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Preferential host-guest coordination of nonactin with ammonium and hydroxylammonium

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I. INTRODUCTION

Nonactin is a naturally occurring macrotetrolide with a recognized potential as carrier of metal cations, ammonium, and protonated amines.1–3 The oxygen atoms from the oxolane (tetrahydrofuran) and ester linkages of the macrocycle backbone (see Fig. 1) promote the encapsulation of the cation and the outer exposure of a hydrophobic surface. Nonactin complexes can therefore incorporate guest cations into organic phases and constitute fundamental benchmark systems for the regulation of ionic transport through the lipid bilayers of cell membranes, leading to selective antibiotic action.4–5 The salient ionophoric features of nonactin have inspired the synthesis of a considerable number of model compounds aimed at specific transport or sensing applications in biotechnology. In particular, the outstanding affinity of nonactin for NH3+ has motivated the development of a range of molecular ions.

The early pioneering studies of the supramolecular chemistry of nonactin already established the large ammonium affinity of this macrocycle in crystallographic x-ray diffraction11,12 and Raman vibrational spectroscopy13 measurements, which was attributed to a tight coordination of the charged N—H5+ bonds with the ether oxygen atoms of the oxolane rings of nonactin. This scenario may change for less symmetric and larger secondary amines, whose coordination arrangements are likely to involve a more active role of the oxygen atoms from the ester carbonyl groups of the macrocycle. Hydroxylammonium, the model compound of choice for this study, incorporates a simple polar —OH substituent with respect to ammonium. In addition to the physiological, environmental, and technological importance of hydroxylamine, its molecular structure conforms an excellent benchmark to pinpoint the ability of nonactin to adopt stretched non-symmetric conformations in order to cope with the multipodal coordination and steric effects imposed by guest molecular ions.

This study combines mass spectrometry and laser action spectroscopy with quantum chemical modelling, to obtain insights into the dominant conformations and coordination structures that sustain the complexes formed by nonactin with ammonium and hydroxylammonium. Similar recent investigations have served to assess fine conformational aspects of the selective complexation of alkali cations by nonactin, with a detailed evaluation of the influence of hydration.14,15 In this work, we extend the scope of the investigation to
negative modes leads to fragmentation. The IRMPD spectrum is trapped ions at wavenumbers associated with specific vibrations, which in this study was scanned between 900 cm$^{-1}$ and 1800 cm$^{-1}$. The radiation amounts to 0.5% of the central wavelength, ∼10$^{-20}$ FELIX macro-pulses of 5 µJ energy. Each macro-pulse consists of trains of micropulses with a repetition rate of 1 GHz. The spectral bandwidth of the radiation amounts to 0.5% of the central wavelength, which in this study was scanned between 900 cm$^{-1}$ and 1800 cm$^{-1}$.

The resonant absorption of multiple photons by the trapped ions at wavenumbers associated with specific vibrational modes leads to fragmentation. The IRMPD spectrum is obtained by monitoring the total yield of ionic fragments, with linear corrections to account for changes in laser pulse energy during the frequency scans. The main fragments observed in our experiments have masses $m/z = 737, 553, 369, \text{ and } 185$ and are identified as protonated oligomers of the form $(C_{16}H_{18}O_3)nH^+$, $n = 4$, corresponding to the full nonactin macrocycle. Weaker signals from fragments resulting from additional H$_2$O loss were also observed. For the NH$^+$ complex, the intensity of the fragments decreased as $n = 2 > 3 > 1 > > 4$, whereas for the NH$_3$OH$^+$ complex, the intensity trend was $n = 4 > 2 > 3 > 1$. Hence, the main fragmentation product of the NH$_3$OH$^+$ complex (protonated nonactin, $n = 4$) was not appreciable for the NH$^+$ complex. It seems timely to remark that the analogous fragments observed in a previous IRMPD study of the alkali cation complexes of nonactin followed the similar trend $(C_{10}H_{16}O_3)nM^+$, with $n = 2, 3$ (M$^+$ representing the alkali cation).$

B. Determination of relative stabilities of the complexes

Electrospray ionization mass spectrometry was also employed to assess the relative stabilities of the complexes of nonactin with NH$_2^+$, NH$_3$OH$^+$, and K$^+$. In this case, the measurements were performed in a Q-Exactive Focus Orbitrap Mass Spectrometer (Thermo-Fisher). Methanol solutions 10 µM in nonactin and 200 µM in chlorides of ammonium, hydroxylammonium, and potassium were sprayed at a needle voltage of 3.8 kV. The mass spectrum was recorded at a resolution of M/ΔM = 70 000 and displayed neat signals from the three cation complexes as described below.

C. Quantum chemical calculations

Density functional theory (DFT) computations were employed to characterize the most stable conformations of the isolated complexes of nonactin with ammonium and hydroxylammonium. The procedure started with a survey of the conformational landscape of the complexes performed with simulated annealing, combining the predictions of well known force fields (Universal, Dreiding). The approximately forty non-redundant conformations of lowest energy were optimized in B3LYP/6-31+G(d) computations. Finally, the resulting twenty most stable conformations were reoptimized at the B3LYP/6-311++G(d,p) level. The conformers have been ranked throughout this study according to their zero-point corrected electronic energies. Natural bond orbital (NBO) theory was employed for a detailed assessment of the proton bonding interactions that sustain the complexation process. The IR spectrum of each conformer was built from the convolution of the predicted fundamental mode frequencies and intensities with a Gaussian line broadening of 20 cm$^{-1}$ (full width at half maximum). The computed harmonic vibrational frequencies were scaled by a factor 0.98 in comparison with the experiment, in line with standard recommendations.

The role of anharmonicities in the vibrational spectrum was studied for the most stable conformer of the NH$_2^+$ complex. The full anharmonic treatment of a system of the size of the nonactin complexes was not affordable. Therefore, a restricted mode computation was performed, in which anharmonicity...
was incorporated to a selected ensemble of fundamental modes particularly relevant in the comparison of the computational predictions with the IRMPD experiment. Specifically, for this study, the effective anharmonic transition frequencies of the three main modes related to umbrella vibrational motions of the NH$_4^+$ guest were computed within the second-order vibrational perturbation approximation (VPT2) at the B3LYP/6-311++G(d,p) level, while the rest of modes were kept harmonic. This approach is based on the strategies outlined in seminal methodologies for the modelling of large molecular systems and has been applied as implemented in the Gaussian 09 suite of programs.

III. RESULTS

The quantum chemical survey of the ammonium and hydroxylammonium complexes of nonactin converged to the most stable conformations that are depicted in Fig. 2. The ammonium complex will be discussed in the first place, as it constitutes a consolidated benchmark for the ionophore behavior of nonactin and should guide the rationalization of the recognition of small protonated amines by this macrocycle.

A. Nonactin-NH$_4^+$ complex

The ammonium complex displays two low energy conformations of $S_4$ symmetry, both of which share a similar arrangement of the nonactin backbone. The two conformers are essentially connected by a rotation of the NH$_4^+$ cation replacing the coordination with the oxygen atoms of the four oxolane groups in the most stable conformer N1 with those of the four carbonyl groups in the conformer next in energy, N2. The H-bonding NH· · · O distances are similar in the two conformations (1.9 Å). This implies a somewhat greater stretching of the nonactin backbone in conformer N2 in comparison to N1, in order to accommodate to the optimum coordination distance between the cation and the inward-oriented carbonyl groups. Figure 2 shows that the opening of the cage-like conformation adopted by nonactin is ∼0.5 Å larger in N2 versus N1.

The B3LYP computation yields as much as 20 kJ mol$^{-1}$ energy difference between conformers N1 and N2. Higher energy conformers were found at relative energies at least 40 kJ mol$^{-1}$ above N1, featuring less compact coordination arrangements associated with more open and asymmetric structures of the nonactin backbone. Conformer N1 is therefore predicted to account for the dominant conformation of the nonactin-NH$_4^+$ complex under the present experimental conditions. The structural features of conformer N1 are in fact in excellent agreement with the crystal structure determined for the NH$_4$NCS complex of nonactin, which resulted in a $S_4$ conformation with a N· · · O distance in the oxolane coordination moiety of 2.9 Å, which is coincident with the one obtained for the N1 conformer of the isolated complex in the present B3LYP computation.

Natural bond orbital analysis provides further structural and energetic insights into the relevance of the competitive H-bonding attained by NH$_4^+$ inside the nonactin host. In the N1 conformer, the H-bonds are formed at 45° from the COC plane of the oxolane groups, while in the N2 conformer, they lie at 60° from the ester carbonyl plane. Otherwise, both types of coordination arrangements feature roughly collinear H bonds, with NH· · · O angles ∼160°–170°. Figure 2 highlights the main donor and acceptor orbitals that sustain the host-guest coordination in each case. The transfer of electronic charge occurs from the lone pairs of the oxygen atoms in the oxolane or ester carbonyl groups towards the antibonding σ* orbitals of the NH$_4^+$ bonds of ammonium. The stabilization energy associated with the charge transfer from the oxolane groups in conformer N1 (38 kJ mol$^{-1}$ per bond) is almost a factor of two larger than that from the carbonyl groups in conformer N2 (20 kJ mol$^{-1}$), which serves to explain the greater stability of oxolane coordination.

It is interesting to notice that the directional tetradentate coordination that drives the recognition of ammonium by nonactin is in contrast with the scenario associated with s-shell metal cation complexes. Previous studies have shown that the complexes of nonactin with alkali and alkaline earth cations

FIG. 2. Top panels: Top and side views of the two most stable conformations of the complexes of nonactin with the cations NH$_4^+$ (N1 and N2) and NH$_3$OH$^+$ (H1 and H2). The difference in zero-point corrected electronic energy between the conformers is indicated. Note that conformers N1 and H1 involve coordination of the ammonium moieties with the oxygen atoms in the oxolane (tetrahydrofuran) groups of nonactin, whereas in N2 and H2, the coordination takes place with the carbonyl groups of the ester bonds. Bottom panels: Natural bond orbitals responsible for the redistribution of charge that sustains the stability of each conformation. Transfer of electronic charge occurs from the lone pairs of the oxygen atoms of nonactin to the antibonding σ* orbitals of the −NH$_4^+$ and −OH bonds of the guest cations, leading to the average stabilization energies per bond indicated in the lower part of each panel.
adopt a $S_4$ configuration similar to the one found for $\text{NH}_4^+$. However, the spherical symmetry of the atomic guest yields an effective electrostatic eight-fold coordination with all the oxolane and carbonyl groups at $M^+ \cdots O$ distances ranging from 2.8–3.0 Å for $K^+$ to 3.2–3.3 Å for Cs$^+$.\textsuperscript{13,15} The NBO analysis leads in this case to stabilization energies of similar magnitude in the coordination of the alkali cation with the oxolane and carbonyl groups, e.g., of $\sim\!15$ kJ mol$^{-1}$ per bond for $K^+$.

The vibrational signatures of the nonactin-$\text{NH}_4^+$ complex should serve to assess the accuracy of the computational predictions described above. Figure 3 shows the IRMPD spectrum recorded for this complex, along with the IR spectra associated with conformers N1 and N2. A good overall agreement is found between computation and experiment for the structure of the vibrational spectrum, which supports the reliability of the technique for the structural characterization of nonactin-amine complexes. A rich progression of vibrational bands is observed within the range of wavenumbers 900–1800 cm$^{-1}$ scoped in these experiments. The main band structures are labelled A–G for discussion, are described qualitatively assigned to normal vibrational modes of the complex as described in Table I. It can be noted that the ammonium–carbonyl coordination induces a significant coupling of the vibrational motions of the nonactin backbone with the bending modes of the $\text{NH}_4^+$ moiety (or $\text{NH}_4^+$ in hydroxylamine).

It is particularly interesting to note that the coordination of the carbonyl groups in conformer N2 induces a red shift of the C$=$O stretching band (band A) by $\sim\!35$ cm$^{-1}$ with respect to conformer N1. This is illustrated in Fig. 3 in terms of the relative position between band A and band E in the IR spectra computed for the two conformers. Note that band E is associated with nonactin backbone vibrations (C$\cdots$O–C stretching of the ester bonds and C$\cdots$C stretching in the oxolane rings) that appear to be weakly affected by the precise $\text{NH}_4^+$ coordination arrangement attained in the complex, as long as the conformation of the macrocycle stays roughly unchanged as it is the case. The position of band A in the experimental IRMPD spectrum (1711 cm$^{-1}$, versus 1198 cm$^{-1}$ for band E) supports then a situation of weakly interacting carbonyl groups and, hence, the coordination of ammonium with the oxolane groups predicted by the computation for conformer N1.

Despite the good overall agreement between the IRMPD measurement and the computational IR spectrum of conformer N1, there is one outstanding discrepancy for one particular spectral feature. The B3LYP computation predicts a pronounced vibrational band at around 1500 cm$^{-1}$ for which no apparent trace is found in the experiment. The three vibrational transitions that contribute to this band are highlighted with red colour bars in Fig. 3 and are assigned by the computation to umbrella modes of the $\text{NH}_4^+$ cation, with a virtually static nonactin host. Previous studies have shown that bending modes in ammonium and protonated primary amines are likely to display anharmonic behavior.\textsuperscript{26} In order to explore this possibility for the present complexes, we performed an additional B3LYP computation for the N1 conformer in which the frequencies of the three umbrella modes of ammonium were treated anharmonically within the VPT2 approximation, while the remaining vibrational modes of the complex were kept harmonic. Given the size of nonactin, a full anharmonic computation of the complex was not possible with our computational resources. The partial anharmonic treatment applied here must be interpreted as a preliminary approximation to the modelling of the complex useful to assess possible trends inferred by anharmonicity in its spectral signatures.\textsuperscript{20,22–24} Figure 3 shows that the result of the anharmonic computation is a red shift of the three modes by $\sim\!50$ cm$^{-1}$. Such a shift merges these modes with band B, thereby reconciling the qualitative structure of the computational IR bands with the one displayed.

FIG. 3. IRMPD spectra of the complexes of nonactin with $\text{NH}_4^+$ and $\text{NH}_3\text{OH}^+$ (top panels), and the IR spectra predicted by the B3LYP/6-311++G(d,p) computations for the corresponding conformers of lowest energy (middle and bottom panels). See Fig. 2 for a representation of the conformers. The main vibrational bands, labelled A–G for discussion, are described qualitatively in Table I. The position of band A with respect to band E is indicated in terms of the relative position between band A and band E in the IR spectra computed for the two conformers. Note that band E is associated with nonactin backbone vibrations (C$\cdots$O–C stretching of the ester bonds and C$\cdots$C stretching in the oxolane rings) that appear to be weakly affected by the ammonium–carbonyl coordination.
by the IRMPD spectrum in the 1300–1500 cm$^{-1}$ range. In summary, the anharmonic treatment corroborates the finding that conformer N1 constitutes the configuration of the nonactin-NH$_4^+$ complex that is dominantly populated at ambient temperature.

### B. Nonactin-NH$_3$OH$^+$ complex

The hydroxylammonium guest introduces a differentiated coordination, involving specific H-bonding and steric interactions of its OH group, in addition to those of the NH$_4^+$ bonds. As a result, this complex does not display the symmetry found for the ammonium complex, and mixed oxolane/carbonyl coordination arrangements become feasible. Figure 2 depicts the two most stable conformations for the hydroxylamine complex of nonactin. The conformation of lowest energy, H1, features H-bonding of the three ammonium bonds with oxolane groups of nonactin (at NH···O distances 1.80–1.85 Å and angles 160°–180°), while the OH group displays a bifurcated coordination with the oxygen atoms from a carbonyl group (at 2.05 Å and 140°) and from the fourth oxolane group (at 2.04 Å and 114°). The situation reverses in the H2 conformer, in which the ammonium moiety of hydroxylamine coordinates with three carbonyl groups of nonactin (at 1.75–1.80 Å and 155°–165°), while the OH groups bind to an oxolane group (at 1.70 Å and 175°). The B3LYP computation assigns an energy difference, between conformers H1 and H2, of 8.5 kJ mol$^{-1}$. Figure 2 shows that the coordination of hydroxylammonium with the carbonyl groups in conformer H2 stretches the nonactin backbone, leading to a cavity opening as much as ~2 Å larger than the one found for conformer H1.

The NBO analysis for the NH$_3$OH$^+$ complex corroborates the trend found for the NH$_4^+$ complex. The NH$^{6+}$···O coordination of the three ammonium bonds with the oxolane groups of the host in conformer H1 leads to a much larger stabilization energy (58 kJ mol$^{-1}$ per bond in average) than the coordination with the carbonyl groups in conformer H2 (38 kJ mol$^{-1}$ per bond). Interestingly, the H2 conformer displays a strong OH···O interaction (62 kJ mol$^{-1}$) between the OH bond of hydroxylamine and one oxolane group of nonactin. In comparison, the bifurcated interaction of the OH bond with the oxolane and carbonyl groups amounts to only 9 and 13 kJ mol$^{-1}$, respectively. This finding serves to rationalize the fact that the relative energy of the H2/H1 conformers (8.5 kJ mol$^{-1}$) is more than a factor of two smaller than the one found for N2/N1 (20 kJ mol$^{-1}$).

The IRMPD spectrum recorded for the nonactin–NH$_3$OH$^+$ complex is represented in Fig. 3. The analysis of the corresponding IR spectra predicted for conformers H1 and H2 leads to a rationalization of the experiment in similar terms as outlined above for the NH$_4^+$ complex. Hydroxylammonium incorporates NOH bending and N−O stretching vibrational modes to bands F and G, respectively. Coupling of C=O stretching and NH$_3^+$ bending modes is also observed in band A for conformer H2. The vibrational band structure associated with conformer H1 resembles closely the IRMPD measurement throughout the full spectral range investigated. In particular, the position of the C=O stretching band is consistent with that found in the IRMPD spectrum. Although not obvious at first sight, in the IRMPD spectrum, the C=O stretching band broadens slightly towards its red flank, with respect to that of the NH$_4^+$ complex. This is interpreted in terms of a red shift by ~10 cm$^{-1}$ of two modes associated with the motions of the single C=O group that is H-bonded to the OH group of the guest cation in conformer H1. In contrast, it can be noted that in the H2 conformer, the three coordinated C=O bonds lead to a splitted stretching band whose main component is clearly red shifted with respect to the experiment. The present experimental and computational results hence suggest that conformer H1 is the only arrangement of the complex that is significantly populated at ambient temperature.

### C. Relative complex stabilities

It is interesting to notice that, whereas the nonactin-NH$_4^+$ complexes could be readily characterized with crystallographic techniques, this has not been possible for the NH$_3$OH$^+$ complexes. Attempts to form nonactin-NH$_3$OHCl crystals have been reported, which failed presumably due to an unfavorable balance of solvent and crystal field interactions. In order to shed some light into this finding, we close the study with an assessment of the relative stability of the nonactin complexes of ammonium and hydroxylammonium. For this purpose, electrospray ionization measurements were performed on methanol solutions equinomolar in NH$_4^+$, NH$_3$OH$^+$, and K$^+$, all of them in excess with respect to nonactin (see Sec. II). The inclusion of K$^+$ provides a valuable benchmark and serves to estimate the potential competitive binding of both species in the presence of common alkali metal cations. The resulting mass spectrum is shown in Fig. 4 and reflects the relative abundances of the three complexes. It can be observed that the signal detected for the NH$_4^+$ complex is four-fold and

<table>
<thead>
<tr>
<th>Band</th>
<th>Range (cm$^{-1}$)</th>
<th>Mode assignment</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>1695–1730</td>
<td>C=O stretching (str.) NH$_3^+$ bending (N) NH$_4^+$ bending/umbrella (H)</td>
</tr>
<tr>
<td>B</td>
<td>1410–1480</td>
<td>CH$_2$/CH$_3$ scissoring NH$_4^+$ umbrella (N)</td>
</tr>
<tr>
<td>C</td>
<td>1360–1400</td>
<td>CH/CH$_2$ wagging, CH$_3$ umbrella NOH bending (H)</td>
</tr>
<tr>
<td>D</td>
<td>1300–1345</td>
<td>CH$_2$ rocking/wagging</td>
</tr>
<tr>
<td>E</td>
<td>1180–1225</td>
<td>COC/CC str., CH$_2$ twisting</td>
</tr>
<tr>
<td>F</td>
<td>1100–1180</td>
<td>COC/CC str., CH$_2$ twisting, CH$_3$ rocking</td>
</tr>
<tr>
<td>G</td>
<td>1010–1090</td>
<td>CO str. (oxolane), CH$_2$ rocking N−O str (H)</td>
</tr>
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eight-fold more intense than the signals associated with the K\(^+\) and NH\(_3\)OH\(^+\) complexes, respectively. Hence, the binding of ammonium by nonactin can be expected to be robust under a broad range of environmental conditions, whereas the stabilization of the hydroxylammonium complex can plausibly be more sensitive to the presence of other cations and to solvent interactions.

**IV. CONCLUSIONS**

The infrared spectra of isolated nonactin complexes with NH\(_4\)\(^+\) and NH\(_3\)OH\(^+\) have been characterized with IRMPD action spectroscopy and modelled by means of DFT quantum chemical calculations. The most stable computational structures for the two complexes (conformers N1 and H1) involve tight coordination arrangements of the ammonium moieties with the oxolane ether oxygen of the nonactin host. In the ammonium complex, a particularly compact conformation of S4 symmetry is attained. In the hydroxylammonium complex, such symmetry is disrupted, as the OH group of the guest cation forms a complementary bifurcated H-bond with the fourth oxolane group and a carbonyl group of the macrocycle. The computational structures next in energy for the two complexes (N2 and H2) feature complementary coordination arrangements of ammonium with carbonyl groups of the macrocycle and involve a more stretched conformation of the nonactin backbone.

Natural bond orbital analysis rationalizes the stability of the two nonactin complexes in terms of an efficient distribution of charge from the lone pair orbitals of the oxolane ether oxygen atoms of the macrocycle to the antibonding orbitals of the NH\(^4\)+ bonds in the ammonium moieties of the guest cations. The stabilization energies from such interactions are roughly a factor of two stronger than those associated with the carbonyl oxygen atoms from the ester groups of the macrocycle. The bifurcated coordination of the OH group of hydroxylammonium contributes more moderately to the stability of the complex in the H1 conformation.

The vibrational band structure observed in the IRMPD spectrum supports the preferred coordination of ammonium with the oxolane ether oxygen atoms of nonactin, in particular, the position of the C\(=\)O stretching bands in the spectra of the two complexes is consistent with conformers N1 and H1 and rules out any significant population of higher energy conformers involving significant ammonium-carbonyl interactions. These results corroborate earlier assignments in condensed phases from Raman and crystallography measurements.

Anharmonicity appears to play a relevant role in the binding modes of the ammonium guest moieties in the complexes. The partial VPT2 treatment, restricted to these modes, appears to constitute a fair approximation to the modelling of these systems. Future work in our group will seek further challenges to modelling approaches by considering complexes of nonactin with protonated amine guests of increasing complexity, including the important case of amino acids.

**ACKNOWLEDGMENTS**

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17. See http://www.ru.nl/felix/ for more information on the FTICR mass spectrometer coupled to the FELIX beam line and for the specifications of the FELIX infrared radiation.