

Thermodynamic Reversal and Structural Correlation of 24-Crown-8/Protonated Tryptophan and 24-Crown 8/Protonated Serine Noncovalent Complexes in the Gas Phase vs in Solution: Quantum Chemical Analysis

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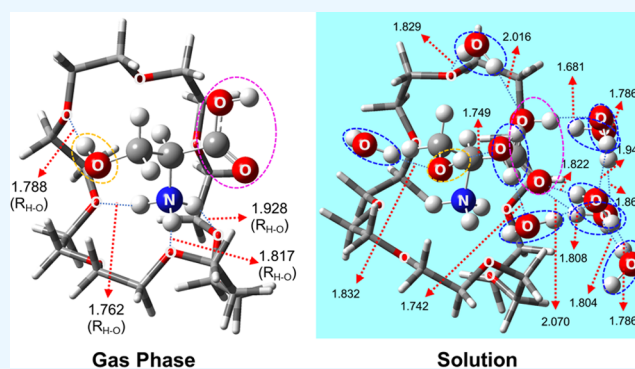


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Supporting Information

ABSTRACT: We investigate the structures of 24-crown-8/ H^+ /L-tryptophan (CR/Trp H^+) and 24-crown-8/ H^+ /L-serine (CR/Ser H^+) noncovalent host–guest complex both in the gas phase and in an aqueous solution by quantum chemical methods. The Gibbs free energies of the complex in the two phases are calculated to determine the thermodynamically most favorable conformer in each phase. Our predictions indicate that both the carboxyl and the ammonium in CR/Trp H^+ and the ammonium in the CR/Ser H^+ complexes in the lowest Gibbs free energy configurations form hydrogen bonds (H-bonds) with the CR host in the gas phase, while the conformer with the “naked” (devoid of H-bond with the CR host) $-CO_2H$ (and/or $-OH$) is much less favorable (Gibbs free energy higher by >3.6 kcal/mol). In the solution phase, however, a “thermodynamic reversal” occurs, making the higher Gibbs free energy gas-phase CR/Trp H^+ and CR/Ser H^+ conformers thermodynamically more favorable under the influence of solvent molecules. Consequently, the global minimum Gibbs free energy structure in solution is structurally correlated with the thermodynamically much less gas-phase conformer. Discussions are provided concerning the possibility of elucidating host–guest–solvent interactions in solution from the gas-phase host–guest configurations in molecular detail.



INTRODUCTION

Host–guest interactions are of fundamental importance as the principle of molecular recognition and self-assembly.^{1–18} While extensive studies have focused on examining host–guest configurations, scrutinizing them in the solution phase at the molecular level is often a challenging task. Conversely, for gas-phase host–guest complexes, infrared multiple photon dissociation (IRMPD) spectroscopy^{19–30} in combination with density functional theory (DFT)-based methods has proven to be a powerful tool for elucidating the structural features of gas-phase host–guest noncovalent interactions. This is exemplified by chiral differentiation^{31–35} of permethylated β -cyclodextrin (perm-CD) host and protonated L- and D-AAH⁺ (AA = Ala, Ile, Lys) guest.

The electrospray ionization/mass spectroscopy (ESI/MS)^{36–40} technique has been one of the most common and efficient tools for producing gas-phase guest–host complexes. Despite their long-standing application in host–guest chemistry, the most profound implications of these theoretical/experimental techniques concerning host–guest structures in both gas and solution phases seem to be emerging only recently.

In our previous studies^{41–44} aimed at identifying the structures of gas-phase perm-CD/L- an/D-AAH⁺ (AA = alanine, isoleucine, and lysine) complexes, we revealed striking features regarding the environment around the functional groups in AAH⁺. Thermodynamically disadvantageous gas-phase host–guest complexes were identified, with Gibbs free energies higher by >17 kcal/mol than the most stable conformer. In these complexes, the carboxyl absorption band appeared in an extremely high-frequency (>3560 cm^{-1}) regime due to the complete isolation of $-COOH$. These observations were attributed to the most stable host–guest complexes in the solution phase from which the gas-phase complexes were produced by the ESI/MS procedure. The thermodynamic reversal of stability from the gas phase to the solution phase led us to propose a novel scheme for unraveling host–guest–

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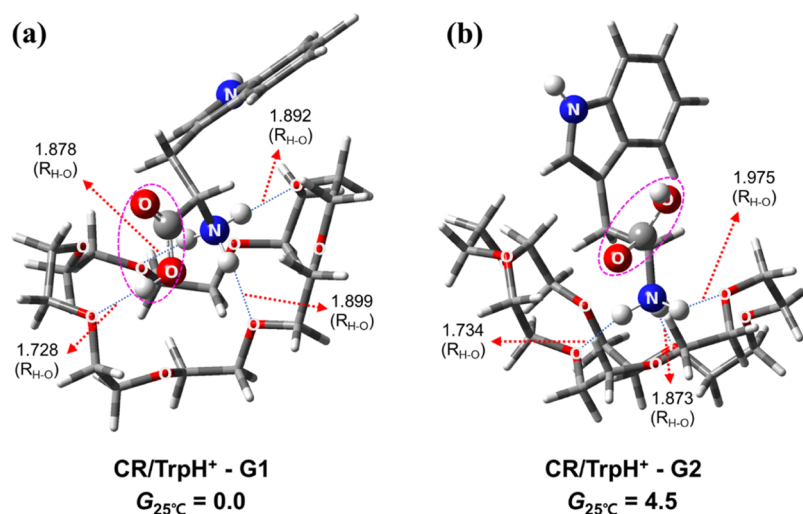
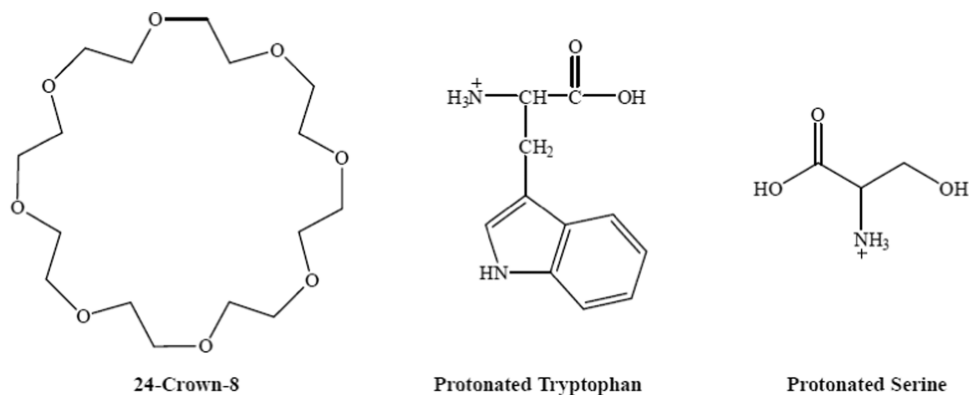
Chart 1. Components of 24-Crown-8/H⁺/L-tryptophan and 24-Crown-8/H⁺/L-serine Noncovalent Host–Guest Complexes

Figure 1. Calculated lowest Gibbs free energy structures of gas-phase 24-crown-8/TrpH⁺ in which (a) both the ammonium and carboxyl interact with the CR host and (b) the ammonium only interacts with the CR. Relative Gibbs free energy in kcal/mol and distance in Å.

solvent interactions in solution from the gas-phase host–guest structures.⁴⁴

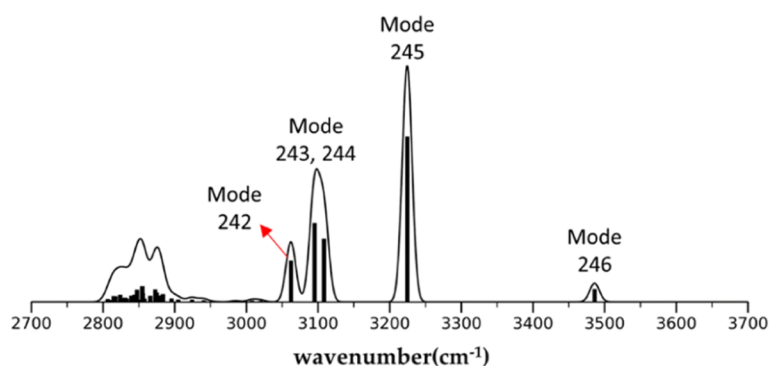
Here, in this study, we examine the complexes of the two protonated AAs (TrpH⁺ and SerH⁺) with the 24-crown-8 (Chart 1) with a larger ring that may allow multiple interactions between the host and guest functional groups (ammonium, carboxyl, hydroxyl) in contrast with the AAH⁺/18-crown-6 system for which it was elucidated⁴⁵ that only the ammonium interacts with the host. We study the present systems both in the gas phase and in solution to investigate the structural connectivity of the noncovalent host/guest complexes in these two phases. We calculate the structures of the CR/TrpH⁺ and CR/SerH⁺ host–guest systems in solution by “solvating” both the high Gibbs energy conformers and the most stable conformers in the gas phase. We find that their relative thermodynamic stability (relative Gibbs free energies) in the gas phase is *reversed* in solution. Moreover, the lowest Gibbs free energy conformer with a solvated (devoid of interactions with the CR host) carboxyl (and/or the hydroxyl) is closely related to the thermodynamically disadvantageous gas-phase complex with a “naked” –COOH. From these observations, we propose that the latter gas-phase conformer of the CR/TrpH⁺ and CR/SerH⁺ noncovalent complexes produced by the ESI/MS procedure may originate from the most stable complex in solution. Furthermore, we discuss the close structural connection and suggest the possibility of using

the ESI/MS/IRMPD technique to elucidate solution-phase host–guest–solvent interactions based on the structures of the host–guest complex in the gas phase.

COMPUTATIONAL DETAILS

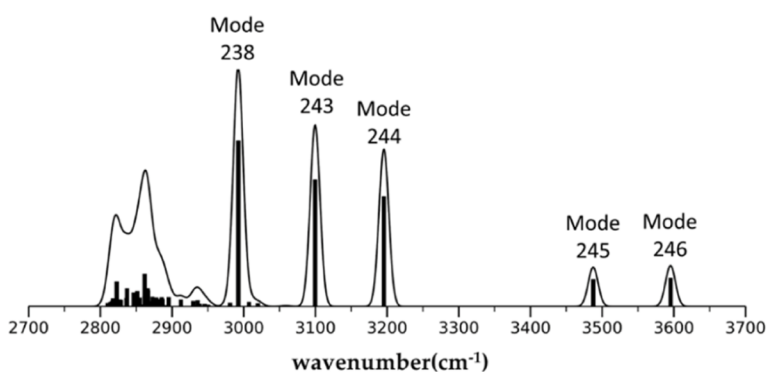
All calculations were performed using the wB97X-D functional⁴⁶ within DFT, which is known for its effective treatment of weak interactions, including hydrogen bonding. The 6-311G** and 6-31G* basis sets were employed, which were implemented in the Gaussian 16 suite of programs.⁴⁷ For structures in solution, single-point calculations were also conducted using the wB07X-D/6-311G* method at the wB97X-D/6-31G* optimized geometry. A scale factor of 0.9382 was applied to fit the calculated IR frequency of the carboxyl –OH stretch mode to the experimental value of 3560 cm⁻¹.⁴⁸ All structures underwent verification by checking all real vibrational frequencies.

In the case of the CR/TrpH⁺ and 24-crown-8/SerH⁺ complexes in an aqueous solution, a supramolecule/continuum approach was employed. This approach treated the eight solvent molecules directly interacting with –COOH in the first shell around the complex as explicit molecules while considering numerous other H₂O molecules in the second shell and beyond as part of the water continuum, utilizing the SMD method.⁴⁹ Extensive exploration over the potential energy landscape to search for the minimum Gibbs free energy

(CR/TrpH⁺ - G1: scale factor = 0.9382)

| Mode # | Frequency | Scaled Freq |
|--------|-----------|-------------|
| 242 | 3263.87 | 3062.16 |
| 243 | 3299.07 | 3095.19 |
| 244 | 3312.94 | 3108.20 |
| 245 | 3436.86 | 3224.47 |
| 246 | 3715.63 | 3486.01 |

242 : NH₃⁺ symmetric stretching vibration
 243,244 : NH₃⁺ asymmetric stretching vibration
 245 : carboxylic acid -OH stretch
 246 : indole -NH stretch

(CR/TrpH⁺ - G2 : scale factor= 0.9382)

| Mode # | Frequency | Scaled Freq |
|--------|-----------|-------------|
| 238 | 3189.56 | 2992.45 |
| 239 | 3195.32 | 2997.84 |
| 240 | 3205.48 | 3007.38 |
| 241 | 3218.57 | 3019.66 |
| 242 | 3260.37 | 3058.88 |
| 243 | 3303.84 | 3099.67 |
| 244 | 3406.08 | 3195.59 |
| 245 | 3717.29 | 3487.56 |
| 246 | 3832.27 | 3595.44 |

238 : NH₃⁺ symmetric stretching vibration
 243,244 : NH₃⁺ asymmetric stretching vibration
 245 : indole -NH stretch
 246 : carboxylic acid -OH stretch

Figure 2. IR spectra of the gas-phase 24-crown-8/TrpH⁺ complexes (CR/TrpH⁺-G1 and CR/TrpH⁺-G2). Frequency in cm⁻¹.

conformers of the 24-crown-8/AA⁺/(H₂O)_n complexes is carried out. The resulting structures are also compared with those obtained by MD calculations for smaller n.

RESULTS

Structures and Thermodynamic Stability of 24-Crown-8/TrpH⁺ Noncovalent Complexes in the Gas Phase. Figure 1 presents the calculated lowest Gibbs free energy structures of gas-phase 24-crown-8/TrpH⁺, showcasing two classes of distinct structural features obtained through extensive exploration of the landscape of the potential surface of the complex. In both complexes, the indole side chain is isolated, exerting little influence on the thermodynamic stability of the complexes. The lower Gibbs free energy complex CR/TrpH⁺-G1 features the CR unit coordinating both functional groups, while in the higher Gibbs free energy complex CR/TrpH⁺-G2, only the ammonium forms a hydrogen bond with the O atoms in 24-crown-8 (the carboxyl OH bends away from the CR). The absence of hydrogen bonding between the “naked” carboxyl and the CR unit is clearly the origin of the calculated higher Gibbs free energy (by 4.6 kcal/mol) for the conformer CR/TrpH⁺-G2. This structural feature is also evident in the corresponding infrared spectra (Figure 2): the strong band at 3595 cm⁻¹ in Figure 2(b) indicates the absorption of the isolated -COOH in CR/TrpH⁺-G2, while those for CR/TrpH⁺-G1 at 3225 cm⁻¹

correspond to the strongly red-shifted -COOH absorption, indicating the formation of hydrogen bonds between the -COOH and etheric O atoms. The strong red shifts of the symmetric and asymmetric -NH stretch modes of the ammonium in the 2990–3200 cm⁻¹ regime in both complexes signify the strong interactions between -NH₃⁺ and the CR unit.

The most relevant question concerning the gas-phase 24-crown-8/TrpH⁺ complexes is which of the two forms of the complexes is observed in the gas phase? In our previous studies, it was demonstrated that the relative thermodynamic stability (relative Gibbs free energy) of gas-phase host-guest complexes might not determine the populations of the complexes if the gas-phase environment produced in the ESI/MS experiments is not in thermal equilibrium. In this latter situation, the most stable host-guest configuration in the solution phase may give rise to the structure of the host-guest observed in the gas phase. If the lowest Gibbs free energy 24-crown-8/TrpH⁺ complex in solution is stripped off the solvent molecules by the ESI/MS and if the produced gas-phase host-guest complex is detected in the gas phase before thermal equilibrium is attained, then thermodynamically less favorable (higher Gibbs free energy) structures would be observed.

It is crucial to note that the Gibbs free energy of the conformer CR/TrpH⁺-G2 with the “naked” -COOH is calculated to be higher than that for CR/TrpH⁺-G1, which is

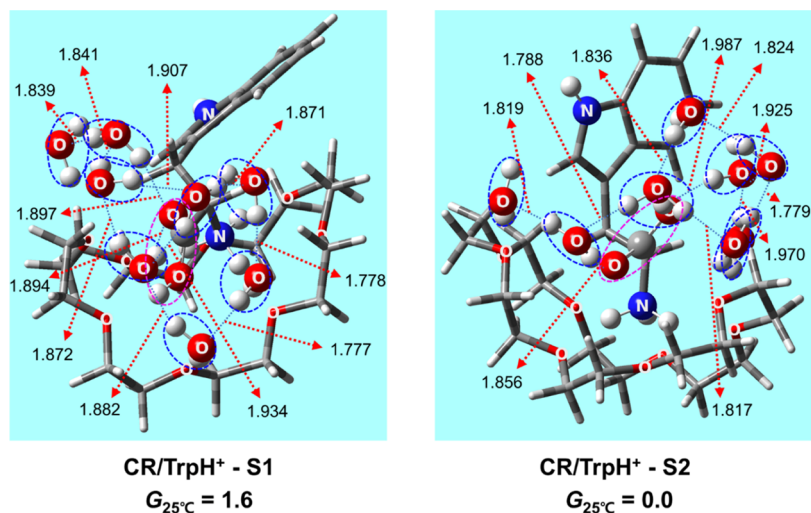


Figure 3. Calculated structures of 24-crown-8/TrpH⁺ complexes in an aqueous solution obtained by adding 8 H₂O molecules and water continuum to the gas-phase configurations CR/TrpH⁺-G1 and CR/TrpH⁺-G2. Relative Gibbs free energy in kcal/mol and distance in Å. The blue background represents the solvent continuum.

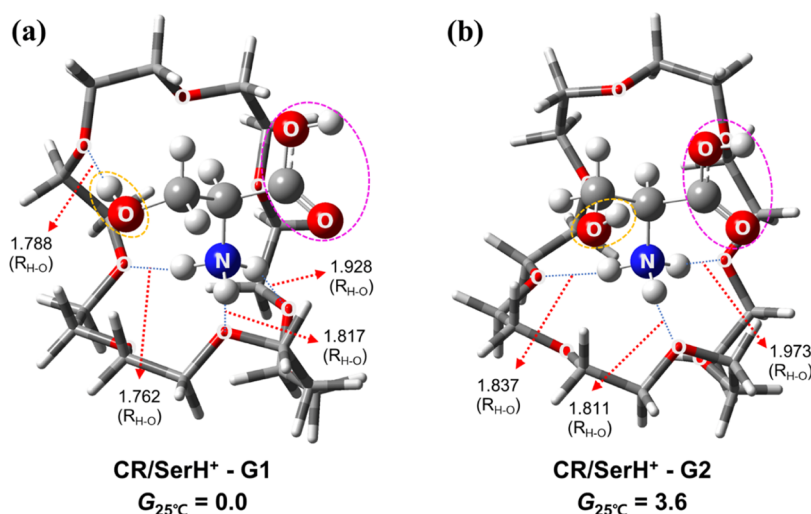


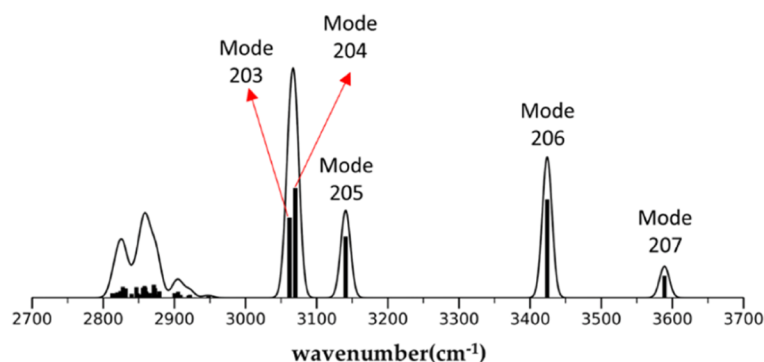
Figure 4. Calculated lower Gibbs free energy structures of gas-phase 24-crown-8/SerH⁺ in which (a) both the ammonium and hydroxyl interact with the CR host and (b) the ammonium only interacts with the CR. Relative Gibbs free energy in kcal/mol and distance in Å.

stabilized by the hydrogen bonding of the carboxyl groups with the CR unit. The thermodynamically disadvantageous gas-phase host–guest complex CR/TrpH⁺-G2 produced by the ESI/MS protocol may originate from the most stable conformer in the solution phase. In this case, the confirmed reversal of the relative thermodynamic stabilities of the CR/TrpH⁺ complexes in solution and in the gas phase may lead us to a profound proposition, as discussed below.

Structures of 24-Crown-8/TrpH⁺ Noncovalent Complexes in an Aqueous Solution. The relative thermodynamic stability of the gas-phase conformers CR/TrpH⁺-G1 and CR/TrpH⁺-G2 in Figure 1 (their thermodynamic properties are listed in Table S1 in the Supporting Information) is easily understood based on their structures. In CR/TrpH⁺-G1, the carboxyl and ammonium form hydrogen bonds with the CR unit, whereas in CR/TrpH⁺-G2, only the ammonium interacts with the CR. This latter feature is the origin of the higher Gibbs free energy of CR/TrpH⁺-G2.

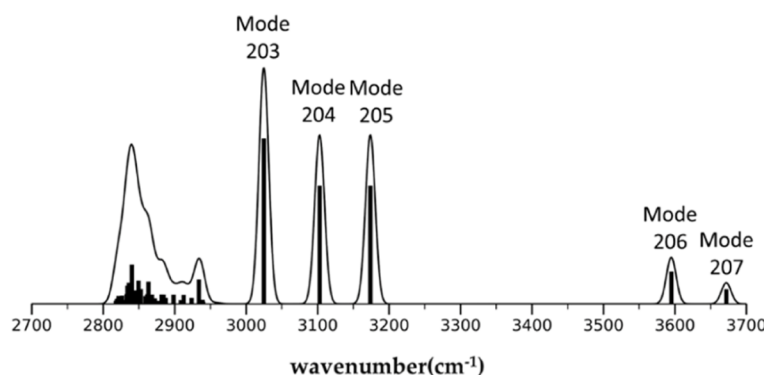
The key question now is whether the carboxyl group of TrpH⁺ in solution prefers to interact with the host CR (by

binding to the O atoms) or with solvent molecules. If the former is the case, then the carboxyl (and ammonium) of TrpH⁺ will form hydrogen bonds with the CR unit and avoid the solvent. On the other hand, if the carboxyl in the guest prefers to interact with the solvent molecules by hydrogen bonding, not with the CR host, the carboxyl will be located away from the host in the solution phase. To address this intriguing question, we conducted quantum chemical calculations for the CR/TrpH⁺ host–guest pair in solution by incorporating solvent molecules into the gas-phase conformers in Figure 1. The ammonium is located deep inside the CR ring in the two gas-phase complexes CR/TrpH⁺-G1 and CR/TrpH⁺-G2, inaccessible to solvent molecules, whereas the indole side chain is off the CR unit. Thus, we focus on the interactions between carboxyl and (H₂O)_n in solution. By increasing the number of molecules directly interacting with the host–guest complex (and by treating the rest as a dielectric continuum), we monitored the effects of solvation on the relative thermodynamic stability (relative Gibbs free energy) of

(CR/SerH⁺ - G1: scale factor = 0.9382)

| Mode # | Frequency | Scaled Freq |
|--------|-----------|-------------|
| 203 | 3263.56 | 3061.88 |
| 204 | 3272.09 | 3069.87 |
| 205 | 3347.65 | 3140.77 |
| 206 | 3649.60 | 3424.06 |
| 207 | 3825.34 | 3588.94 |

203 : NH₃⁺ symmetric stretching vibration
 204, 205 : NH₃⁺ asymmetric stretching vibration
 206 : hydroxyl stretch
 207 : carboxylic acid -OH stretch

(CR/SerH⁺ - G2 : scale factor= 0.9382)

| Mode # | Frequency | Scaled Freq |
|--------|-----------|-------------|
| 203 | 3224.03 | 3024.78 |
| 204 | 3307.22 | 3102.83 |
| 205 | 3382.94 | 3173.87 |
| 206 | 3831.77 | 3594.96 |
| 207 | 3913.78 | 3671.91 |

203 : NH₃⁺ symmetric stretching vibration
 204, 205 : NH₃⁺ asymmetric stretching vibration
 206 : carboxylic acid -OH stretch
 207 : hydroxyl stretch

Figure 5. IR spectra of the gas-phase 24-crown-8/SerH⁺ complexes (CR/SerH⁺-G1 and CR/SerH⁺-G2). Frequency in cm⁻¹.

the two configurations based on CR/TrpH⁺-G1 and CR/TrpH⁺-G2.

We found that eight H₂O molecules completely envelop the first shell around the carboxyl. Utilizing this model (eight H₂O molecules and the solvent dielectric continuum) of the CR/TrpH⁺ complex for the solution phase led to a reversal of the relative Gibbs free energies of the gas-phase CR/TrpH⁺ host-guest complexes (Figure 3). The Gibbs free energy of CR/TrpH⁺-S2, originating from the higher Gibbs free energy gas-phase complex CR/TrpH⁺-G2, is now lower (by 1.6 kcal/mol) than that for the solution-phase conformer CR/TrpH⁺-S1 based on CR/TrpH⁺-G2 under the effects of full solvation. In the most stable solution-phase complex CR/TrpH⁺-S2, the carboxyl, which was naked in the gas phase, is now fully surrounded by eight explicit H₂O molecules in the first shell around the complex, explaining the calculated thermodynamic stability of solution-phase CR/TrpH⁺-S2 compared to CR/TrpH⁺-S1.

Structures and Thermodynamic Stability of 24-Crown-8/SerH⁺ Noncovalent Complexes in the Gas Phase and in Solution. Our motivation for the CR/SerH⁺ host-guest system is that the SerH⁺ guest possesses the three close-lying functional groups (carboxyl, ammonium, and hydroxyl) that are capable of H-bonding with the CR host and/or with solvent. Consequently, it is interesting to examine which of these three moieties interacts with the CR ring through H-bonds in the lower Gibbs free energy gas-phase configurations and which of these correlates to the most

thermodynamically favorable host-guest conformer in solution. If the thermodynamically less favorable host-guest configuration, in which the carboxyl and/or the hydroxyl are naked, is observed in the gas phase produced in the ESI/MS experiments from the solution-phase configuration, then the thermodynamic reversal would be more prominent than that predicted for the CR/TrpH⁺ system.

Figure 4 depicts the lower Gibbs free energy configurations of the gas-phase CR/SerH⁺ complex, in all of which ammonium commonly binds to the CR ring. In CR/SerH⁺-G1, which is calculated to be the thermodynamically most favorable one, the hydroxyl interacts with the CR host, along with the ammonium. On the other hand, in CR/SerH⁺-G2, the ammonium only binds to the CR ring, with the carboxyl and hydroxyl being devoid of H-bonding with the CR unit. This conformer is thermodynamically less advantageous, and its calculated Gibbs free energy of these latter structures is 3.6 kcal/mol higher than that of CR/SerH⁺-G1. The other conformers (CR/SerH⁺-G3, CR/SerH⁺-G4) in which the carboxyl interacts with the CR host are presented in Figure S1 in the Supporting Information. The Gibbs free energies of these latter structures are 4.5–5.4 kcal/mol higher than that of CR/SerH⁺-G1.

The calculated IR spectra for these gas-phase host-guest structures are illustrated in Figure 5. The strong bands at 3595 and 3672 cm⁻¹ for CR/SerH⁺-G2 would be the clear signatures of the naked carboxyl and hydroxyl, respectively, which may be observed in the experimental IRMPD spectra for

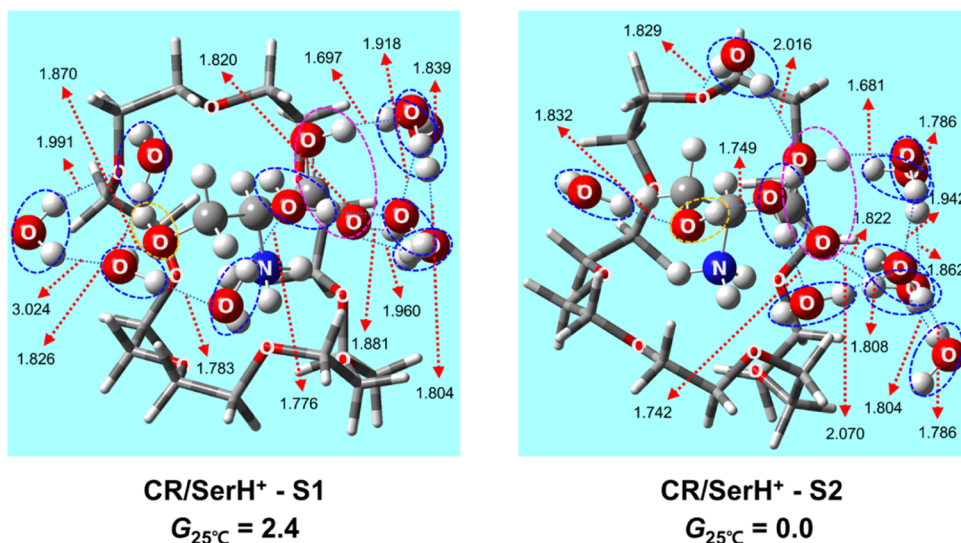


Figure 6. Calculated structures of 24-crown-8/SerH⁺ complexes in an aqueous solution obtained by adding 9 H₂O molecules and a water continuum to the gas-phase configurations. Relative Gibbs free energy in kcal/mol and distance in Å. The blue background represents the solvent continuum.

structural identification. On the other hand, the absorption bands for the hydroxyl in CR/SerH⁺-G1, interacting with the CR host by H-bonding, significantly red-shifts to 3424 cm⁻¹.

The structures of the CR/SerH⁺ complex in an aqueous solution corresponding to the gas-phase complexes CR/SerH⁺-G1 and CR/SerH⁺-G2 are presented in Figure 6 (two other structures, in which both the ammonium and the carboxyl interact with the CR host, are illustrated in Figure S1, Supporting Information). We find that nine explicit H₂O molecules in the first shell around the carboxyl and the hydroxyl and water continuum in the second shell and beyond is the most appropriate model for the complex in the solution phase. The calculated relative free energies of the complexes indicate that CR/SerH⁺-S1, which conforms to the thermodynamic less favorable gas-phase configuration CR/SerH⁺-G2, is now the most favorable solution-phase configuration (Gibbs free energy lower by 2.4 kcal/mol than for the other configuration CR/SerH⁺-S1). This indicates that the effects of solvation of the -OH and -CO₂H are much larger than the thermochemical stabilization of the complex due to the interactions of these functional groups with the CR host. Consequently, a thermodynamic reversal (by 6.0 kcal/mol) is also observed for the CR/SerH⁺ noncovalent complexes, which is in line with the observed propensity for the CR/TrpH⁺ host-guest system discussed above.

Which of the CR/SerH⁺ conformers in Figure 4 would be observed in the gas phase produced from the solution phase by ESI/MS techniques? If there exists a strong structural correlation between the CR/SerH⁺ configurations in solution and in the gas phase, then the thermodynamically disadvantageous conformer CR/SerH⁺-G2, which is structurally conforming to the thermodynamically most favorable one in solution, may actually be observed in the gas phase. On the other hand, if thermal equilibrium is attained in the gas phase before the IRMPD experiments are carried out, then the thermodynamically more favorable gas-phase conformer CR/SerH⁺-G1 would be identified.

DISCUSSION

We discuss the implications of the present findings with regard to the ESI/MS/IRMPD experiments for host-guest complexes. The most intriguing question will be which configurations will be observed in the gas-phase CR/TrpH⁺ and CR/SerH⁺ complexes manufactured from the solution phase by the ESI/MS procedure? In our previous works,^{9,41-44} we examined the origin of the experimentally observed thermodynamically unfavorable (high Gibbs free energy) perm-CD/L-AAH⁺ (AA = Ala, Ile, and Lys) complexes. We suggested that the gas-phase complexes identified by the IRMPD/DFT methods originated from the global minimum Gibbs free energy perm-CD/L-LysH⁺ configurations in solution. These findings signified a direct link between the host-guest structure in solution and in the gas phase. If this holds true for our present system, the most stable solution-phase complexes CR/TrpH⁺-S2 and CR/SerH⁺-S2 would be instantly “frozen” to CR/TrpH⁺-G2 and CR/SerH⁺-G2, respectively, in the gas phase produced in thermal non-equilibrium environment from the solution phase by the ESI/MS techniques. As for the origin of the observed thermodynamically disadvantageous gas-phase host-guest conformers, we hypothesize that solution-phase host-guest complexes are effectively kinetically trapped in the gas phase without fully transitioning to the equilibrium configurations due to the extremely low pressure and the consequent absence of significant collisions. Therefore, it seems that the gas-phase structures within the Fourier-transform ion cyclotron resonance (FT-ICR) mass spectrometry tend to remain stable over extended periods beyond the typical relaxation time of several μs.⁵⁰ The observation of the host-guest complexes CR/TrpH⁺-G2 and CR/SerH⁺-G2, which are thermodynamically less favorable in the gas phase, would then provide invaluable information for the host-guest-solvent interactions in solution. Experimental determination of the gas-phase host-guest configurations by the IRMPD procedure would provide further clues to this intriguing topic.

CONCLUSIONS

We have presented the calculated structures of the 24-crown-8/TrpH⁺ and 24-crown-8/SerH⁺ complexes both in the gas phase and in solution. Our primary focus was on exploring the structural connectivity of the complexes in the two phases. We have proposed that the lowest Gibbs free energy 24-crown-8/TrpH⁺ and 24-crown-8/SerH⁺ configurations in solution may potentially lead to energetically less favorable host–guest complexes through the ESI/MS procedure in thermal non-equilibrium gas-phase environment. We believe that these findings exemplify our approach to characterizing host–guest–solvent interactions in solution by utilizing the gas-phase structures of host–guest complexes. Further experimental investigations for these captivating host–guest systems would be an extremely promising avenue for future research endeavors to directly observe the structural correlation in the gas phase vs in solution.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.4c01782>.

Higher Gibbs free energy structures of the gas-phase 24-crown-8/SerH⁺ complex in which both the ammonium and carboxyl interact with the CR host; and Cartesian coordinates of all structures of the 24-crown-8/TrpH⁺ and 24-crown-8/SerH⁺ complexes (PDF)

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Author Contributions

S.L., H.B.O., and X.K. designed the overall concept. Y.-H.O. and S.Y.L. carried out the DFT calculations. Y.-H.O. and S.L. devised the modeling of the system. S.L., H.B.O., and X.K. analyzed the results. Y.-H.O. and S.Y.L. prepared the draft of the manuscript. S.L., H.B.O., and X.K. wrote the final version.

Notes

The authors declare no competing financial interest.

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