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ARTICLE

Diarylferrocene tweezers for cation binding

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The host-guest chemistry of ferrocene derivatives was explored by a combined experimental and theoretical study. Several 1-arylferrocenes and 1,1'-diarylferrocenes were synthesized by the Suzuki-Miyaura cross-coupling reaction. The ability of these compounds to bind small cations in the gas phase was investigated experimentally by electrospray ionization mass spectrometry (ESI-MS). The results evidenced a noticeable ability of all 1,1'-diarylferrocenes studied to bind cations, while the same was not observed for the corresponding 1-arylferrocenes nor ferrocene. The 1,1'-diarylferrocene···cation relative interaction energies were evaluated by ESI-MS and quantum chemical calculations and showed that cation binding in these systems follows electrostatic trends. It was found that, due to their unique molecular shape and smooth torsional potentials, 1,1'-diarylferrocenes can act as molecular tweezers of small-sized cations in the gas phase.

Introduction

The properties and applications of ferrocene and its derivatives is currently an active research topic in many areas of chemistry. Apart from their unique molecular properties,[1] these compounds have found interesting applications in materials science,[2] catalysis,[3] supramolecular chemistry,[4] and biology,[5] with some ferrocene derivatives showing high biological activity against several diseases like malaria, HIV and cancer.[5] Molecular tweezers are within the field of host-guest chemistry and consist of relatively large molecules (the guests) that can bind, non-covalently, other molecules or ions (the hosts), incorporating them inside some sort of molecular cavity.[6] The exploration of this kind of molecular properties is associated with important discoveries in the field of supramolecular chemistry. Some examples are the rationalization of cation···π interactions and their role in Nature,[7] and many types of host-guest complexes, like those resulting from cation or anion binding by cyclodextrins, crown ethers and calix[n]arenes.[8]

Herein, the ability of some 1,1'-diarylferrocenes to act as supramolecular acceptors of cations was demonstrated through a combined Electrospray Ionization Mass Spectrometry (ESI-MS) and theoretical study. ESI-MS has become a useful tool in supramolecular chemistry, providing a practical and powerful experimental way of evaluating the stoichiometry and relative binding energies of non-covalent complexes involving molecules and ions.[9]

Experimental section

Synthesis and characterization of the ferrocene derivatives

The compounds studied are presented in figure 1 and were synthesized by the Suzuki-Miyaura cross-coupling reaction by reacting 1-bromoferrocene or 1,1'-dibromoferrocene with the corresponding arylboronic acid. The compounds were obtained in moderate to good yields (40-60 %) and were purified by recrystallization and sublimation under reduced pressure. The identity of the compounds was confirmed by ^{1}H and ^{13}C NMR and their purity attested by gas chromatography showing a %(m/m) purity higher than 99% in all cases. The detailed synthetic procedure and characterization data are presented as the ESI.

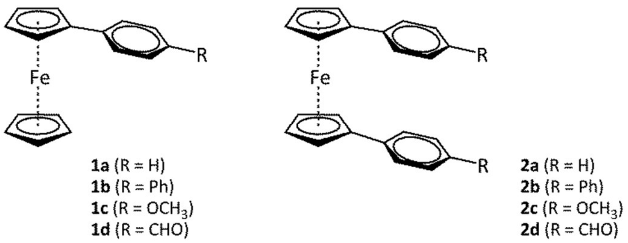

Fig 1 The 1-arylferrocenes (**1a–d**) and 1,1'-diarylferrocenes (**2a–d**) studied herein.

Mass spectrometry analysis

Electrospray ionization mass spectra (ESI-MS) and tandem mass spectra (ESI-MS-MS) were acquired with a Micromass Q-Tof 2 (Micromass, Manchester, UK), operating in the positive ion mode, equipped with a Z-spray source. Source and

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Electronic Supplementary Information (ESI) available: detailed synthetic procedures and compound characterization, and detailed ESI-MS and computational chemistry results. See DOI: 10.1039/x0xx00000x

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desolvation temperatures were 353 K and 373 K, respectively. Ferrocene and ferrocene derivatives in methanol were introduced at 10 µL·min^{-1} flow rate. For the interaction studies of **2d** (R = CHO) with Li$^+$ and NH$_4^+$ equimolar mixtures of the compound and lithium chloride (or ammonium chloride) were used. The capillary and the cone voltage were 3000 V and 30 V, respectively. Nitrogen was used as nebulisation gas and argon as collision gas.

ESI-MS-MS spectra were acquired by selecting the precursor ion with the quadrupole, performing collisions with argon at variable energies (E_{LAB}) in the hexapole and analysing the fragment ions thus produced with the TOF analyser. The spectra represent an average of approximately 100 scans. To implement energy-variable collision induced dissociation the applied collisional activation voltage (E_{Lab}) is increased by small increments while the relative abundances of the precursor and fragment ions are monitored. The energy required to dissociate 50% of the precursor ion was registered as $E_{Lab,1/2}$. In this inelastic collision of the projectile ion with the target neutral, the total available energy for conversion of translational (or kinetic) to internal (or vibrational) energy of the projectile ion is the center of mass energy, E_{cm}, which can be calculated from $E_{Lab,1/2}$ and the masses for the neutral target (m_t) and precursor ion (m_p), according to equation (1):

$$E_{cm} = E_{lab}\left(\frac{m_t}{m_p + m_t}\right) \qquad (1)$$

Computational details

All quantum chemical calculations were performed using the Gaussian 09 software package.[10] A conformational analysis was carried out for the 1,1'-diarylferrocenes (**2a-d**) at the M06-2X/6-31+G(d,p)/SDD(Fe) level of theory (the SDD Effective Core Potential basis set was used for Fe and 6-31+G(d,p) was used for the other atoms).[11] Potential Energy Surface (PES) scans, at the same level of theory, were performed in order to accurately predict the optimized gas phase geometries corresponding to the absolute minima of the complexes formed between the studied 1,1'-diarylferrocenes (**2a-d**) and Na$^+$. This was done through a partial optimization of the system by optimizing the whole 1,1'-diarylferrocene molecule while fixing the distance between the Fe centre and Na$^+$ at regular intervals [i.e. taking the d(Fe···Na$^+$) degree of freedom as the frozen variable], with Na$^+$ placed equidistant between the two aryl substituents. For all minima found a full geometry optimization of the complex, at the same level of theory, was performed to obtain the molecular geometries corresponding to the absolute minima. For the complexes of **2d** (R = CHO) with Li$^+$ and NH$_4^+$ the full geometry optimizations were carried out using the optimized geometry of the complex with Na$^+$ as the initial geometry. For all minima considered the 1,1'-diarylferrocene···Na$^+$ electronic interaction energies in the gas phase, $\Delta_{int}E_m$, corrected for BSSE by the counterpoise method,[12] were determined at the M06-2X/6-31+G(d,p)/SDD(Fe) and MP2/6-31+G(d,p)/SDD(Fe) levels of theory. Additionally, the geometry distortion energy, $\Delta_{dist}E_m$, which translates the energy cost associated with the geometry deformation that the isolated 1,1'-diarylferrocenes undergo upon complex formation, was calculated for each case using M06-2X/6-31+G(d,p)/SDD(Fe) and MP2/6-31+G(d,p)/SDD(Fe). To simulate the influence of the solvent (CH$_2$Cl$_2$ and EtOH) on the interaction energy of **2d** (R = CHO) with Na$^+$, the optimized geometries and energies in solution were obtained at the M06-2X/6-31+G(d,p)/SDD(Fe) and MP2/6-31+G(d,p)/SDD(Fe)//M06-2X/6-31+G(d,p)/SDD(Fe) levels of theory using the Polarizable Continuum Model (PCM) as a self-consistent reaction field.[13] The BSSE correction in solution was assumed to be same as in the gas phase. Frequencies calculations, at the M06-2X/6-31+G(d,p)/SDD(Fe) level, were performed for all minima considered in the computational study and no imaginary frequencies were found, confirming that the structures correpond to true minima. With the exception of $\Delta_{dist}E_m$, all electronic energies were corrected for the zero-point energy (ZPE) and thermal enthalpies to T = 298.15 K, using no scaling factors (this is a reasonable approximation since their contribution partially cancels out in reaction schemes). The use of the M06-2X functional and MP2 ensures that dispersive interactions, which are important for describing the energetics of the complexes studied, are taken into account.[11] All calculations were performed without symmetry restrictions. The detailed computational results are presented as the ESI.

Results and discussion

ESI-MS evaluation of ferrocene···cation interaction

The relative abundances of the M·$^+$, [M+Na]$^+$ and [2M+Na]$^+$ ions observed in the ESI-MS (+) spectra of all the compounds studied are shown in table 1. For all compounds (including ferrocene), with the exception of **2d** (R = CHO), the base peak corresponded to the radical cation formed by an oxidation procedure in the electrospray ion source. For **2d** (R = CHO), the cationization of the molecule, M, with sodium ion, [M+Na]$^+$, was the base peak. The [M+Na]$^+$ was also observed in **2a** (R = H), **2b** (R = Ph) and **2c** (R = OCH$_3$) in the following increasing order of abundance: **2a** (R = H) < **2b** (R = Ph) < **2c** (R = OCH$_3$) << **2d** (R = CHO). Furthermore, addition of Na$^+$ was not observed for ferrocene nor the 1-arylferrocene derivatives (**1a–c**), with the exception of **1d** (R = CHO), where a small [M+Na]$^+$ peak was detected. Noteworthy was the observation of a [2M+Na]$^+$ dimer for **2d** (R = CHO), consisting of two ferrocene molecules to one Na$^+$, probably due to the direct interaction of Na$^+$ with the oxygen atoms of the formyl substituents. For **2c** (R = OCH$_3$) the presence of the bulky methoxy groups would likely render the approach of a second ferrocene molecule more difficult and no dimer was observed. These results show that the presence of the two aryl substituents on ferrocene is determinant for cationization to occur.

To study the influence of cation size in the formation of **2d** (R = CHO) adducts, 1:1 mixtures of lithium acetate or ammonium acetate with the compound in methanol were analyzed by ESI-MS and energy-variable collision induced

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dissociation of the dimer (ESI-MS-MS). Figure 2 shows the increase in the relative abundance of the $[2M+cation]^+$ peak observed in ESI-MS with decreasing size of the cation.

Table 1 Relative abundances, %, of the $M\cdot^+$, $[M+Na]^+$ and $[2M+Na]^+$ ions observed in the ESI-MS (+) spectra of the compounds studied (figure 1).

Compound	Relative abundance / %		
	$M\cdot^+$	$[M+Na]^+$	$[2M+Na]^+$
Ferrocene	100	-	-
1a (R = H)	100	-	-
1b (R = Ph)	100	-	-
1c (R = OCH_3)	100	-	-
1d (R = CHO)	100	23	-
2a (R = H)	100	10	-
2b (R = Ph)	100	46	-
2c (R = OCH_3)	100	51	-
2d (R = CHO)	1	100	17

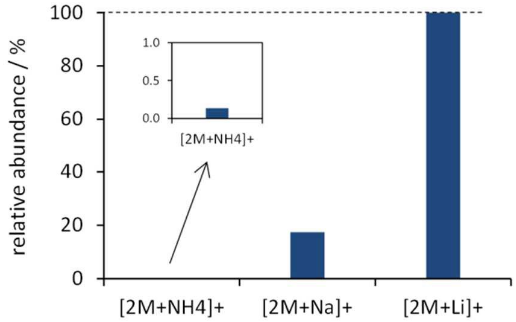

Fig 2 Relative abundances, as obtained by ESI-MS (+), of the peaks corresponding to the molecular mass of the complex formed between **2d** (R = CHO) and the selected cations.

In order to further clarify this relationship, the collision induced dissociation spectra of each isolated dimer ion, at varying collision energies, was recorded and the values of $E_{cm,1/2}$ determined (the detailed results are presented as the ESI). $E_{cm,1/2}$ is the collision energy necessary to separate the $[M+cation]^+$ from the isolated dimer $[2M+cation]^+$ and consequent release of the neutral ferrocene derivative M, as represented by the following reaction: $[2M+cation]^+ \rightarrow [M+cation]^+ + M$. This provides a relative magnitude of the interaction strength between **2d** (R = CHO) and the cations. The relationship between the values of $E_{cm,1/2}$ for Li^+ (0.65 eV), Na^+ (0.49 eV) and NH_4^+ (0.21 eV), and their ionic radii is depicted in Figure 3.[14] The dependence observed reveals that the interaction strength decreases with the increase of the cationic radius, following the weakening of electrostatic interactions.

The ESI-MS and ESI-MS-MS results indicate that the 1,1'-diarylferrocenes (**2a–d**) show significantly higher affinity for cation binding than their 1-arylferrocene analogues (**1a–d**). This is consistent with the fact that cation binding involves the two aryl substituents of the ferrocene, which act like molecular tweezers. It follows that 1,1'-diarylferrrocenes adopt the folded conformation (with the two aryl rings stacked as depicted in figure 1) in the cation complexes.

No evidence of 1,1'-diarylferrocene···cation interaction in solution was observed, as explored by UV-Vis spectroscopy for **2d** (R = CHO) in CH_2Cl_2 and EtOH using sodium acetate as the sodium salt, and concentrations of about $5{\cdot}10^{-5}$ M of the ferrocene and $1{\cdot}10^{-4}$ M of the salt – totally superimposable spectra were observed with and without the presence of the salt in the ferrocene solution. This can be rationalized by the effects of solvation and of the counter-ions.[7c,15]

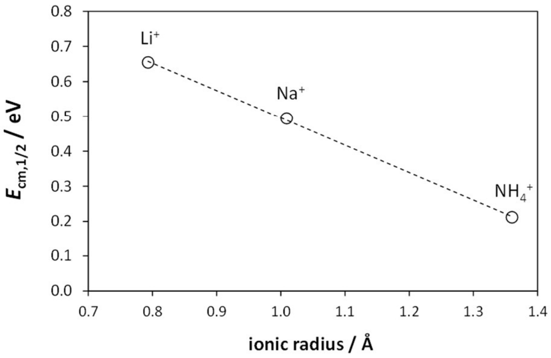

Fig 3 Dependence of the experimental $E_{cm,1/2}$ values for **2d** (R = CHO) on the ionic radii of the cations.[14]

Evaluation of ferrocene···cation interaction by computational quantum chemistry

The ability of 1,1'-diarylferrocenes for cation binding in the gas phase was further evaluated by computational chemistry. A conformational analysis for the 1,1'-diarylferrocenes (**2a-d**) was carried out prior to the computational evaluation of interaction energies. These molecules can exist in two main configurations: the folded and unfolded conformers, as depicted in figure 4. In the folded conformer the two aryl substituents are stacked and thus able to establish intramolecular aromatic interactions with each other.

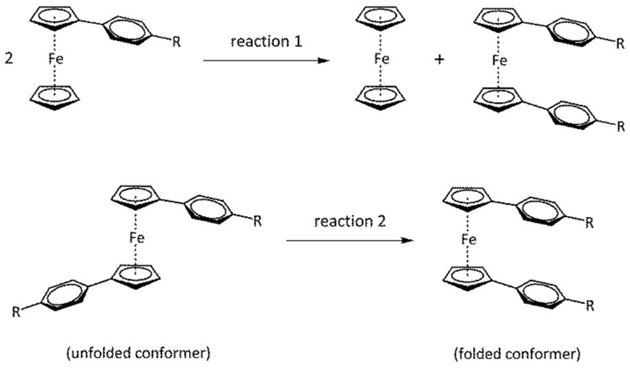

Fig 4 Reaction schemes used to evaluate the folded/unfolded energetics in the ferrocenes studied.

The strength of this interaction and the folded/unfolded energetics were qualitatively evaluated at the M06-2X/6-31+G(d,p)/SDD(Fe) level. The results are presented in table 2 and clearly indicate that the folded conformer is the preferred

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one. The results are consistent with the reported trends in aromatic interactions, with larger aromatic systems (R = Ph) and the substituents $-OCH_3$ and $-CHO$ leading to stronger interactions.[16] Only the folded conformation was considered in the subsequent computational calculations.

Table 2 Reaction enthalpies, Δ_rH_m, calculated at the M06-2X/6-31+G(d,p)/SDD(Fe) level of theory, for the reactions presented in figure 4.

R	Δ_rH_m / kJ·mol^{-1}	
	reaction 1	reaction 2
H	−10	−10
Ph	−41	−32
OCH_3	−23	−21
CHO	−21	−18

Moreover, the folded molecules **2c** (R = OCH_3) and **2d** (R = CHO) can exhibit *syn*/*anti* isomerism relative to the two OCH_3 and CHO groups, respectively. This was also evaluated computationally and the results presented as the ESI indicate that the *anti*- conformer is the most stable in both cases. Hence, only the *anti*- conformer was considered henceforth.

The results for the PES scans on these systems are presented in figure 5 as $\Delta_{int}E_m = f\,[d(\text{Fe}\cdots\text{Na}^+)]$, where $\Delta_{int}E_m$ is the calculated 1,1'-diarylferrocene···Na$^+$ interaction energy.

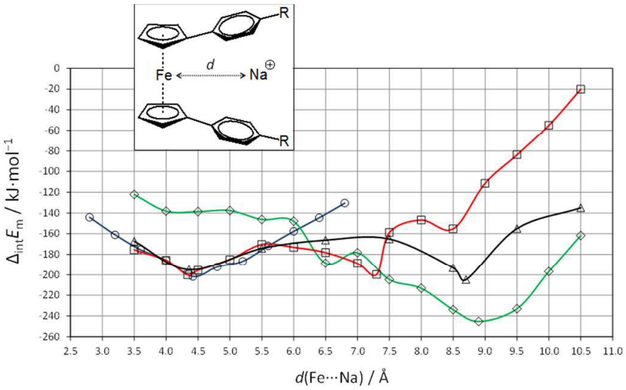

Fig 5 Scans of the potential energy surface (PES) relative to the *d*(Fe···Na) degree of freedom for the 1,1'-diarylferrocenes, obtained at the M06-2X/6-31+G(d,p)/SDD(Fe) level of theory. Legend: **2a** (R = H) (blue line, ○), **2b** (R = Ph) (black line, Δ), **2c** (R = OCH_3) (red line, □), **2d** (R = CHO) (green line, ◊).

As it can be observed in figure 5 some systems present more than one minimum. For **2a** (R = H) only the minimum corresponding to Na$^+$ sandwiched between the two rings was found, while for **2b** (R = Ph) two minima similar in energy ($\Delta\Delta_{int}E_m \approx 10$ kJ·mol^{-1}) were obtained, which consist of Na$^+$ sandwiched between each pair of adjacent phenyl rings (the pair of the rings directly bound to the cyclopentadienyls and the pair of the outer phenyls). For **2c** (R = OCH_3) two main and nearly isoenergetic minima were found – in one of those Na$^+$ is sandwiched between the two phenyls [like for **2a** (R = H)] and in the other Na$^+$ interacts directly with the two methoxy oxygens (the two OCH_3 groups are perpendicular to the plane of the phenyl rings so as to enhance the interaction). For **2d** (R = CHO), in spite of the PES scan revealing more than one minimum, the one corresponding to the structure presented in figure 6 was found to be significantly lower in energy, and thus only this minimum was considered henceforth. The optimized structures of all complexes studied are shown as the ESI. For the direct interaction of Na$^+$ with the aromatic rings [d(Fe···Na) ≈ 4.5 Å] the PES scans follow the expected trend in cation···π interactions, with the ring bearing the electron-withdrawing $-CHO$ group showing the weakest interaction.[7]

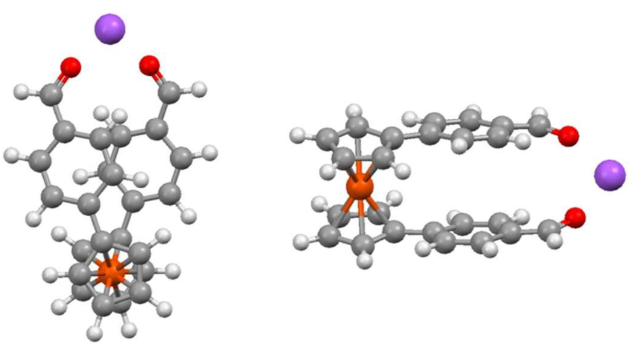

Fig 6 The M06-2X/6-31+G(d,p)/SDD(Fe) optimized geometry corresponding to the absolute minimum of the gas phase complex formed between **2d** (R = CHO) and Na$^+$, d(Fe···Na$^+$) = 8.9 Å.

Essentially, there are two modes of binding in these systems: cation···π binding as observed in **2a** (R = H), **2b** (R = Ph) and one minimum of **2c** (R = OCH_3), and a direct cation···O binding as found in **2c** and **2d** (R = CHO) (for the complex of **2d** with NH_4^+ there is a NH···O binding). The calculated interaction enthalpies, $\Delta_{int}H_m$, corrected for BSSE, for the gas phase complexes studied herein are presented in table 3 – these values correspond to the reaction: ferrocene + cation$^+$ → [ferrocene···cation]$^+$, where all species are in their absolute minimum geometries.

Table 3 Interaction enthalpies, $\Delta_{int}H_m$, corrected for BSSE, calculated at the M06-2X/6-31+G(d,p)/SDD(Fe) and MP2/6-31+G(d,p) levels of theory, for the gas phase complexes between the 1,1'-diarylferrocenes studied (see figure 1) and the selected cations.[a]

Complex		d(Fe···Na) / Å	$\Delta_{int}H_m$ / kJ·mol^{-1}	
cation	ferrocene		M06-2X [b]	MP2 [b]
Na$^+$	**2a** (R = H)	4.4	−190 (16)	−139 (20)
	2b (R = Ph)	4.4	[c]	[c]
		8.7	−187 (20)	−135 (23)
	2c (R = OCH_3)	4.3	−191 (28)	−145 (32)
		7.3	−194 (44)	−184 (25)
	2d (R = CHO)	8.9	−235 (24)	−200 (20)
Li$^+$	**2d** (R = CHO)	8.3	−317 (31)	−280 (26)
Na$^+$		8.9	−235 (24)	−200 (20)
NH_4^+		9.8	−182 (25)	−161 (19)

[a] The optimized geometries were obtained at the M06-2X/6-31+G(d,p)/SDD level of theory. [b] The geometry distortion energies associated with the formation of the complex, $\Delta_{dist}E_m$, of each isolated ferrocene derivative are shown in parenthesis. [c] This additional minimum was found in the PES scan but it was not considered in the BSSE calculations since its energy was found to be 10 kJ·mol^{-1} less stable than the absolute minimum.

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One important feature of arylferrocene derivatives for improved cation binding is their high molecular flexibility, namely in what concerns the relatively low torsional potentials associated with the cyclopentadienyl rings and the aryl substituents.[17] This allows for relatively small energetic costs associated with the structural adjustment that the ferrocene molecule must undergo in order to maximize the interaction with the cation. This is translated by the calculated values of $\Delta_{\text{dist}}E_{\text{m}}$ (see table 3), which indicate that, when compared to the magnitude of the interaction, complex formation does not require an energetically significant geometry distortion of the ferrocene molecule. Hence, strong interactions can be achieved without compromising significantly the equilibrium geometries of the interacting partners.

From table 3 it can be observed that the computational results agree qualitatively with the interaction trends observed experimentally by ESI-MS (the values derived from ESI-MS represent relative interaction energies and no absolute comparison with the computational results can be made). This holds for both the cases of varying the ferrocene for Na^+ and of varying the cation for **2d** (R = CHO) – both experiment and theory agree on that stronger interactions are observed for more polar substituents and smaller cations. Moreover, as expected, direct cation···O binding was found to be stronger than cation···π binding. The fact that more than one minimum with similar energies exist for **2b** (R = Ph) and **2c** (R = OCH_3) can also contribute for a stronger binding, due to the higher conformational entropy of the complex state. From the comparison of the results presented in table 3 it can be observed that the two computational methods used (M06-2X and MP2) cannot reproduce very well absolute interaction energies. Interestingly, better agreement between methods is observed for those cases where complexation is established through cation···O binding, whereas when it is through cation···π the results show poorer agreement. This suggests that cation···O binding is ruled by electrostatics (which is relatively easy to describe by theoretical methods) and cation···π has a significant contribution from van der Waals interactions (which are generally harder to reproduce computationally). However, both methods reproduce well the relative trends – they agree with each other and with experiment on predicting the order in interaction strength with substituents and cation size. These facts suggest that the main contribution for cation binding in these systems comes from the electrostatic interaction potential, although a significant contribution from van der Waals interactions may exist in those cases involving direct interactions with the aromatic rings (cation···π binding).

For the complex of **2d** (R = CHO) with Na^+ the PCM results in CH_2Cl_2 and EtOH clearly show a very pronounced decrease of the interaction enthalpy upon solvation – the calculated values of $\Delta_{\text{int}}H_{\text{m}}$ (in kJ·mol^{-1}) in these solvents are of −34 (CH_2Cl_2) and −21 (EtOH) at the M06-2X/6-31+G(d,p)/SDD(Fe) level of theory and of 3 (CH_2Cl_2) and 18 (EtOH) using MP2/6-31+G(d,p)/SDD(Fe). As expected, the major contribution for this decrease in $\Delta_{\text{int}}H_{\text{m}}$ comes from the great exothermicity of Na^+ solvation. These results are in agreement with the fact that no signs of complex formation were observed in the CH_2Cl_2 and EtOH solutions by UV-Vis spectroscopy.Herein, the ability of 1,1'-diarylferrocenes to act as cation tweezers in the gas phase was observed. The effect of solvent on the ferrocene···cation interaction is expected to be an important drawback disfavoring binding in solution, especially in more polar solvents. However, the binding of relatively small cations by 1,1'-diarylferrocenes (or structurally similar compounds) to significant extents is, nevertheless, a process that should be considered in various media; its importance depending, of course, on the identity of the compound and of the cation.

Conclusions

In summary, it was shown by ESI-MS and quantum chemical calculations that 1,1'-diarylferrocenes have the ability to act as cation tweezers in the gas phase, grabbing small-sized cations between the two aryl substituents. Cation binding is enhanced by the specific molecular shape of these ferrocene derivatives and their low torsional potentials, which allow for smooth geometry adjustments on complexation. Both experimental and theoretical results indicate increasing interaction energy with Na^+ following the order: **2a** (R = H) < **2b** (R = Ph) < **2c** (R = OCH_3) << **2d** (R = CHO). Moreover, for **2d** (R = CHO) the binding strength increases with decreasing cationic radius, supporting that the ferrocene···cation interaction has a major contribution from electrostatic forces. A novel capability of ferrocene derivatives for cation binding was presented. Together with the fact that these compounds can be easily synthesized and purified, this study opens new promising pathways for supramolecular chemistry applications, as for instance in the design of new supramolecular motifs for molecular recognition and cation scavenging.

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