Chemistry
A European Journal

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To be cited as: *Chem. Eur. J.* **2024**, e202402766

Link to VoR: https://doi.org/10.1002/chem.202402766

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Probing Noncovalent Interaction Strengths of Host-Guest Complexes Using Negative Ion Photoelectron Spectroscopy

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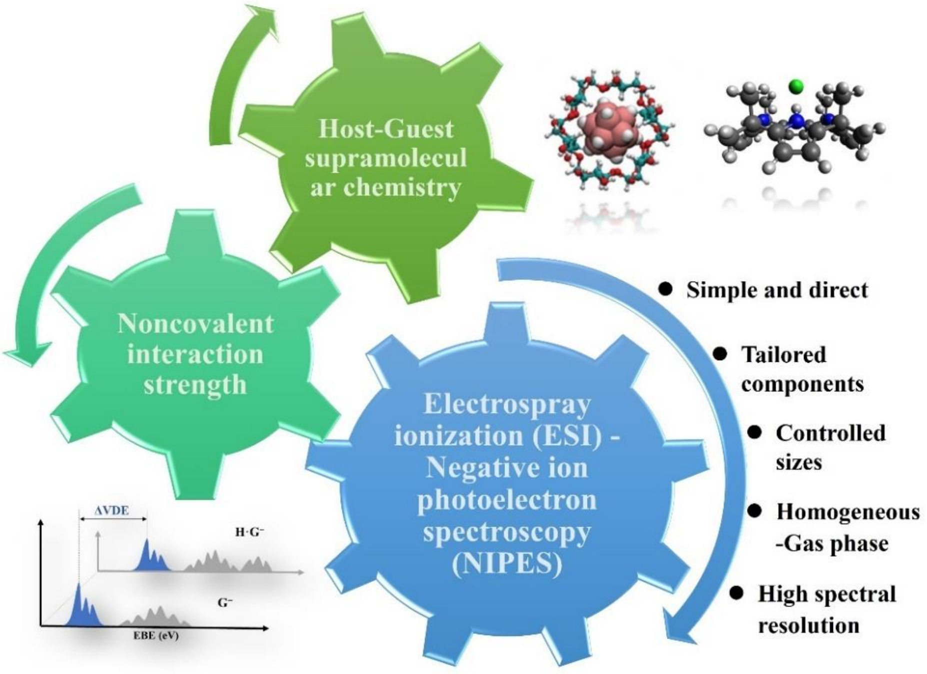
Abstract

Noncovalent interactions (NCIs) are crucial for the formation and stability of host-guest complexes, which have wide-ranging implications across various fields, including biology, chemistry, materials science, pharmaceuticals, and environmental science. However, since NCIs are relatively weak and sensitive to bulk perturbation, direct and accurate measurement of their absolute strength has always been a significant challenge. This concept article aims to demonstrate the gas-phase electrospray ionization (ESI)-negative ion photoelectron spectroscopy (NIPES) as a direct and precise technique to measure the absolute interaction strength, probe nature of NCIs, and reveal the electronic structural information for host-guest complexes. Our recent studies in investigating various host-guest complexes that involve various types of NCIs such as anion–π, (di)hydrogen bonding, charge-separated ionic interactions, are overviewed. Finally, a summary and outlook are provided for this field.



Keywords: noncovalent interaction; host-guest supramolecular chemistry; negative ion photoelectron spectroscopy

Introduction

Host-guest complexes consist of a guest molecule and a host cavity, driven by noncovalent interactions[1] (NCIs, or intermolecular/cohesive interactions) such as hydrogen bonding[2], van der Waals forces[3], halogen bonding[4], chalcogen bonding[5], electrostatic (ionic) interactions[6], π–π interaction, hydrophobic effects[7] and etc. Compared to strong covalent bonds, such NCIs have relatively lower bonding strength (on the order of 5 kcal/mol)[8], typically one order of magnitude weaker than covalent bonds. NCIs are well-known as individually weak but collectively strong, determining the formation and stability of host-guest complexes. Hydrogen bonding as one of the most representative NCIs is highly selective, allowing for the precise recognition and binding of specific guests for a given host. These NCIs connect multiple fields such as supramolecular chemistry, self-assembly materials science, molecular biology, etc. and play a crucial role in numerous applications such as targeted drug delivery, molecular recognition, supramolecular catalysis, sensors for detecting, gas storage/separation, environmental protection, synthetic receptors and ion channels etc.[9]

Various experimental techniques are employed allowing for a comprehensive understanding of host-guest complexes, from structural characterization to spectroscopic and thermodynamic properties in the bulk. For instance, diffraction techniques such as X-ray diffraction[10], electron diffraction[11], and neutron diffraction/inelastic scattering[12], can achieve high-resolution structural characterization of NCI-driven host-guest systems. Spectroscopic techniques, such as solution NMR spectroscopy[13], Infrared/Raman spectroscopy[14], two-dimensional infrared coherent spectroscopy[15], and mass spectrometry[16] can obtain the “relative” strength of NCIs based on the certain shifts of specific frequency modes, and identify NCIs in view of the fragmentation patterns and cluster size. Moreover, the association constants for quantifying NCIs in host-guest systems can been determined by titration experiments through UV-Vis, fluorescence spectroscopy or calorimetry techniques.[17] In solution, solvation effect is considered to compete with the host-guest binding, making the direct and precise measurement of the absolute intrinsic interaction strength of NCIs between guest ion and host receptor challenging.

It should be noting that the precise measurement of absolute strength of NCIs serving as a critical parameter for bond energy[18], is beneficial for revealing the quantum nature of weak interactions and the quantum mechanism of weak-strong bond conversion, thereby verifying the completeness of the electron density topological theory or quantum theory of atoms in molecules (QTAIM)[19] and natural bond orbital (NBO) theory[20], in the case of NCIs. However, due to the relatively weak strength of NCI and its susceptibility to the perturbations of complicated condensed phase/interface environments, the precise measurement of the absolute strength of NCIs has always been a great challenge.

Gas phase spectroscopy is known to be an ideal approach to investigate the intrinsic host-guest interaction without the interference of bulk environments. It has been well documented that techniques such as molecular beam scattering, infrared/UV-vis spectroscopy, microwave Stark spectroscopy have been used to study intermolecular interactions for relatively simple systems like He-HCl, HD-Ar, Ar-HBr, Kr-HCl and Ar-HBr.[21] Thanks to the development of the powerful and robust technique of gas-phase negative ion photoelectron spectroscopy (NIPES) integrated with electrospray ionization (ESI)[22] , the geometric, energetic, and electronic structure information for size-selected and composition-tailored molecular ion clusters can be obtained, and further for efficient probing and untangling such complex NCIs for host-guest systems.

This Concept article is organized as follows. First, we describe the experimental details of ESI-NIPES and the measuring principle for NCIs of host-guest complexes. Then we summarize our recent studies on various host-guest complexes, which serve as ideal model systems for direct measurement of various types of NCIs. Finally, some concluding remarks and future perspectives are outlined.

Principles of NIPES measurement

The PNNL ESI-NIPES apparatus integrates an ESI source, a cryogenic ion-trap time-of-flight (TOF) mass spectrometer with a magnetic-bottle TOF photoelectron spectrometer.[22c] A schematic overview of the apparatus was presented in **Figure 1**.The

ESI source generates solution-phase species, including isolated anions and host-guest anionic complexes with specified compositions and size distributions. The desired isolated anions and host-guest anionic complexes are transported into the gas phase by two radio frequency quadrupole ion guides, cryogenically cooled via collisions in the cold trap, subsequently mass-selected along TOF mass spectrometer, and interrogated by NIPES to investigate the electronic structures, stability, energetics of the isolated guest anions, and how these properties vary with complexation of host molecules at an atomic/molecular level. The introduction of the cryogenic ion trap has significantly improved spectral resolution by eliminating vibrational hot bands.[23] The final NIPE spectra, presented as a function of electron binding energy (EBE), has an energy resolution of ca. 20 meV full width at half-maximum (fwhm) for 1 eV electrons. The vertical detachment energy (VDE), measured from the first spectral band maximum, represents the energy required to complete the transition from the anion ground state to the corresponding neutral ground state. For further details regarding the principles and the NIPES technique, we refer the interested readers to refs[22].

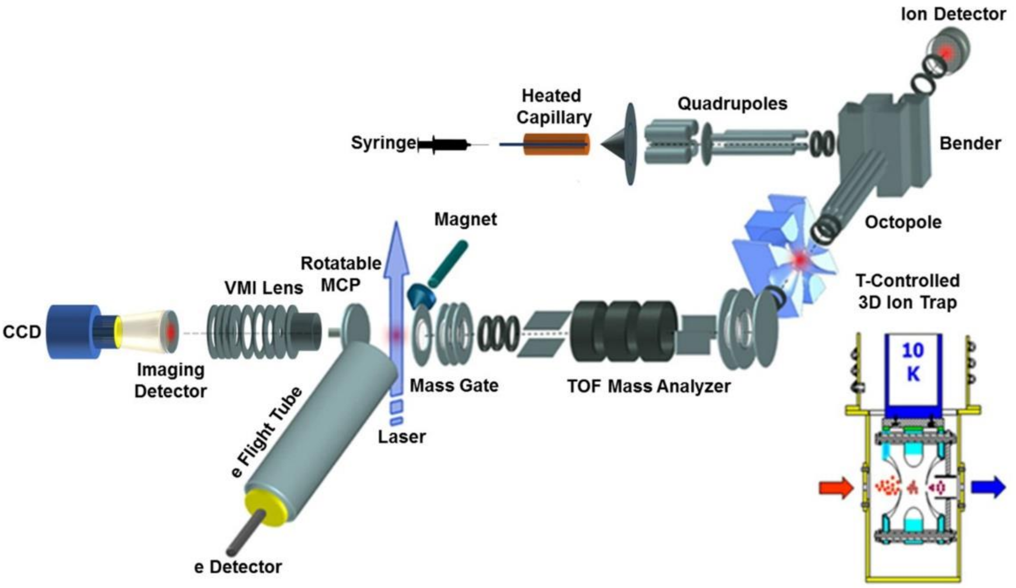


Figure 1. Schematic diagram of the ESI-NIPES apparatus at PNNL.

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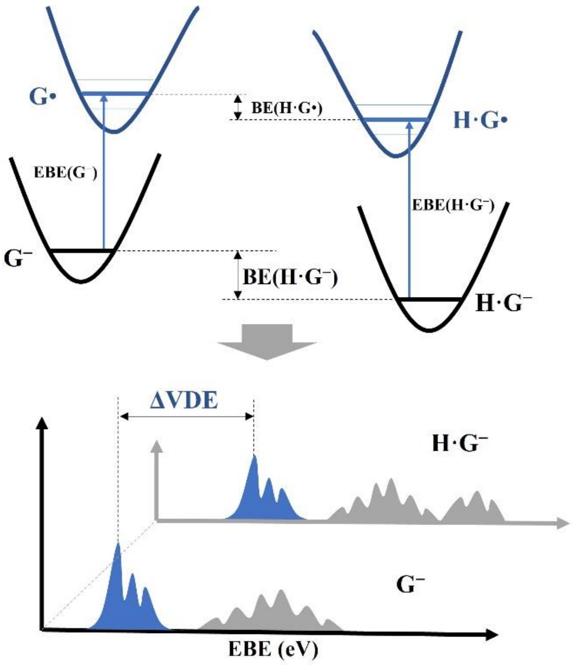

Figure 2. Schematic interpretation of the principles of NIPES measurement.

Based on the host-guest cluster model in which an anion guest G^- binding with host molecule H, the key experimental data obtained from NIPES is the VDE difference (ΔVDE) of G^- and $H\cdot G^-$, which equals the EBE difference between $H\cdot G^-$ and G^-, i.e., $\Delta VDE = \Delta EBE = EBE(H\cdot G^-) - EBE(G^-) = BE(H\cdot G^-) - BE(H\cdot G\bullet)$, where BE denotes the association binding energy between H and G^-(G•). The increase in electron binding energy, ΔEBE, can be a good approximation to the interaction energy (IE) between the guest anion and host molecule since the interaction of the neutral G• and H BE(H·G•) is substantially weaker than $BE(H\cdot G^-)$ (**Figure 2**). In addition, to allow for a direct comparison to the experimental values, theoretical VDEs as the energy differences between the neutral (post-detached) and anion (pre-detached) both at the fixed anion's geometry are computed using density functional theory (DFT) or/and high-level coupled cluster (CC) method. Meanwhile, the IE between a guest anion and a host can be directly calculated as the energy difference between the host-guest complex and the sum of the energies of the guest anion and host, with basis set superposition error (BSSE) corrections applied using the Boys and Bernardi's counterpoise method.[24a] The symmetry adapted perturbation theory (SAPT)[24b] is often performed to reveal the nature of NCIs by decomposing the total IEs into physically meaningful components. Overall, NIPES has been demonstrated as a powerful and direct experimental technique that can quantitatively and precisely measure absolute interaction energies between the host and guest anion. Meanwhile, it is worth noting that some limitations for such a technique exist: (1) what we measured (i.e. ΔVDE) is a lower limit of true IE between host and guest, which represents a good approximation to the true IE for singly charged anions, but not for the cases of multiply charged anions (MCAs); (2) currently we can only measure the intrinsic host-guest interaction strength (albeit it is possible to extend with a few solvent molecules attached), but largely leave the solvation effect unaddressed.

Systems being investigated and what we have learned

Anion–π NCI

Anion–π interaction was first recognized in 2002 as a new type of NCIs between anions and electron deficient aromatic systems, and has since been proven to play a vital role in many key chemical and biological processes.[25] Various experimental and theoretical evidences support the existence of anion–π interactions in both solid and solution through using Cambridge Structural Database (CSD) search, crystallographic technique, and quantum chemical calculations,[26] mainly focusing on the structural characterization without information for interaction strength. The strength of anion–π interactions were recently investigated for a series of the systems composed of an electron-deficient and cavity self-tunable macrocyclic host, tetraoxacalix[2]arene[2]triazine (**TAT**), with four typical polyatomic anions of varying geometries and shapes (NO_3^- , BF_4^- , PF_6^- , SCN^-) that form 1:1 host-guest complexes.[27] Combined X-ray crystallography, electrospray ionization mass spectrometry and fluorescence titration revealed the dominant anion–π interactions and measured their association constants in acetonitrile ranging from 16,950 to 239 M^{-1}, in the order **TAT**·NO_3^- > **TAT**·BF_4^- > **TAT**·PF_6^- > **TAT**·SCN^-.

Inspired by the above mentioned work, , we employed NIPES to probe NCIs of **TAT** interacting with a variety of guest anions with distinct difference in shape and charge state, including halides (Cl^-, Br^-, I^-), thiocyanate (SCN^-), nitrate (NO_3^-), iodate (IO_3^-), and sulfate (SO_4^{2-}) (**Figure 3**). The IEs of the resulting gaseous 1:1 host-guest complexes were measured experimentally, revealing significant noncovalent interactions and distinct anion-specific effects. The strongest interactions were observed with Cl^-, NO_3^-, and IO_3^-, each exhibiting

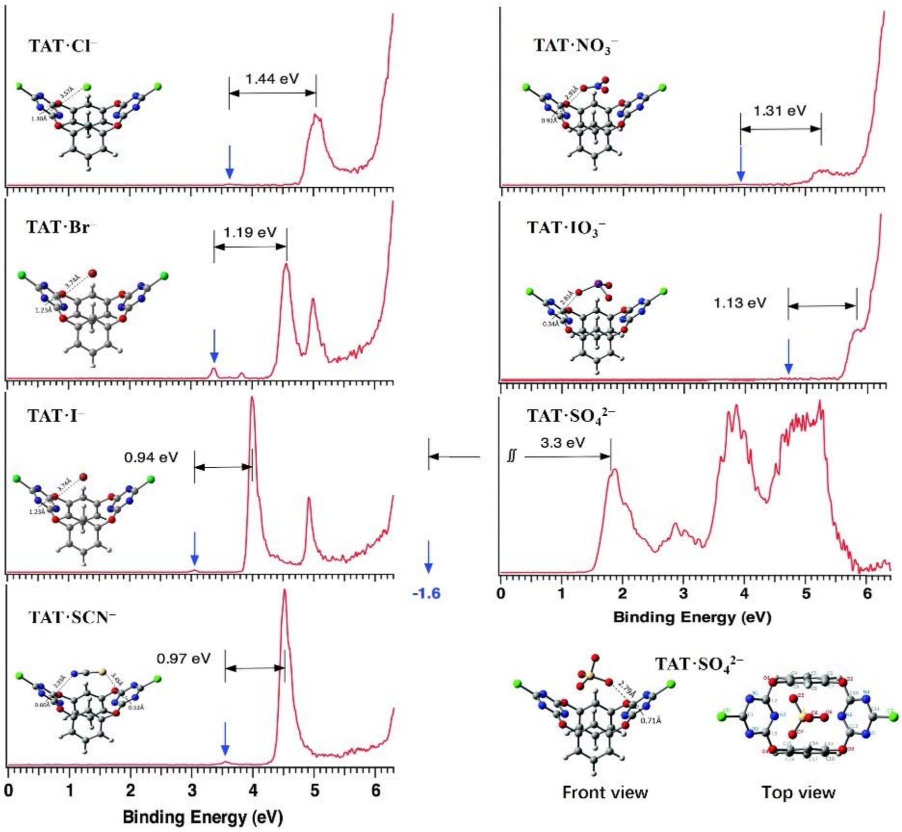

Figure 3. 20 K 193 nm negative ion photoelectron spectra of **TAT** host interacting with a variety of guest anions, including Cl^-, Br^-, I^-, SCN^-, NO_3^-, IO_3^-, and SO_4^{2-} through the anion–π interaction. The increase of electron binding energy of each complex relative to that of the free anion (downward blue arrow), displayed as a double-arrow with a numeric number, is a good approximation for the anion–π interaction except for the SO_4^{2-} case (see the text for discussion). The front view of all studies complexes and the top view for **TAT**·SO_4^{2-} are displayed. Adapted from ref.[28] with permission from Royal Society of Chemistry, Copyright 2015.

IEs of approximately 30 kcal/mol (1.3 eV), which is, however, only about 40% of the IE between **TAT** and SO_4^{2-}. Furthermore, theoretical calculations indicate that all anions occupy the center of the **TAT** cavity which is self-tunable to better accommodate different guest anions. NBO charge distributions and electron density surface analyses corroborate the formation of anion–π bindings and the calculated IEs closely match the experimentally determined ΔEBEs except for **TAT**·SO_4^{2-}, which can be attributed to the nonnegligible interaction between **TAT** and photodetached SO_4^-.[28] Encouraged by the results of **TAT** complexed with the anions, we subsequently reported, together with the Wang group, the construction of sophisticated tetrahedral anion–π receptors with tetrahedral cages (**T**) consisting of resorcinol-linked electron-deficient triazine aromatic triad and a flexible glycol linker. The host molecule **T** shows favorable accommodation for various anions through cooperative anion–π interactions (**Figure 4**). The NIPE spectra of the complexes **T**·SO_4^{2-}, **T**·HSO_4^- and **T**·ClO_4^- were obtained, and the corresponding ΔVDE values were determined to be 3.66, 1.7 and 1.5 eV, respectively, suggesting a strong anion–π binding strength. The interaction strength between SO_4^{2-} and **T** is notably much stronger, due to its higher charge density and optimal fit with the tetrahedral cage.[29]

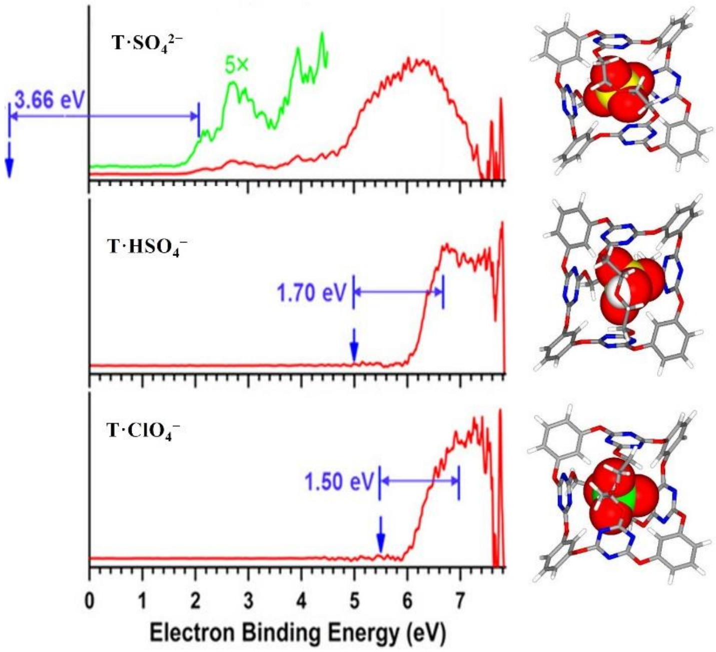

Figure 4. 10 K 157 nm negative ion photoelectron spectra of **T**·SO_4^{2-}, **T**·HSO_4^- and **T**·ClO_4^- through the anion–π interaction. B3LYP-D3(BJ)-optimized geometries are also shown on the right. Adapted from ref.[29] with permission from John Wiley and Sons, Copyright 2024.

Hydrogen bond (HB) and dihydrogen bond (DHB) NCIs

Hydrogen bond (HB) as a classic type of NCIs, represents a central research topic in modern chemistry.[30] HBs play a critical role in the formation, stability, and functionality of host-guest complexes, enabling the precise molecular recognition and stabilization required for various applications, including drug delivery, molecular sensing, and biological processes.[31] Therefore, accurate measurement of HB strength and control of HB interactions between host and guest offer vast potential for designing advanced supramolecular systems with tailored properties and functions. For instance, the formation of host-guest complexes is one useful strategy for effective delivery of drug molecules into cells by binding them within the cavities of water-soluble organic host molecules. The *closo*-dodecaborate $B_{12}H_{12}^{2-}$ dianion and the halogenated derivatives $B_{12}X_{12}^{2-}$ (X = F, Cl, Br and I) have recently attracted increasing interest due to their important applications in medical diagnosis and treatment, such as boron neutron capture therapy (BNCT).[32] High boron content, low toxicity and high stability of the $B_{12}X_{12}^{2-}$ dianions are crucial for the practical BNCT treatments .[33] The cyclodextrins (CDs), typically divided into three categories (α-CD, β-CD, and γ-CD) according to their cavity size, represent a class of macrocyclic oligosaccharide hosts providing excellent HB binding sites.[34] Nau and coworkers systematically studied the affinity binding behavior of dodecaborate clusters to γ-CD in aqueous solutions and found γ-CD·$B_{12}Br_{12}^{2-}$ complex possesses the largest association constants (K_a up to 10^6 L/mol) among the whole series.[35] Other groups employed the ESI-MS to study the intrinsic NCIs between dianionic halogenated $B_{12}X_{12}^{2-}$ (X= F, Cl, Br and I) and neutral organic receptors such as tetrathiafulvalene(TTF)- and CD-based hosts.[33b] As commented in the Introduction, the absolute interaction strengths without bulk perturbation for these HB-dominated host-guest complexes remain unknown.

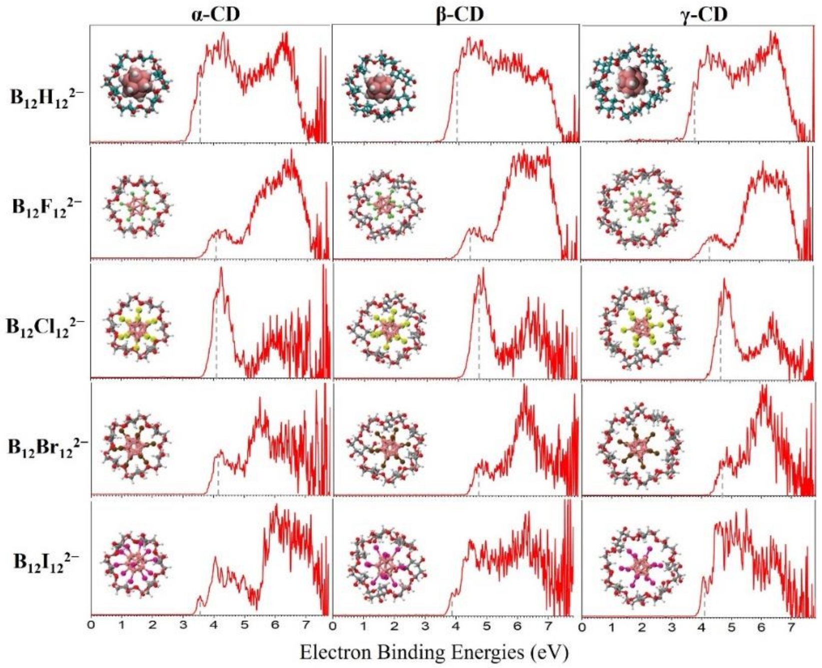

Figure 5. 20 K 157 nm negative ion photoelectron spectra of χ-CD·$B_{12}X_{12}^{2-}$ (χ = α, β, γ; X = H, F – I). Experimental VDE was determined from the maximum of the lowest EBE band in each spectrum (dashed line). Adapted from ref.[36] with permission from

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Recently, we reported a combined NIPES and theoretical study on a series of cyclodextrin-*closo*-dodecaborate dianion complexes, χ-CD·$B_{12}X_{12}^{2-}$ (χ = α, β, γ; X = H, F –I)[36] (**Figure 5**). The measured VDEs for the α-CD/β-CD/γ-CD·$B_{12}X_{12}^{2-}$ dianion complexes are 3.55/3.90/3.85 eV for X = H, 4.00/4.33/4.30 eV for the X = F, 4.09/4.64/4.69 eV for X = Cl, 4.11/4.58/4.70 eV for X = Br, and 3.54/3.88/4.05 eV for X = I, respectively. The corresponding measured VDEs are 1.15, 1.90, 2.95, 3.20 and 2.80 eV for isolated $B_{12}X_{12}^{2-}$ (X = H, F, Cl, Br and I), respectively. It can be seen that binding to CDs significantly stabilizes the $B_{12}X_{12}^{2-}$ core, resulting in larger VDEs compared to the isolated $B_{12}X_{12}^{2-}$. The stabilization effect for β-CD/γ-CD is significantly stronger than for α-CD. The calculated VDEs closely match the experimental results, accurately reproducing the EBE trends. A multi-point interlocking binding motif is observed for the lowest-lying geometries of all complexes that all $B_{12}X_{12}^{2-}$ tend to bind to the wide openings of CDs, and their binding motif and insertion depth show strong dependence on the size of CD and halogen X. The fluorine series exhibits stronger binding effects compared to other halogens, with the βCD·$B_{12}F_{12}^{2-}$ complex showing the largest BE of 4.60 eV among all halogenated complexes. Compared to the isolated $B_{12}X_{12}^{2-}$, significant changes in the signal patterns are observed, with the VDEs of the complexes shifted to larger values and new bands appearing at high EBE due to photoionization of CD oxygens. Energy decomposition analysis reveals that electrostatic interaction plays a dominant role in the total binding energy, driven by forming an O/C-H···X-B HB network. Herein, the observation of B-X···H-O (X = H, F-I) hydrogen bonds further sparked our interest to direct evaluate their absolute interaction strengths.

It has been well studied and documented that conventional HB adopts the $X–H^{\delta+}\cdots A^{\delta-}$ formulation, in which a protonic hydrogen (HB donor) of an $X–H^{\delta+}$ bond (X represents a highly electronegative atom) interacts with an adjacent lone pair of an electronegative atom (HB acceptor).[37] If replacing the HB acceptor $A^{\delta-}$ with a hydridic $H^{\delta-}$, it will lead to the so-called “dihydrogen bond” (DHB) with a specific HB pattern of $X–H^{\delta+}\cdots H^{\delta}–Y$ (Y is an electropositive atom such as boron or transition metal).[38] Since its first recognition several decades ago, DHBs have showed broad applications in ion recognition, supramolecular assembly, and advanced drug design.[38a, 39] Many condensed-phase experimental techniques [40,41,42] and theoretical calculations[38a, 39b, 43] have been performed. Despite these efforts, the nature and strength of DHBs compared to conventional HBs have not been addressed except in rare cases.[44] Recently, a combined NIPES and multiscale theoretical investigation using monohydrated *closo*-dodecaborate clusters $B_{12}X_{12}^{2-}\cdot H_2O$ (X = H, F, I) was carried out. As shown in **Figure 6**, one water molecule stabilizes the EBE of $B_{12}X_{12}^{2-}$ by 0.31, 0.26, and 0.11 eV for X = H, F, and I, respectively. Unequivocally, we demonstrated that the B-H···H-O DHBs in $B_{12}H_{12}^{2-}\cdot H_2O$ outperform the conventional B-X···H-O HBs by 0.05 eV (1.15 kcal/mol) and 0.20 eV (4.61 kcal/mol) than that of X = F and I,[45] in which the induction and dispersion made significant contributions leading to a stronger B-H···HO DHB. The exceptional molecular properties of DHBs revealed in this study can enhance our understanding of nature of HBs and benefit potential applications in catalysis and selectivity based on unique dihydrogen interactions.

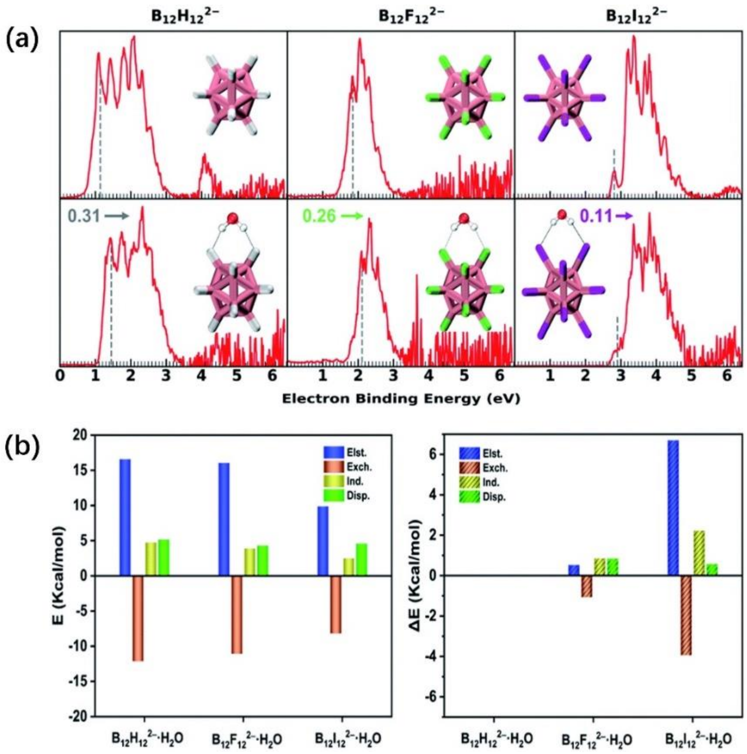

Figure 6. 20 K 193 nm negative ion photoelectron spectra of $B_{12}X_{12}^{2-}\cdot nH_2O$ (X = H, F, I; n = 0, 1). The spectral vertical detachment energy (VDE) positions are indicated by dashed gray lines to show the increase of electron binding energies (color-coded number with a horizontal arrow) through binding one water molecule (a); SAPT-based energy decomposition analysis and energy difference (ΔE, in kcal mol^{-1}) of each term (b). Adapted from ref.[45] with permission from Royal Society of Chemistry, Copyright 2022.

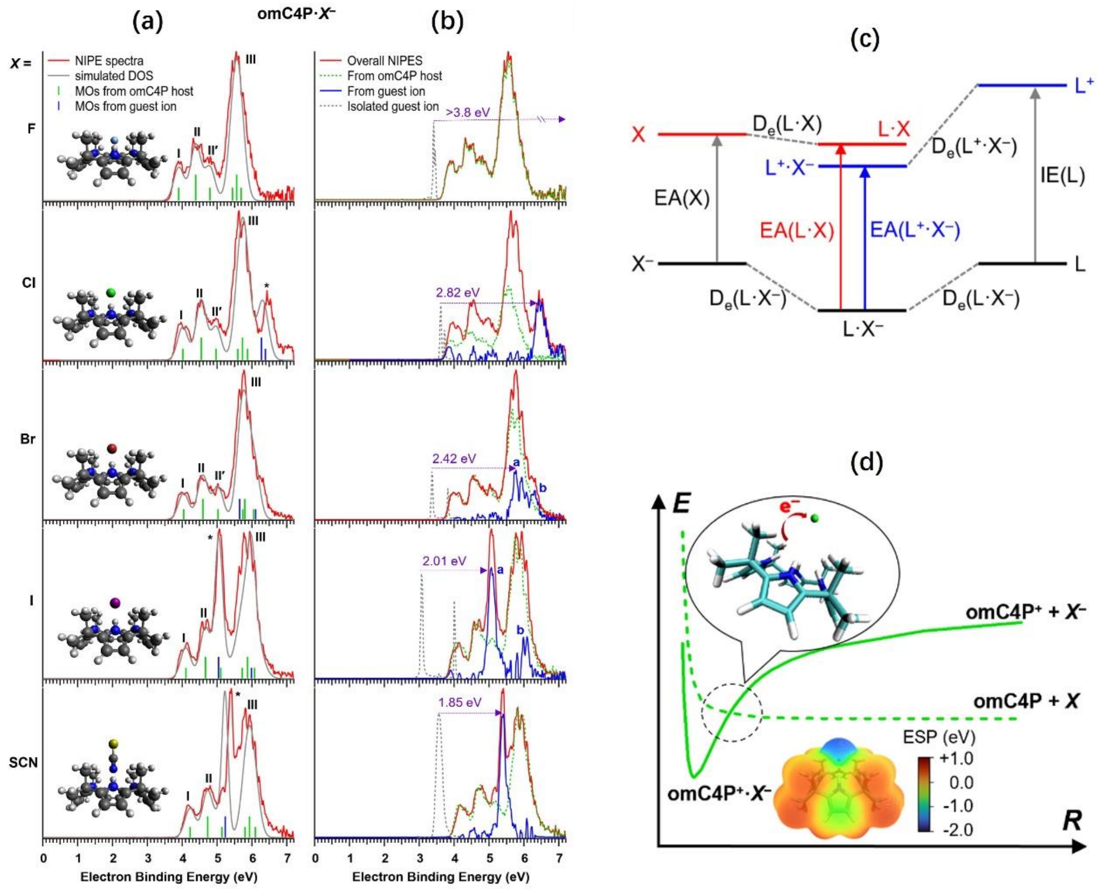

Figure 7. 20 K 157 nm NIPE spectra of (red trace) and simulated density of state (DOS) spectra (gray trace) (a), as well as deconvolutions of NIPE spectra (red trace) into contributions from omC4P host (green dotted lines) and guest ions (blue trace) respectively (b). Schematic diagrams showing the energy profile of photodetaching an anion (X^-) bound to a ligand (L) (c). One–dimensional potential energy curves for neutral and charge–separated states of omC4P+Cl with plot of electrostatic potential (ESP) inserted (d). Adapted from ref.[46] with permission from John Wiley and Sons, Copyright 2024.

Observation of charge-separated (CS) ionic type of neutral host-guest complexes

As introduced above, NIPES can be served as a robust technique to probe the electronic structure and bonding nature of the neutral (post-detached) complexes which can be views as reaction products between the chosen host molecules and halogens by photodetaching the corresponding halide complexes. So far, no evidence of charge-separated (CS) ground state of host-guest neutral complexes has been found. Very recently, we reported combined gas-phase NIPES studies and high-level quantum chemical computations on a set of host–guest anionic complexes, consisting of a octamethylcalix[4]pyrrole (omC4P) – a renowned and versatile organic host molecule,[47] and various (pseudo)halogen anions (X^-) (X = F, Cl, Br, I, and SCN).[46] Photodetaching these anionic complexes allows us to access them in their neutral charge state. As indicated in **Figure 2**, the ΔVDE typically serves as an effective measurement for the IE of the anionic complex since that of neutral complex is much smaller and can be neglected. Given the VDEs of 3.40/3.61/3.36/3.06/3.55 eV for isolated F^- /Cl^- /Br^- /I^- /SCN^-, ΔVDEs of these complexes, i.e., 0.51, 0.36, 0.64, 1.04, and 0.62 eV, exhibit no correlation to interaction strength when compared to either calculated values or previously measured association constants.[47a] The observation of similar spectral patterns in the low EBE region (*i.e.*, bands I & II) for each omC4P·X^- complex (**Figure 7a**) strongly suggests they all have dominant photodetachment channel taking place from the host omC4P, instead of from the guest X^-, leading to the formation of a CS ionic complex omC4P$^+$·X^- in their detached ground state. A different scheme is suggested in **Figure 7b**, in which the lowest EBE bands are contributed from ionization of the host omC4P, leading to a consistent four-band spectral feature (see the fluoride case in Figure 7a). Subtracting the host features from the overall spectrum of each complex gives rise to the spectral bands coming from detaching the respective guest ion X^- (**Figure 7b**, blue curves). The experimental EBE increase (ΔEBE) for each X^- due to its complexation with omC4P determined from the deconvoluted halide contribution descends with halide size and is in good agreement with the calculated omC4P-halide IEs in the anionic charge state (**Figure 7b**). As explained by the schematic diagram of **Figure 7c**, in a conventional scheme when photodetachment takes place from the anionic part (red arrow), the electron affinity (EA) difference between X and L·X complex measures dissociation energy (D_e) or IE in L·X^- since D_e(L·X) is negligible. When photodetachment occurs from the ligand L (blue arrow), the experimental VDE of L·X^- or approximately EA of L^+·X^- is equal to $D_e(L\cdot X^-)$ + IE (L) − $D_e(L^+\cdot X^-)$. The formation of the CS omC4P$^+$·X^- complexes can be viewed as a biomolecular chemical reaction product between omC4P and X via electron harpooning from the host to the halogens at a distance that correlates to the energy difference between the ionization potential of omC4P and EA of X (**Figure 7d**).

Long-range electron transfer as a ubiquitous and fundamental chemical reaction is crucial in numerous chemical and biochemical processes.[48] Alkali metals are known to have the capacity to facilitate long-range electron transfer reactions with halogens.[49] To date, translational motion induced reactions between host (donor) and guest (acceptor) via the harpoon mechanism that form a stable ionic complex are still limited to those with alkali metals as electron donors. This work demonstrates that common organic molecules can imitate alkali metals in facilitating long-range harpooning reactions. Taking into account the widespread presence of organic molecules, this work provides a crucial insight to shed light on the intricacy of biological electron transfer reactions and novel possibility of ionic bond formations in material syntheses.

Table 1 Experimental and theoretical VDE differences (ΔVDEs, eV) of the host-guest complexes relative to free guest anions, calculated interaction energies (IEs, eV) and determined association constants K_a (10^3 L mol^{-1}) of each complex.

NCIs	H-G Com.	Host[a]	Guest	VDEs[b] (H-G Com. / G)	ΔVDE[b] (expt.)	ΔVDE[c] (theo.)	IE[c]	K_a[d]	Refs.
Anion – π	**1**	TAT	Cl^-	5.05 / 3.61	1.44	1.42	1.24	4.25	[28]
	2		Br^-	4.55 / 3.36	1.19	1.28	1.13		
	3		I^-	4.00 / 3.06	0.94	1.10	1.00		
	4		SCN^-	4.51 / 3.54	0.97	0.99	1.07	0.24	
	5		NO_3^-	5.25 / 3.94	1.31	1.59	1.22	16.95	
	6		IO_3^-	5.90 / 4.77	1.13	1.14	1.29		
	7		SO_4^{2-}	~ 1.7 / −1.6	3.30	2.70	2.94		
	8	T	SO_4^{2-}	2.06 / −1.6	3.66	-	4.47		[29]
	9		HSO_4^-	6.7 / 5.0	1.70	-	1.46		
	10		ClO_4^-	7.0 / 5.5	1.50	-	1.53		
HB and DHB	**11**	α-CD	$B_{12}H_{12}^{2-}$	3.55 / 1.15	2.40	1.73	3.65		[36a]
	12	β-CD	$B_{12}H_{12}^{2-}$	3.90 / 1.15	2.75	2.52	3.28		
	13	γ-CD	$B_{12}H_{12}^{2-}$	3.85 / 1.15	2.70	2.72	3.57	2.00	
	14	α-CD	$B_{12}F_{12}^{2-}$	4.00 / 1.90	2.10	1.63	3.10		
	15	β-CD	$B_{12}F_{12}^{2-}$	4.33 / 1.90	2.43	2.33	4.64		
	16	γ-CD	$B_{12}F_{12}^{2-}$	4.30 / 1.90	2.40	2.24	4.50		
	17	α-CD	$B_{12}Cl_{12}^{2-}$	4.09 / 2.95	1.14	0.97	2.25		
	18	β-CD	$B_{12}Cl_{12}^{2-}$	4.64 / 2.95	1.69	1.39	3.61		
	19	γ-CD	$B_{12}Cl_{12}^{2-}$	4.69 / 2.95	1.74	1.39	3.69	17.00	
	20	α-CD	$B_{12}Br_{12}^{2-}$	4.11 / 3.20	0.91	0.85	2.09		
	21	β-CD	$B_{12}Br_{12}^{2-}$	4.58 / 3.20	1.38	1.22	3.50		

	22	γ-CD	$B_{12}Br_{12}^{2-}$	4.70 / 3.20	1.50	1.22	3.56	960.00	[36b]
	23	α-CD	$B_{12}I_{12}^{2-}$	3.54 / 2.80	0.74	0.71	2.29		
	24	β-CD	$B_{12}I_{12}^{2-}$	3.88 / 2.80	1.08	1.06	3.46		
	25	γ-CD	$B_{12}I_{12}^{2-}$	4.05 / 2.80	1.25	1.02	3.32	67.00	
	26	H_2O	$B_{12}H_{12}^{2-}$	1.46 / 1.15	0.31	0.34	0.62		[45]
	27		$B_{12}F_{12}^{2-}$	2.11 / 1.85	0.26	0.27	0.57		
	28		$B_{12}I_{12}^{2-}$	2.91 / 2.80	0.11	0.19	0.38		
CS Ionic	**29**	omC4P	F^-	>7.20 / 3.40	>3.80	-	4.26	17.17	[46]
	30		Cl^-	6.43 / 3.61	2.82	-	2.82	0.35	
	31		Br^-	5.78 / 3.36	2.42	-	2.51	0.01	
	32		I^-	5.07 / 3.06	2.01	-	2.15	< 0.01	
	33		SCN^-	5.40 / 3.55	1.85	-	2.37		

[a] TAT: tetraoxacalix[2]arene[2]triazine; T: covalent tetrahedral cage consisting of resorcinol-linked electron-deficient triazine aromatic triad and a flexible glycol linker; omC4P: octamethylcalix[4]pyrrole; [b] note that experimental VDEs are determined with uncertainties within ± 0.10 eV or smaller. [c] calculated ΔVDEs and IEs using various theoretical levels including ωB97XD/B3LYP-D3(BJ)/M06-2X-D3/DLPNO-CCSD(T). [d]association constants K_a for 1:1 host-guest complexes between guest anions and hosts in various solvents at 298 K and values are from refs[27, 35a, 46]. Note that the χ-CD·$B_{12}H_{12}^{2-}$ was measured using ^1H NMR titration in D_2O and the χ-CD·$B_{12}X_{12}^{2-}$ (X = Cl, Br, I) were measured by isothermal titration calorimetry in neat water.

Summary and Outlook

This Concept article summarizes our recent studies on a series of host-guest complexes involving various types of NCIs such as anion–π, hydrogen bonding or dihydrogen bonding, and the formation of CS ionic complexes using ESI-NIPES combined with high-level quantum chemical calculations. We have demonstrated the gas-phase NIPES as a direct and precise tool to measure the absolute interaction strength without bulk environment interference, to probe nature of noncovalent interactions, and to reveal the electronic structure information for host-guest complexes (**Table 1**). It is encouraging to see the gas-phase measured ΔVDE values are in good line with the solution-determined K_a for complexes of small anions with omC4P for instance. However, such a consistent trend is not observed for the χ-CD·$B_{12}X_{12}^{2-}$ complexes (**Table 1**). This discrepancy is mainly due to the so-called chaotropic effect of guest dodecaborate anions, that tend to have large binding enthalpy also accompanying with large entropic penalty.[35a]

From the theoretical perspective, quantum chemical calculations complementary to NIPE spectra can provide additional key information for geometrical and electronic structure of host-guest complexes. It has been proved that efficient DFT with Grimme's dispersion correction[50] and high-level CCSD(T)-based methods reproduce the experimental trends of VDEs in both qualitative and quantitative way. Particularly, when comparing the calculated IEs with experimental ΔVDE values, DFT methods with suitable functionals (i.e., M062X-D3, ωB97XD, B3LYP-D3) can produce accurate and efficient prediction for the interaction strength between host and guest anions. However, it should be pointed out that, when considering the case of MCA guest G^{n-} ($n > 1$), the measured ΔVDE values can be underestimated to a certain extent due to the existence of moderate and nonnegligible interaction between host and photodetached $G^{(n-1)-}$ species. Moreover, the SAPT-derived energy decomposition analysis can benefit the fundamental understanding of quantum nature of various types of NCIs.

Future research efforts in our view can extend the host-guest interactions to many other important application scenarios.

(1) Ion separation and recognition:[51] Despite decades of research on molecular recognition complexes, a complete and predictive understanding of noncovalent interactions in ion separation and recognition, especially for anions, has yet to be achieved. Conventional experimental techniques, particularly solution-phase NMR spectroscopy, have been valuable in obtaining their structural information. However,

how to account for the solvation effects, especially that in the immediate solvation environment[52] for both the host and guest ion remains challenging. Thus, there remains an urgent need for a homogeneous, gas-phase study and atomic/molecular-level understanding of NCIs to help better design of novel synthetic hosts with high selectivity for specific ionic guests.

(2) Broadly, the host systems are not limited to organic supramolecular cages or receptors such as TAT, cyclodextrins, omC4P discussed in this article. More general host-guest systems including microsolvated guest anions, in which host solvents and guest solute anions interacting with each other via NCIs, also represent interesting topics in solution chemistry (i.e. structural evolution of first solvent shell[53] and Hofmeister series[22a, 35b]) and atmospheric chemistry (nucleation and growth of aerosol particles[54]).

(3) As an extension to the work of omC4P$^+$·X$^-$ complex, we hope to exploit the host stabilization strategy to interrogate the electronic structures of unstable MCAs such as ($B_{10}H_{10}^{2-}$)[55] and polysulfide dianions (S_n^{2-})[56] that are otherwise not feasible by forming gaseous host-MCA complexes.

(4) Ionization (detachment) cross section in a photoelectron spectrum refers to the quantification of the probability that a photon will ionize (detach) an atom or molecule (anion), leading to the ejection of a photoelectron. They have inherent correlations with the electronic structures, molecular orbitals, and bonding dynamics of the atomic and molecular cluster systems.[57] Given the fact that the measured NIPE spectrum could be independently deconvoluted into the host component and the guest anion component, the ratio of the host/guest cross section can be obtained by integrating the areas of each independent peaks. If assuming the detachment cross section of the host molecule remaining the same, this perspective will provide a potential pathway to experimentally determine the ratio in photodetachment cross sections for different guest anions investigated.

(5) As discussed in **Table 1**, large anions such as $B_{12}X_{12}^{2-}$ cages often show pronounced chaotropic effects. To link the homogeneous gas-phase study to the bulk solution environment where strong solvation affects, it will be interesting to apply liquid jet (LJ) photoemission technique.[58] This will lead to see a holistic host-guest interactions, from gas-phase homogeneous measurements without solvation, to partially solvated interactions at interfaces, and finally back to bulk solution measurements. Considering that chaotropic anions prefer to locate at the liquid-air interfaces, it will be particularly feasible for the LJ technique.

Acknowledgements

We are grateful to our group members including students, post-doctoral research associates who contributed to the research discussed in this article, in particular, Dr. Wenjin Cao (PNNL), Dr. Qinqin Yuan (PNNL, now at Anhui University), Dr. Yanrong Jiang (ECNU, now at Shaoxing University), Dr. Zhubin Hu (ECNU) and Dr. Jian Zhang (ECNU, now at Donghua University). We thank D.-X. Wang and her group for fruitful collaboration. This work was partly supported by the National Natural Science Foundation of China (Nos. 12274128, 12034008, 12250003, and 12204172), Shanghai Rising-Star Program (No. 21QA1402600), and the Program of Introducing Talents of Discipline to Universities 111 Project (B12024). The NIPES work was supported by the U.S. Department of Energy (DOE), Office of Science, Office of Basic Energy Sciences, Division of Chemical Sciences, Geosciences, and Biosciences, Condensed Phase and Interfacial Molecular Science program, FWP 16248. We acknowledge the ECNU Multifunctional Platform for Innovation (001) and HPC Research Computing Team for providing computational and storage resources and the support of NYU-ECNU Center for Computational Chemistry at NYU Shanghai.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable, for no new data are created or analyzed in this article.

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