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Probing the hydrogen bonding of guest functional groups with [2.2.2]-cryptand/KF host vs. with solvent by ^{19}F -NMR spectroscopy

So Yeon Lee,^{†a} Young-Ho Oh, Han Bin Oh *^a and Sungyul Lee *^b

We present a method for probing the local environment surrounding ammonium, hydroxyl, and carboxyl functional groups in solution by analyzing the ^{19}F -NMR chemical shifts of [2.2.2]-cryptand ([2.2.2])/KF/protonated amino acid (AAH^+) complexes. Specifically, we examine two competing structural features—solvation of guest functional groups *versus* complexation with the host—by monitoring hydrogen bonding interactions in deuterated ethylene glycol ($\text{EG}-d_6$) and deuterated acetonitrile (CD_3CN). Model systems including [2.2.2]/KF/ NH_4^+Cl^- , [2.2.2]/KF/choline $^+\text{Cl}^-$ ([2.2.2]/KF/ Ch^+Cl^-), and 24-crown-8/CsF/betaine/ H^+Cl^- were employed to benchmark the chemical shift signatures associated with specific hydrogen bonding motifs. Based on the observed ^{19}F NMR peaks, we assign the structures of [2.2.2]/ AAH^+ (AA = proline (Pro), threonine (Thr)) complexes in each solvent. In $\text{EG}-d_6$, both complexes exhibit $[-\text{NH}_3^+ \cdots \text{F}^-]$ hydrogen bonding, while the carboxyl group in ProH^+ and the carboxyl and hydroxyl groups in ThrH^+ remain solvated and unbound to the host. In contrast, in CD_3CN , the carboxyl group in ProH^+ and both the carboxyl and ammonium groups in ThrH^+ directly engage in hydrogen bonding with F^- . These findings support the use of ^{19}F -NMR spectroscopy as a sensitive probe of the [2.2.2]/KF/protonated amino acid system in solution and provide insight into potential structural correlations between solution-phase and gas-phase complexes.

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Introduction

Understanding host–guest interactions^{1–6} in solution is of significant interest, both as a foundation for molecular recognition principles^{7–9} and self-assembly processes,^{10–13} and for the rational design of supramolecular systems such as artificial enzymatic catalysts,^{14–17} gene delivery vectors,^{18,19} bioimaging agents,^{20,21} and stimuli-responsive materials.^{22–25} In contrast with the gas phase, where techniques such as electrospray ionization/mass spectrometry combined with infrared multiphoton dissociation (ESI/MS/IRMPD)^{26–37} allow probing of host–guest configurations, investigating these interactions in solution remains challenging. Specifically, acquiring detailed structural information on guest biomolecules and deciphering the microenvironment, *i.e.*, host complexation *vs.* solvation, of their functional groups is often difficult using conventional experimental methods such as ^1H -NMR spectroscopy, collision-induced dissociation,^{38,39} or ion-mobility spectrometry.^{40–42} While these techniques can offer valuable insights into some

aspects of host–guest behaviours, they often fall short of providing a comprehensive picture.

In this study, we investigate the complexes of ProH^+ and ThrH^+ with [2.2.2]/KF in solution (CD_3CN and $\text{EG}-d_6$; see Fig. 1), as model systems for macrocyclic host–biomolecule guest interactions. We use ^{19}F -NMR spectroscopy as a sensitive probe of the [2.2.2]/KF/protonated amino acid system in solution, remedying the ineffectiveness (missing or extreme broadening of resonance signals) of ^1H -NMR technique for examining H-bonding features of bio/organic functional groups such as carboxyl, hydroxyl and ammonium. The notable sensitivity of the ^{19}F chemical shifts on the H-bonding environment around the metal fluorides as agents for nucleophilic reactions⁴³ and also as a probe for determining the interactions between the [2.2.2]/KF/choline chloride model system⁴⁴ is harnessed here to elucidate the interactions between [2.2.2]/KF and protonated forms of the amino acids proline and threonine. For the [2.2.2]/

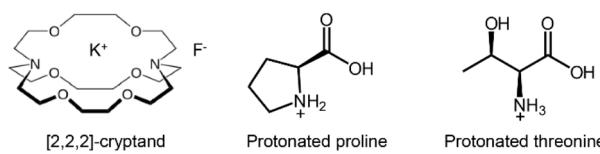


Fig. 1 Components of [2.2.2]/KF/ ProH^+ and [2.2.2]/KF/ ThrH^+ non-covalent host–guest complexes.

^aDepartment of Chemistry, Sogang University, Seoul 121-742, Republic of Korea.
 E-mail: hanbinoh@sogang.ac.kr

^bDepartment of Applied Chemistry, Kyung Hee University, Gyeonggi 17104, Republic of Korea. E-mail: sylee@khu.ac.kr

† These authors contributed equally to this work: So Yeon Lee and Young-Ho Oh.



KF/ProH⁺ complex, we examine which of the two functional groups (ammonium or carboxyl) interacts with the host and/or the solvent molecules in EG-*d*₆ and in CD₃CN. In the case of [2.2.2]/KF/ThrH⁺, which features three adjacent acidic functional groups (Fig. 1), we explore which combinations (–NH₃⁺/–OH, –NH₃⁺/–CO₂H, or –NH₃⁺/–OH/–CO₂H) engage in hydrogen bonding with the [2.2.2]/KF host.

To interpret the observed ¹⁹F-NMR chemical shifts, we leverage the high sensitivity of ¹⁹F NMR to H-bonding interactions involving F[–].^{43,44} Reference complexes, *i.e.*, [2.2.2]/KF/NH₄⁺Cl[–], [2.2.2]/KF/Ch⁺Cl[–], and 24-crown-8/CsF/Betaine/H⁺Cl[–], are employed to benchmark the configurations of [2.2.2]/KF/ProH⁺ and [2.2.2]/KF/ThrH⁺ in solution. The [2.2.2]-cryptand ([2.2.2]; Fig. 1) was selected as a host component due to its strong affinity for coordinating metal cations. This macrocyclic ligand is well known as a highly effective K⁺ chelator, making it useful in applications such as metal ion sensing and phase-transfer catalysis (PTC).⁴⁵ When complexed with KF, [2.2.2] can bind K⁺ and position F[–] as a sensitive probe to detect the local environment of guest molecules bearing acidic functional groups, *e.g.*, –NH₃⁺, –OH, and –COOH. The chemical shift of F[–] in the ¹⁹F NMR spectrum can indicate whether F[–] interacts with the ammonium group, carboxylic/hydroxyl groups, or solvent molecules.

We also perform gas-phase structure calculations for the [2.2.2]/KF/AAH⁺ (AA = Pro, Thr) complexes to provide insight into potential structural correlations between solution-phase and gas-phase complexes. The most thermodynamically stable forms of these complexes correspond to configurations where the carboxyl (and hydroxyl, in the case of ThrH⁺) are solvated in solution but become ‘naked’, that is, disengaged from the [2.2.2]/KF host, in the gas phase. We discuss the configurations and relative thermodynamic stabilities (based on Gibbs free energy) of these gas-phase species, focusing on the structural correlation between the solution and gas phases, as bridged by ESI/MS procedures.

Computational details

All calculations were performed using the wb97X-D⁴⁶ density functional theory (DFT) method. A 6-311G** basis set was applied for all atoms. All computations were carried out using the Gaussian 16 software package.⁴⁷ We employed the supramolecule – continuum model, treating the solvent in the first shell around the complex as explicit molecules while others are accounted for as SMD continuum.⁴⁸

Vibrational frequency analyses were conducted to confirm the nature of all stationary points; all minima were verified to have no imaginary frequencies. A scaling factor of 0.927 was applied to the calculated IR frequencies of the free hydroxyl and carboxyl groups to match the experimental reference values (3680 and 3560 cm^{–1}, respectively).^{29,49}

Results and discussion

Structures of [2.2.2]/KF/ProH⁺ and [2.2.2]/KF/ThrH⁺ non-covalent host-guest complexes in solution (CD₃CN and EG-*d*₆)

Fig. 2 presents the ¹⁹F-NMR spectra and calculated structures for two model systems: [2.2.2]/KF/NH₄⁺Cl[–] in EG-*d*₆ and 24-crown-8/CsF/Betaine/H⁺Cl[–] in CD₃CN. In Fig. 2a, the intense ¹⁹F resonance at –137.54 ppm observed for [2.2.2]/KF/NH₄⁺Cl[–] is readily assigned to a [F[–]···NH₃⁺] hydrogen bond. This chemical shift serves as a diagnostic marker for [F[–]···NH₃⁺]

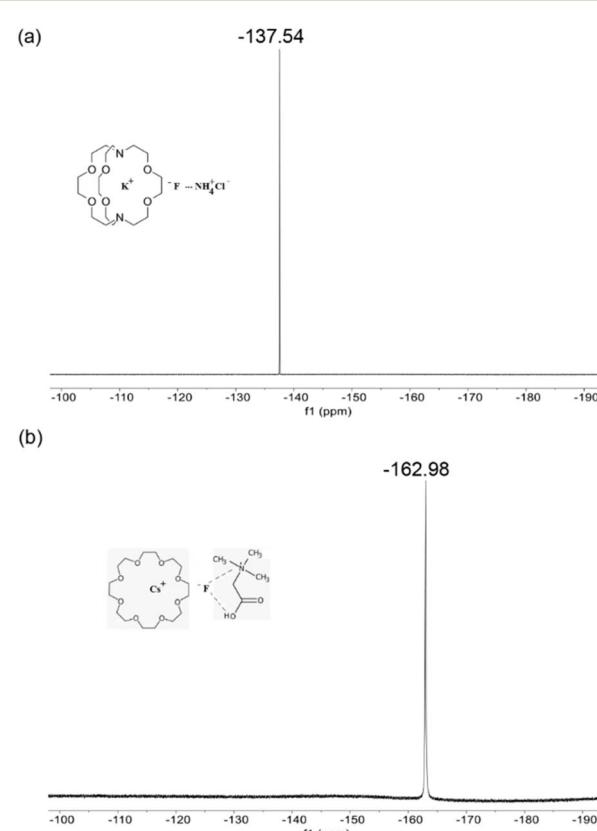


Fig. 2 ¹⁹F-NMR spectrum and schematic structure of (a) [2.2.2]/KF/NH₄⁺Cl[–] in EG-*d*₆ (b) 24-crown-8/CsF/BetH⁺Cl[–] in CD₃CN. Chemical shift in ppm.

Experimental: methods and materials

All chemicals and solvents used in this study were purchased from commercial suppliers and used without further purification. 24-crown-8, cesium fluoride, potassium fluoride, betaine hydrochloride, ammonium chloride, deuterated acetonitrile (CD₃CN), deuterated ethylene glycol (EG-*d*₆), proline, and threonine were obtained from Sigma Aldrich (St. Louis, MO, USA). For NMR analysis, sample mixtures such as 24-crown-8/CsF/amineH⁺ and [2.2.2]/CsF/ProH⁺ were prepared by mixing the components in a 1:1:1 molar ratio and dissolving them in CD₃OD or EG-*d*₆. Both ¹H and ¹⁹F NMR spectra were recorded at 298 K using a JEOL 500 MHz spectrometer (JNM-ECZL500R, JEOL Ltd, Tokyo, Japan). Chemical shifts (δ) are reported in parts per million (ppm), referenced externally to trimethylsilane (TMS; δ 0.0 ppm) for ¹H NMR and trifluorotoluene (TFT; δ –63.72 ppm) for ¹⁹F NMR.

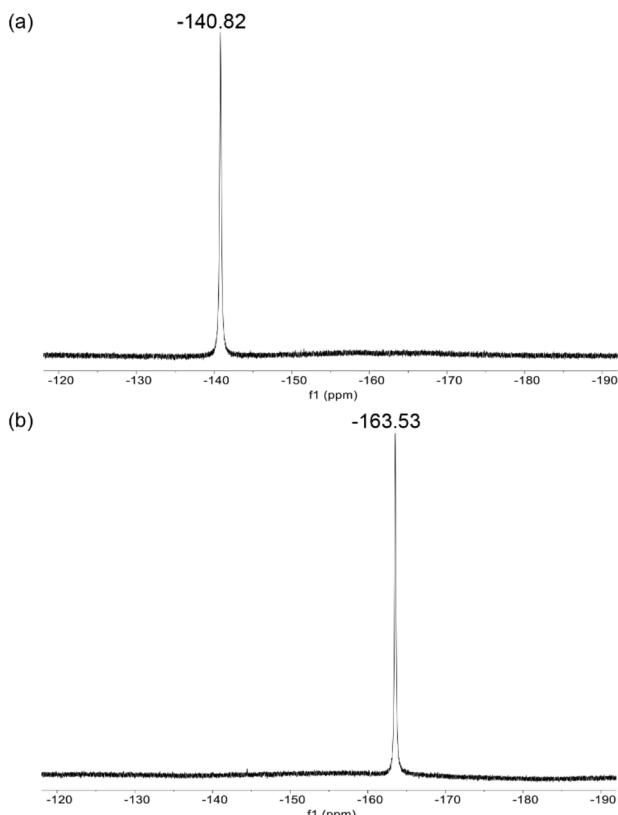


Fig. 3 ^{19}F -NMR spectrum of $[2.2.2]/\text{KF}/\text{ProH}^+$ (a) in $\text{EG}-d_6$ (b) in CD_3CN . Chemical shift in ppm.

interactions in $\text{EG}-d_6$. Fig. 2b shows the ^{19}F -NMR spectrum of 24-crown-8/CsF/Betaine/ H^+Cl^- in CD_3CN , featuring a prominent signal at -162.98 ppm, characteristic of a $[-\text{NH}_3^+ \cdots \text{F}^- \cdots \text{HO}_2\text{C}-]$ hydrogen bonding motif. Similar downfield shifts are observed for the $[2.2.2]/\text{KF}/\text{ProH}^+$ and $[2.2.2]/\text{KF}/\text{ThrH}^+$ complexes in CD_3CN , as discussed below.

Fig. 3 shows the ^{19}F -NMR spectra of the $[2.2.2]/\text{KF}/\text{ProH}^+$ complex in $\text{EG}-d_6$ and CD_3CN . In $\text{EG}-d_6$, a sharp peak at -140.82 ppm closely matches that of the NH_4^+Cl^- model system (Fig. 2a), suggesting that only the ammonium group binds to the $[2.2.2]$ host, while the carboxyl group remains solvated and excluded from host interaction. In contrast, in CD_3CN , the appearance of a strong peak at -163.53 ppm indicates that both the ammonium and carboxyl groups participate in the $[-\text{NH}_3^+ \cdots \text{F}^- \cdots \text{HO}_2\text{C}-]$ hydrogen bonding with F^- , in analogy with the 24-crown-8/CsF/Betaine/ H^+Cl^- complex (see Fig. 2b; -162.98 ppm).

Quantum chemical calculations⁵⁰⁻⁵³ (Fig. 4) support these structural assignments. In $\text{EG}-d_6$, the $\text{H} \cdots \text{F}$ distance is 1.590 \AA , indicating no proton transfer from the ammonium group to F^- . Additionally, an $\text{EG}-d_6$ molecule appears to solvate and spatially separate the carboxyl group from the $[2.2.2]$ ring. In CD_3CN , the carboxyl proton seems to be transferred to F^- ($R_{\text{H} \cdots \text{F}} = 1.017 \text{ \AA}$), while the ammonium group is shielded by solvent molecules, remaining distant from the host. Although K^+ is chelated inside the cavity of the cryptand $[2.2.2]$, it still exists as a contact ion-

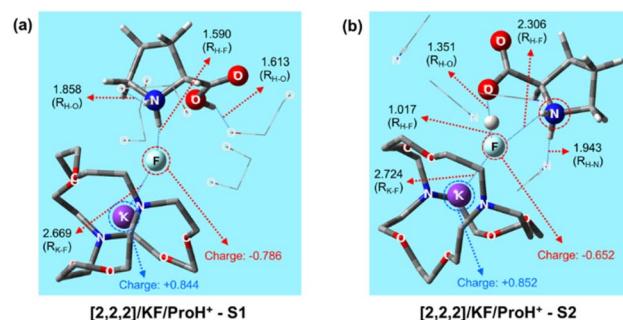


Fig. 4 Calculated lowest Gibbs free energy structure of $[2.2.2]/\text{KF}/\text{ProH}^+$ (a) in $\text{EG}-d_6$ (b) in CD_3CN . Distance in \AA . Natural bond orbital charges in e unit. Blue background represents the solvent continuum.

pair, not as a naked ion, as revealed in our previous paper.⁴³ We may also rule out the possibility of the formation of the complex $[2.2.2]/\text{KCl}/\text{AAH}^+\text{F}^-$ in which the solvent-separated F^- (devoid of Coulomb interaction with K^+) forms H-bond with the ammonium or carboxyl in AAH^+ , because the latter complex would give rise to a peak at ~ -101 ppm (Fig. S10 in SI, ref. 43).

Fig. 5 shows the ^{19}F -NMR spectra of the $[2.2.2]/\text{KF}/\text{ThrH}^+\text{Cl}^-$ complex in solution. In $\text{EG}-d_6$, a strong peak at -140.91 ppm closely resembles that of the ProH^+ complex (-140.82 ppm), indicating that only the ammonium group binds to the host, while both the hydroxyl and carboxyl groups are solvated and

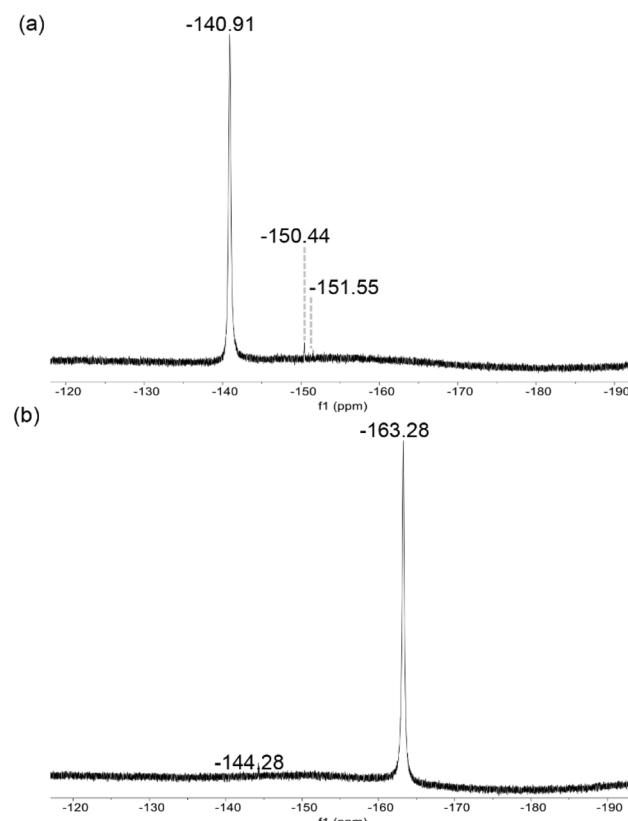


Fig. 5 ^{19}F -NMR spectrum of $[2.2.2]/\text{KF}/\text{ThrH}^+\text{Cl}^-$ (a) in $\text{EG}-d_6$ (b) in CD_3CN .



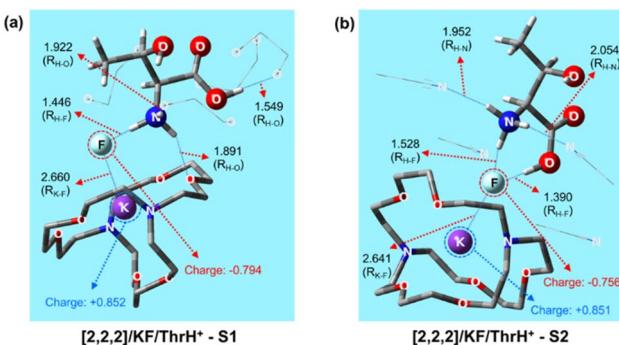


Fig. 6 Calculated lowest Gibbs free energy structure of [2.2.2]/KF/ThrH⁺ (a) in EG-*d*₆ (b) in CD₃CN. Distance in Å. Blue background represents the solvent continuum.

excluded from interaction with [2.2.2]. In CD₃CN, a peak at -163.28 ppm is observed, comparable to the signals at -162.98 ppm (BetaineH⁺) and -163.53 ppm (ProH⁺), suggesting that a $[-\text{NH}_3^+ \cdots \text{F}^- \cdots \text{HO}_2\text{C}-]$ interaction forms, with the hydroxyl group remaining solvated and unbound to the host. This observation is consistent with the greater acidity of the carboxyl group compared to the hydroxyl, as F⁻ preferentially forms hydrogen bonds with the more acidic proton. Notably, the absence of a signal near -178 ppm, associated with a fully formed $[\text{F}^- \cdots \text{HO}_2\text{C}-]$ interaction, indicates that proton transfer from the carboxyl to F⁻ does not occur in this case. This conclusion is further supported by the lack of a peak near -117 ppm (Fig. S1, SI), which would correspond to a $[-\text{NH}_3^+ \cdots \text{F}^- \cdots \text{HO}-]$ hydrogen bond as observed in [2.2.2]/KF/Ch⁺Cl⁻ in DMSO-*d*₆.⁴⁴

These NMR interpretations align well with the calculated lowest Gibbs free energy structures of the [2.2.2]/KF/ThrH⁺ complex in both solvents. In EG-*d*₆ (Fig. 6a), a $[-\text{NH}_3^+ \cdots \text{F}^-]$ interaction is observed ($R_{\text{H}\cdots\text{F}} = 1.446$ Å), along with a possible weak hydrogen bond ($R_{\text{H}\cdots\text{O}} = 1.891$ Å) between the ammonium and an oxygen atom of the host. In CD₃CN, both the ammonium and carboxyl groups interact with F⁻ ($R_{\text{H}\cdots\text{F}} = 1.528$ and 1.390 Å), while the hydroxyl remains fully solvated and excluded from interaction with the [2.2.2] ring. Importantly, neither proton is fully transferred to F⁻ in this case.

Calculated structures of [2.2.2]/KF/ProH⁺ and [2.2.2]/KF/ThrH⁺ non-covalent host-guest complexes in the gas phase

The ESI/MS and IRMPD techniques have proven to be powerful tools for generating and characterizing gas-phase host-guest complexes. One of the most intriguing questions in supramolecular chemistry is whether the structural features of host-guest complexes in solution is preserved upon transfer to the gas phase. Although there is no definitive experimental proof for this proposition, recent observations offer compelling clues. Notably, highly unfavorable gas-phase configurations of permethylated cyclodextrin (perm-CD) complexes with AAH⁺ (AA = alanine, isoleucine) have been reported.^{42,54} Subsequent theoretical studies proposed that these gas-phase conformers originate from the most stable solution-phase configuration⁵⁴⁻⁵⁸ suggesting a structural correlation between the two phases.

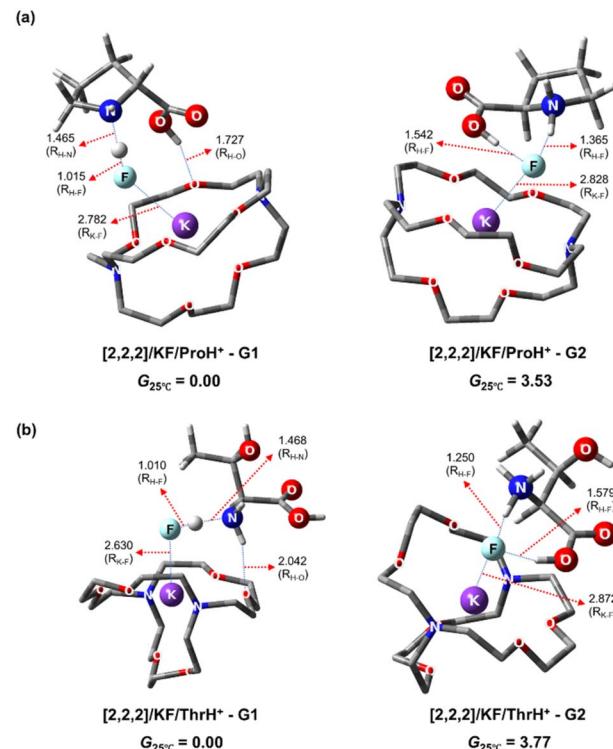


Fig. 7 Calculated structures of (a) [2.2.2]/KF/ProH⁺ (b) [2.2.2]/KF/ThrH⁺ complex in the gas phase. Relative Gibbs free energy in kcal mol⁻¹, distance in Å.

To facilitate experimental validation of this hypothesis in the present systems, we performed DFT calculations on the gas-phase structures and IR spectra of [2.2.2]/KF/AAH⁺ complexes (AA = Pro, Thr). Fig. 7a displays the lowest Gibbs free energy structures of the [2.2.2]/KF/ProH⁺ complex in the gas phase. In the thermodynamically more favored (Gibbs free energy lower by 3.5 kcal mol⁻¹) configuration, [2.2.2]/KF/ProH⁺-G1, the ammonium group alone forms a hydrogen bond with F⁻, closely resembling the solution-phase structure [2.2.2]/KF/ProH⁺-S1 (Fig. 4a). This structural similarity suggests a clear correlation between the gas- and solution-phase structures. However, the removal of solvent during the ESI/MS process induces subtle changes: (1) the ammonium proton is transferred to F⁻ ($R_{\text{H}\cdots\text{F}} = 1.015$ Å), and (2) the carboxyl group engages in a weak hydrogen bond with the [2.2.2] ring ($R_{\text{H}\cdots\text{O}} = 1.727$ Å).

In contrast, the second gas-phase structure, [2.2.2]/KF/ProH⁺-G2, mirrors the solution-phase structure [2.2.2]/KF/ProH⁺-S2, in which both the ammonium and carboxyl groups form hydrogen bonds with F⁻. However, in the gas phase, the H⁺...F bond in G2 is considerably elongated (1.542 Å) compared to the corresponding bond in the solution-phase counterpart (1.017 Å). These two contrasting proton transfer behaviors may underlie the higher thermodynamic stability of G1 over G2 in the gas phase.

Fig. 7b shows the two lowest Gibbs free energy structures of the [2.2.2]/KF/ThrH⁺ complex in the gas phase. In the more stable conformer [2.2.2]/KF/ThrH⁺-G1, the ammonium group forms a hydrogen bond with F⁻, while a proton is transferred



from the carboxyl group to F^- ($R_{\text{H}\cdots\text{F}} = 1.010 \text{ \AA}$), indicating an acid–base reaction. Additionally, the ammonium group forms a weak hydrogen bond with the [2.2.2] ring ($R_{\text{H}\cdots\text{O}} = 2.042 \text{ \AA}$). The carboxyl and hydroxyl groups, previously solvated in the solution-phase structure [2.2.2]/KF/ThrH⁺-S1, are now ‘naked’ in the gas phase. In the second gas-phase conformer, [2.2.2]/KF/ThrH⁺-G2 (Gibbs free energy higher by 3.5 kcal mol⁻¹ than G1), both the ammonium and carboxyl groups interact with F^- , while the hydroxyl group remains unbound, *i.e.*, ‘naked’. Thus, the gas-phase structures [2.2.2]/KF/ThrH⁺-G1 and [2.2.2]/KF/ThrH⁺-G2 appear to correspond closely to the solution-phase structures [2.2.2]/KF/ThrH⁺-S1 and [2.2.2]/KF/ThrH⁺-S2, respectively, with minor adjustments due to the absence of solvent. Fig. S2 and S3 in SI present the calculated infrared spectra of these two gas-phase complexes to be compared with the experimental IRMPD spectra for structural identification in the gas phase.

A natural question arises: which gas-phase structures of [2.2.2]/KF/AAH⁺ (AA = Pro, Thr) are most likely to be observed in ESI/MS experiments? If our hypothesis holds – that gas-phase structures reflect the most thermodynamically stable solution-phase configurations – then [2.2.2]/KF/AAH⁺-S1 is expected to predominate in the gas phase when generated from EG-*d*₆ solution, while [2.2.2]/KF/AAH⁺-S2 should be observed when CD₃CN is the solvent. The thermodynamically disadvantageous gas phase complexes, which were observed in our past works, may eventually relax thermodynamically. In the thermal non-equilibrium gas-phase environment produced from the solution phase by the ESI/MS techniques, however, the rearrangement of the H-bonds in the complexes may be difficult, giving rise to ‘kinetically trapped’ gas-phase host–guest complexes.

The appearance of thermodynamically less favorable gas-phase species originating from the most stable CD₃CN solution structures would thus provide further evidence for what we term a ‘thermodynamic reversal’. This concept offers a valuable framework for inferring solution-phase host–guest configurations from their gas-phase counterparts.

Conclusions

We have elucidated the structures of the [2.2.2]/KF/ProH⁺ and [2.2.2]/KF/ThrH⁺ host–guest complexes in solution using ¹⁹F-NMR spectroscopy. By monitoring the hydrogen bonding behavior of guest functional groups (ammonium, hydroxyl, and carboxyl) with [2.2.2]/KF host *versus* solvent molecules, we identified distinct ¹⁹F chemical shifts characteristic of each interaction type. Our results reveal that the local environment surrounding the hydroxyl group is highly dependent on the solvent nature, with significant differences observed between the polar aprotic solvent CD₃CN and the protic solvent EG-*d*₆. Although the DFT methods employed here for the [2.2.2]/KF/AAH⁺ complexes seem to predict reasonable solution-phase structures, using more accurate *ab initio* theory and PCM methods would help to validate them rigorously. This will be carried out in our future works.

We also predicted, through gas-phase calculations, that the thermodynamically less favorable complexes featuring ‘naked’

acidic functional groups, originating from solution-phase structures in CD₃CN, would be detectable in the gas phase. These observations support the validity of using gas-phase structures to infer key features of solution-phase host–guest interactions.

Overall, our findings demonstrate the effectiveness of ¹⁹F-NMR spectroscopy as a powerful probe for characterizing the microenvironment of functional groups in small guest molecules. However, for larger hosts (*e.g.*, cyclodextrins, cucurbiturils, calixarenes) and more complex guests (*e.g.*, peptides, proteins), complementary techniques such as ¹H-NMR spectroscopy, collision-induced dissociation, and ion-mobility spectrometry may be required to achieve a comprehensive understanding.

We anticipate that this study will stimulate further investigation into host–guest chemistry, particularly in leveraging combined spectroscopic and computational approaches to unravel the subtle interplay of non-covalent interactions in increasingly complex supramolecular systems.

Author contributions

S. L. and H. B. O. supervised the overall project and secured the funding, conceived the idea and designed the study. S. Y. L. carried out ¹⁹NMR experiments, and Y.-H. O. did quantum chemical calculations. S. Y. L. and Y.-H. O. acquired and analyzed the data, co-writing the draft. S. L. and H. B. O. co-wrote the final version of the manuscript, to which all authors have given approval.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d5ra06750b>.

Acknowledgements

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