counterion distribution between both aggregates. The CsDS aggregate appears to be smaller but more neutralized by counterions than the NaDS mesophase.

Despite the surface charge of the interface, parathion is always strongly associated to the aggregate, located near the interface, and oriented with the nitro group pointing to the charged headgroups and the ethoxy chains toward the hydrophobic core.

When parathion is included into the more neutralized CsDS interface, it seems to stabilize the system by shielding electrostatic interactions among charged species, increasing the degree of order. When included into the more dissociated NaDS aggregate, it increases the distance between the counterions and the sulfate headgroups, producing a decrease in the stabilization of the system.

Experimental

Sample Preparation and NMR Spectra

CsDS and NaDS were prepared from decanol (Aldrich) and chlorosulfonic acid (Merck).^[15] Sodium and cesium sulfate were obtained from Aldrich (>99.99%) and used without further purification. Decanol was enriched 10% with previously prepared 1,1-dideuterodecanol.^[16] Parathion-d₄ was prepared from phenol-d₅ according to a previously reported methodology.^[6]

The NaDS mesophase was prepared by dissolving 786.3 mg of NaDS, 69.6 mg of Na₂SO₄, and 161.7 µL of decanol (10%) 1,1-dideuterodecanol) in $1000 \,\mu\text{L}$ of H₂O (0.1% D₂O). The CsDS mesophase was prepared by dissolving 826.3 mg of CsDS, 104.0 mg of Cs₂SO₄, and 100.0 µL of decanol (10% 1,1dideuterodecanol) in 1000 µL of H₂O (0.1% D₂O). Two volumes of 0.5 mL each were employed for each mesophase, and $10 \,\mu$ L of parathion-d₄ was added to one of them, giving a total of four samples. After being transferred to 5 mm NMR tubes all samples were allowed to equilibrate 24 h at 300 K. ¹H and ²H NMR spectra were obtained at 300 K in a Bruker Avance 400 spectrometer, at Universidad de Santiago de Chile. All NMR spectra were obtained using a 5 mm inverse BB probe, with 90° pulses of 9 µs and 22 µs for ¹H and ²H respectively. ²H-NMR spectra were recorded in 32 kB files, at 61.42 MHz with 40 kHz of spectral window.

Molecular Dynamics

To our knowledge, this work represents the first simulation of CsDS and NaDS mesophase bilayers. Fully extended conformations of decanol, decylsulfate, and sulfate ions were built using the program Hyperchem (Hypercube Inc.). The bilayers setup, trajectory calculations, and further analysis of all simulations were performed using the program package Gromacs version 3.3.^[10] The charges of all species were obtained from ab initio 6-31G* full geometry optimization calculations, using MK fitting.^[17] The program VMD^[18] was used in the visualization of molecular graphics and trajectories. The united atom approximation was used for all hydrogens in the aliphatic chains. A combination of two potentials were employed, the GROMOS parameters^[19,20] were used for most interactions of all atoms, and the potential of Berger et al.^[21] was employed for the Lennard–Jones interactions among the aliphatic chains. The Ryckaert–Belleman^[22] potential was employed in the torsions of the aliphatic chains. Lennard–Jones parameters for Cs⁺ were transferred from the OPLS library.^[23,24] Bond lengths of the surfactant chains were constrained using LINCS^[25] and SETTLE^[26] was employed to restrict the structure of the SPC water molecules.^[27] A 1 nm cut-off was used for the Lennard-Jones potential and real space electrostatic interactions. PME was employed for the long range electrostatic interactions.^[28,29] The neighbour list was updated every 10 time steps. The weak coupling algorithm of Berendsen was used to maintain the temperature constant at 300 K (all species coupled independently) and the pressure constant at 1 bar. Time constants of 0.1 ps and 1.0 ps were used for temperature and pressure, respectively.^[30] The time step size in all simulations was 2 fs.

Accessory Publication

¹H NMR and ²H NMR spectra, as well as calculated mass density profiles of the NaP0 and CsP0 simulations are available from the Journal's website.

Acknowledgements

The authors acknowledge financial assistance from Fondecyt, Grant 1095175, and Facultad de Ciencias de la Universidad de Chile. Victor Bahamonde acknowledges a Doctoral Fellowship from Conicyt. We acknowledge Dr. Rodrigo Montecinos for the estimation of the aggregation numbers.

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