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# Intrinsic Properties of α-Cyclodextrin Complexes with Benzoate Derivatives in the Gas Phase: An Experimental and Theoretical Study

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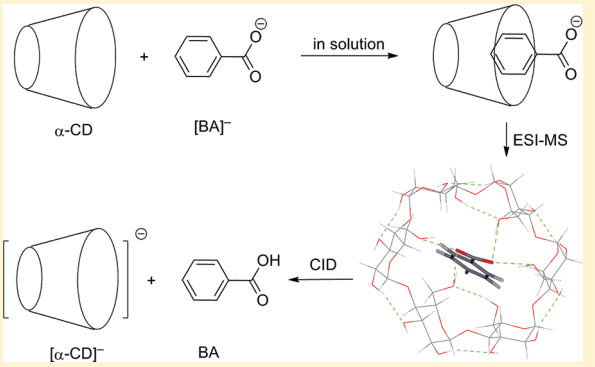
Supporting Information

**ABSTRACT:** The noncovalent interactions in host−guest complexes of α-cyclodextrin (α-CD) with a series of benzoic acid derivatives (RBA) were investigated by electrospray ionization tandem mass spectrometry and density functional theory (DFT) calculations. The 1:1 stoichiometry of the anionic host−guest complexes was unequivocally confirmed by their mass-to-charge ratios ($m/z$) and isotope patterns. Collision-induced dissociation experiments revealed exclusive fragmentation into $[\alpha\text{-CD}]^-$ and neutral RBA and afforded the gas-phase kinetic stability trend $[\alpha\text{-CD}\cdot\text{3,5-diMeBA}]^- < [\alpha\text{-CD}\cdot\text{3-MeBA}]^- < [\alpha\text{-CD}\cdot\text{BA}]^- < [\alpha\text{-CD}\cdot\text{3-OHBA}]^- < [\alpha\text{-CD}\cdot\text{3,5-diOHBA}]^-$. This trend follows that of the gas-phase basicities of the guest anions used, indicating that host−guest pairs with more comparable basicities form more stable complexes. DFT calculations at the M06-L/6-31+G(d,p) level of theory provided detailed structural assignments and further elucidated the experimental observations, suggesting that the anionic $[\alpha\text{-CD}\cdot\text{RBA}]^-$ inclusion complexes are favored over the nonspecific complexes in the gas phase and that hydrogen bonding constitutes the primary host−guest interaction. Additionally, the results provide an estimated gas-phase basicity $\Delta G^0$ = 325−327 kcal mol$^{-1}$ for $[\alpha\text{-CD}]^-$.

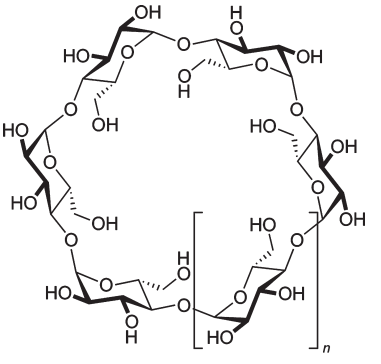



## INTRODUCTION

Cyclodextrins (CDs) are cyclic macromolecules that are widely applied in food, cosmetic, and especially pharmaceutical industry due to their ability to accommodate small molecules of a suitable size as guests.[1,2] The most common of these cyclic glucopyranose oligomers are α-CD, β-CD, and γ-CD (Scheme 1). The sugar units are connected through α-1,4 bonds to afford a toroidal molecular shape with the wider upper rim lined with secondary hydroxyl groups and the narrower lower rim with primary hydroxyl groups. Numerous studies have demonstrated that CDs can host organic compounds to form inclusion complexes in condensed state.[2−7] Their hydrophilic exterior makes CDs water soluble, whereas the hydrophobic internal cavity can accommodate the nonpolar part of a size-matched guest molecule in aqueous solution while leaving any polar part exposed to the bulk solvent. The impetus for the formation of such inclusion complexes in solution is the desolvation of the nonpolar parts of host and guest molecule, i.e., the hydrophobic effect.[6,7]

Electrospray ionization mass spectrometry (ESI−MS) has been intensively applied as a rapid and powerful analytical tool to screen for host−guest complexes.[8−24] However, the specific mass-to-charge ratios ($m/z$) of the detected species may serve to quickly determine their *stoichiometries*, but these observations alone do not provide any *structural* information. Compared with the generally accepted conceptions regarding CD complexation in solution, the nature of such host−guest complexes in the gas phase remains ambiguous or even controversial. When the analytes are transferred from solution to the gas phase, the conditions change dramatically. More precisely, host−guest interactions that are competitive with solvation, such as hydrogen-bonding and electrostatic interactions, are significantly strengthened in the gas phase.[25,26] On the other hand, the hydrophobic effect originates from the gain in entropy of solvent molecules that are released from the solvation shell upon complexation in solution phase, and hence is absent in the gas

**Scheme 1. Molecular Structure of CDs**



α-CD: $n$ = 1; β-CD: $n$ = 2; γ-CD: $n$ = 3

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phase.[27−29] Furthermore, in solution the host−guest complex may be in equilibrium with the free host and guest, but there is no such equilibrium in the high-vacuum environment of a mass spectrometer: the dissociation of host and guest is irreversible. It would thus be premature to conclude that CDs form inclusion complexes in the gas phase as well. Alternatively, the guest molecule may bind with its polar part to the CD's exterior through electrostatic interactions or engage in hydrogen bonding with hydroxyl groups on the rim of the CD, for example; such complexes in which the guest is not inside the CD's cavity are called nonspecific.

In several reports, the gas-phase structures of CD complexes were inferred from mass spectrometric studies. Cunniff and Vouros[30] observed CD adducts with amino acids and peptides in the gas phase, even for guests which did not form inclusion complexes in solution. They therefore claimed that these adducts were merely bound by electrostatic interactions and cannot be assigned to specific inclusion complexes. This "false-positive" conclusion was questioned by Lebrilla and co-workers,[31−34] who reported that the sizes of both the amino acid and the CD cavity affected chiral selectivity in guest-exchange reactions in the gas phase and therefore concluded that these species would be inclusion rather than nonspecific complexes.

Here we present an ESI−MS study of α-CD complexes with benzoic acid derivatives (RBA) to address the questions whether these complexes retain their solution-state structures or whether the binding mode changes dramatically due to alteration of the surrounding environment, and which forces predominantly contribute to or affect their kinetic stability in the gas phase. Adducts of CDs with carboxylate-functionalized guests can be detected by ESI-MS.[35,36] Furthermore, various benzoic acid derivatives are commercially available, which allows us to study the influence of the guest's substitution. The experimental study is complemented by density functional theory (DFT) calculations, which should well mimic the conditions in the high-vacuum environment of a mass spectrometer. Thus, we characterize the intrinsic properties of these noncovalent complexes, i.e., their preferred gas-phase conformations, binding energies, and dominant interaction forces.

## EXPERIMENTAL SECTION

**Materials.** All chemicals were purchased from Aldrich and were used without further purification. Stock solutions of α-CD and benzoic acid derivatives (RBA) were prepared in methanol/water (95:5 v/v) at a concentration of 1.0 mM. For the ESI−MS studies, equal amounts of α-CD and RBA stock solution were mixed and diluted to approximately 10 μM.

**Mass Spectrometry.** All mass spectrometric experiments were performed on a Finnigan MAT TSQ-7000 triple-stage mass spectrometer equipped with a microspray source. No desolvation or nebulization gas was applied. The experimental parameters were kept as similar as possible to maintain comparable conditions for all samples. The ESI parameters were set at an infusion rate of 1−2 μL $min^{-1}$, a spray voltage of 1.7−1.9 kV on the needle, the heated capillary at 150 °C and at −50 V, and the tube lens at −90 to −110 V. The collision-induced dissociation (CID) spectra were obtained by mass-selecting the desired noncovalent complex anions in the first quadrupole, fragmenting them in the collision octapole, and recording the product anions by scanning the second quadrupole. Argon was used as the collision gas at a pressure of 0.5 mTorr. In order to accurately maintain the collision gas pressure for better reproducibility of the CID experiments, a sensitive Pfeiffer Vacuum IMR 265 hot cathode/Pirani gauge combination was connected to the CID chamber. The lab-frame collision offsets $V_{coll}$ were set accordingly for all studied complexes to obtain the same energies in the center-of-mass frame $E_{CM}$ of 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, and 2.0 eV, as calculated according to eq 1:

$$E_{CM} = V_{coll} \times M_{argon}/(M_{argon} + M_{parent}) \quad (1)$$

**Theoretical Calculations.** All calculations were carried out using the Gaussian 09 quantum mechanical package.[37] The large size and flexibility of the α-CD host−guest complexes makes the theoretical investigation of their conformations computationally demanding. We used the semiempirical PM3 quantum chemical method, which has been widely applied to study CDs due to its relatively low computational cost and has been successfully tested for searching global minimum-energy geometries of CD complexes.[38−41] The initial geometry of α-CD was constructed from the available X-ray structure,[42] excluding the hydration water molecules. The optimized global minimum conformation of α-CD was taken for further modeling of the CD complexes with benzoate derivatives. We searched for the global energy minima of $[\alpha\text{-CD}\cdot\text{RBA}]^-$ gas-phase complexes analogous to a recently reported method.[40,43,44] In GaussView, the α-CD molecule was centered with the $C_6$ rotational axis along the $Z$ axis and the wide rim above the $XY$ plane. The $[\text{RBA}]^-$ anion was placed on the $Z$ axis and two possible orientations were considered: a "head" orientation with the carboxylate group pointing in the negative $Z$-direction and the opposite, "tail" orientation. The ipso carbon atom of $[\text{RBA}]^-$ was initially located at +8 Å on the $Z$ axis and was moved in steps of 0.5 Å until −8 Å. Each thus generated starting geometry was optimized without any restriction to find the nearest minimum-energy conformation using the semiempirical method PM3; the computational results are listed in Table S1 in the Supporting Information.

In order to investigate the involved noncovalent interactions more accurately, the lowest-energy PM3 geometries were refined by DFT calculations with the M06-L density functional.[45] Finally, single-point energies were computed at the M06-2X//M06-L level of theory.[46] The M06 family of density functionals is designed to accurately model main-group thermochemistry, kinetics, and noncovalent interactions at a reasonable cost.[47] For all the DFT calculations the 6-31+G(d,p) basis set was applied, which is a Pople-type basis set of double-ζ quality, augmented with one set of polarization functions on all elements and one set of diffuse functions on the non-hydrogen atoms. The host−guest interaction energies were corrected for basis set superposition errors (BSSEs) as calculated with the counterpoise method.[48,49]

## RESULTS AND DISCUSSION

**1:1 Host−Guest Complexation.** For the ESI−MS investigation of anionic host−guest complexes of α-CD with 3,5-diMeBA, 3-MeBA, BA, 3-OHBA, and 3,5-diOHBA, 1:1 mixtures of host and guest were prepared of approximately 10 μM in methanol/water (95:5 v/v). These solutions have a pH around 6 due to dissociation of the benzoic acid derivatives (RBA), while α-CD with $pK_a$ = 12.3[50] remains undissociated at this pH. Figure 1 shows the ESI−MS spectra obtained for the mixtures of α-CD and RBA. The signals observed at $m/z$ 1121, 1107, 1093, 1109, and 1125 correspond to the expected anionic complexes $[\alpha\text{-CD}\cdot\text{3,5-diMeBA}]^-$, $[\alpha\text{-CD}\cdot\text{3-MeBA}]^-$, $[\alpha\text{-CD}\cdot\text{BA}]^-$, $[\alpha\text{-CD}\cdot\text{3-OHBA}]^-$, and $[\alpha\text{-CD}\cdot\text{3,5-diOHBA}]^-$, respectively.

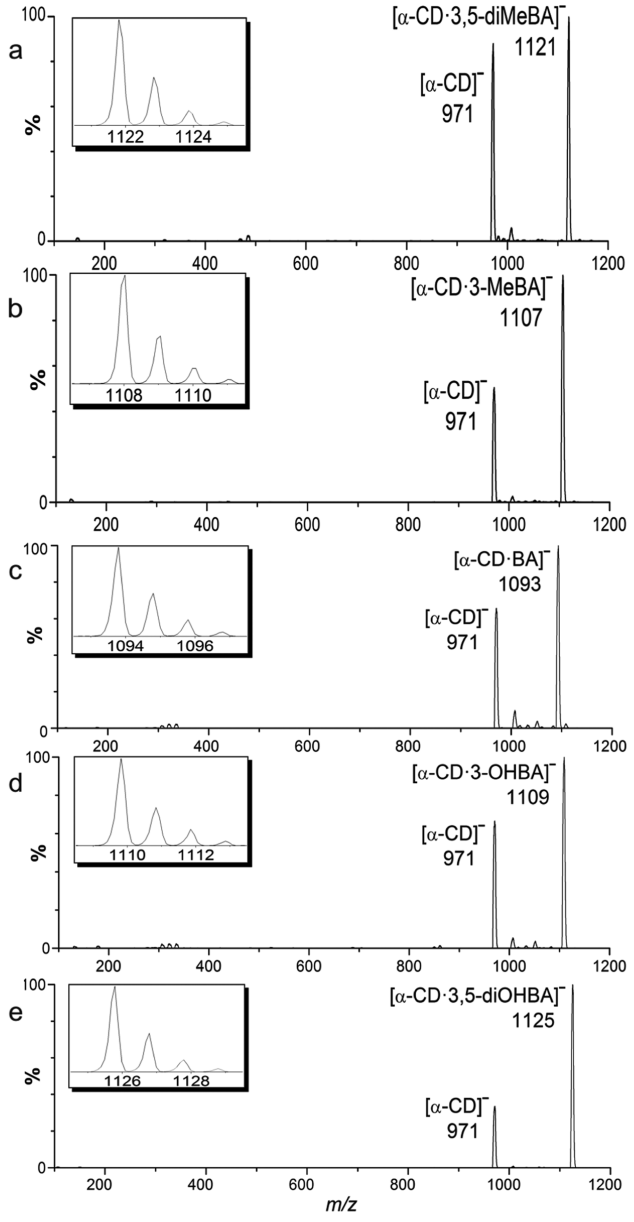


**Figure 1.** Experimental mass spectra and isotope patterns (insets) obtained for 1:1 mixtures of $\alpha$-CD and (a) 3,5-diMeBA, (b) 3-MeBA, (c) BA, (d) 3-OHBA, and (e) 3,5-diOHBA.

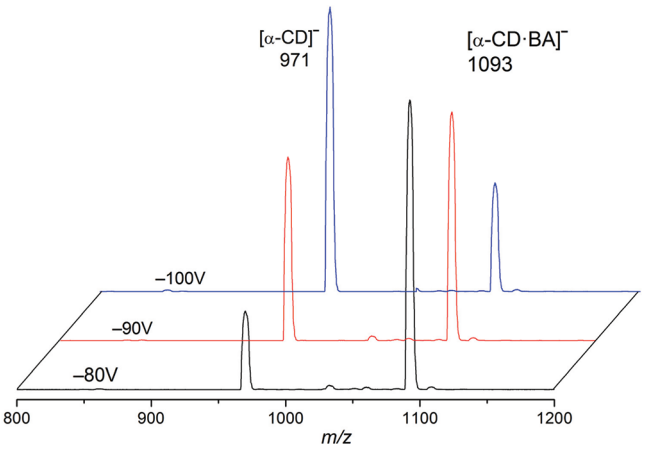


**Figure 2.** Mass spectra obtained for a 1:1 mixture of $\alpha$-CD and BA at different tube lens voltages.

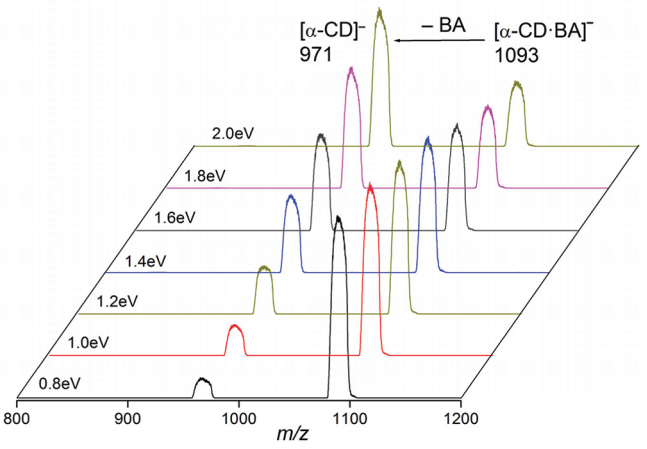


**Figure 3.** CID mass spectra of the $[\alpha\text{-CD}\cdot\text{BA}]^-$ complex at different center-of-mass energies $E_{CM}$.

However, Kralj and co-workers[35] pointed out recently that such signals may also stem in part from doubly charged dimeric cluster ions $[(\alpha\text{-CD}\cdot\text{RBA})_2]^{2-}$. High-resolution mass spectrometric analysis unequivocally excluded the presence of the 2:2 dianionic complexes, as indicated by the unit mass-spaced isotope patterns (see insets in Figure 1).

**Gas-Phase Deprotonation of *α*-CD.** As shown in Figure 1, for all five mixtures a common peak at $m/z$ 971 was also observed, which was assigned to deprotonated $\alpha$-CD, $[\alpha\text{-CD}]^-$. However, this anion could not be detected by spraying a solution of $\alpha$-CD alone, which is in accordance with its high p$K_a$ in solution. Thus, the benzoic acid must play a role in the formation of the $[\alpha\text{-CD}]^-$ anion, either via proton abstraction from $\alpha$-CD by benzoate anions in solution or via proton-transfer fragmentation of the anionic host–guest complexes $[\alpha\text{-CD}\cdot\text{RBA}]^-$ in the mass spectrometer. The difference in p$K_a$ between $\alpha$-CD and RBA in solution rules out the first possibility, leaving the gas-phase fragmentation as the only plausible pathway. Accordingly, the ion intensity of the deprotonated product $[\alpha\text{-CD}]^-$ increased while that of the host–guest complex $[\alpha\text{-CD}\cdot\text{BA}]^-$ decreased when a higher tube lens voltage (from −80 to −100 V) or a higher collision offset was applied, as shown in Figures 2 and 3.

**Gas-Phase Basicity versus Gas-Phase Kinetic Stability.** One question remains, namely, why does gas-phase fragmentation of the $[\alpha\text{-CD}\cdot\text{RBA}]^-$ complexes afford deprotonated $\alpha$-CD rather than the benzoate, as expected on the basis of their p$K_a$ values? We therefore studied the formation of $[\alpha\text{-CD}]^-$ through collision-induced dissociation (CID) experiments on the $[\alpha\text{-CD}\cdot\text{RBA}]^-$ anions with argon as the collision gas. To allow direct comparison, the CID experiments were performed at the same collision energies in the center-of-mass frame (instead of lab frame) for all anionic complexes. As shown in Figure 3 for $[\alpha\text{-CD}\cdot\text{BA}]^-$, the ion intensity of $[\alpha\text{-CD}]^-$ grows with increasing collision energy while the signal of the noncovalent complex decreases accordingly. The other four $\alpha$-CD anionic complexes showed similar CID behavior; formation of benzoate derivatives $[\text{RBA}]^-$ was not observed under any condition. As can be seen in Figure 4, the


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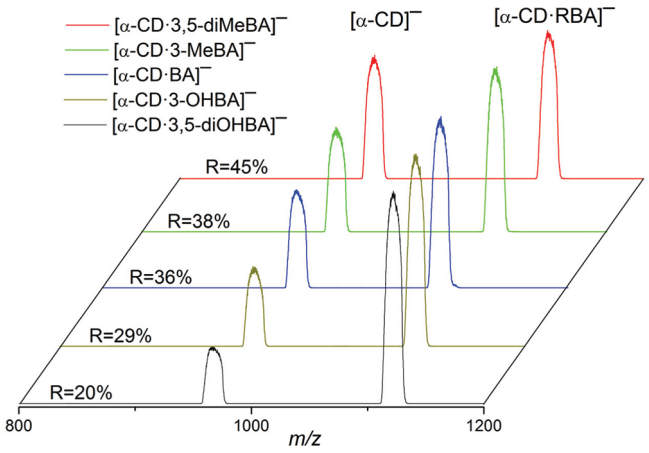


**Figure 4.** CID product spectra of $[\alpha\text{-CD}\cdot\text{RBA}]^-$ anionic complexes at 0.5 mTorr of argon and 1.4 eV center-of-mass collision energy, including conversions $R = I_{[\alpha\text{-CD}]^-}/\Sigma I$.

**Table 1. Gas-Phase Basicities of Substituted Benzoates ($RBA^-$)**

| benzoates ($RBA^-$) | $-\Delta G^0$ (kcal mol$^{-1}$)[a] | ref |
|---|---|---|
| 3,5-dimethylbenzoate ($[3,5\text{-diMeBA}]^-$) | 333.8 | 52 |
| 3-methylbenzoate ($[3\text{-MeBA}]^-$) | 333.4 | 52 |
| benzoate ($[BA]^-$) | 333.1 | 53 |
| 3-hydroxybenzoate ($[3\text{-OHBA}]^-$) | 331.6 | 54 |

[a] Data were taken from the NIST Web site.

gas-phase kinetic stability of the anionic host−guest complexes increases as follows: $[\alpha\text{-CD}\cdot 3,5\text{-diMeBA}]^-$ < $[\alpha\text{-CD}\cdot 3\text{-MeBA}]^-$ < $[\alpha\text{-CD}\cdot\text{BA}]^-$ < $[\alpha\text{-CD}\cdot 3\text{-OHBA}]^-$ < $[\alpha\text{-CD}\cdot 3,5\text{-diOHBA}]^-$.

Cai and Cole studied proton-bridged adducts $[A^-\cdots H^+\cdots B^-]$ formed between anions and polar molecules by ESI−MS.[51] In all cases, CID favored the formation of the anionic species with the lower gas-phase basicity. Furthermore, the most stable adducts were formed between species $A^-$ and $B^-$ of most similar basicity. This relation between gas-phase basicities and adduct stability can be understood by recognizing that the two anionic fragments bind competitively to the bridging proton. If one fragment is more basic, it would bind more strongly to the bridging proton at the expense of the bond to the other fragment, thus reducing the overall kinetic stability of the adduct.

The fact that the only observable CID daughter ion is $[\alpha\text{-CD}]^-$ for all five $[\alpha\text{-CD}\cdot\text{RBA}]^-$ complexes reveals that the gas-phase basicity of $[\alpha\text{-CD}]^-$ is lower than that of any of the substituted benzoates ($RBA^-$) used in this study; i.e., the basicity of deprotonated $\alpha$-CD versus those of the substituted benzoates is reversed in the gas phase as compared to solution. Thus, the lower the benzoate's basicity, the closer it is to that of $[\alpha\text{-CD}]^-$, and hence the higher should be the kinetic stability of the $[\alpha\text{-CD}\cdot\text{RBA}]^-$ complex.

The gas-phase basicities $-\Delta G^0$ of four benzoates used in our study are listed in Table 1 and follow the order $[3,5\text{-diMeBA}]^-$ > $[3\text{-MeBA}]^-$ > $[BA]^-$ > $[3\text{-OHBA}]^-$. The gas-phase basicity of $[3,5\text{-diOHBA}]^-$ was not available from the literature, but it is necessarily yet smaller than that of $[3\text{-OHBA}]^-$ due to the additional electron-withdrawing meta OH group. This is in agreement

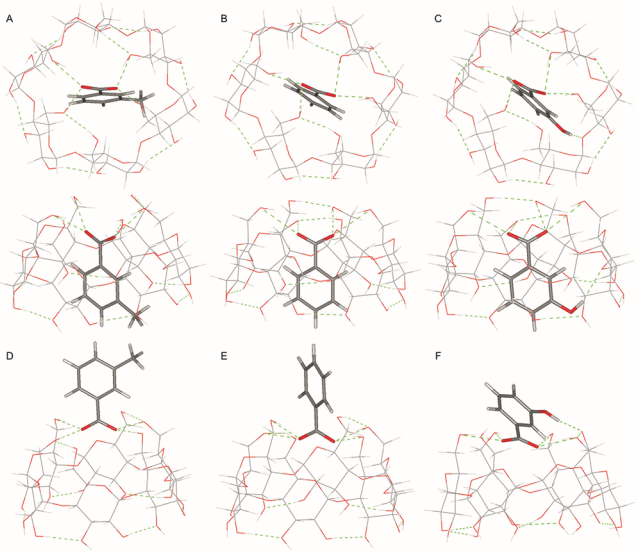


**Figure 5.** M06-L/6-31+G(d,p) optimized geometries for head (A, B, C, side and top views) and tail (D, E, F) orientations of $[\alpha\text{-CD}\cdot 3\text{-MeBA}]^-$, $[\alpha\text{-CD}\cdot\text{BA}]^-$, and $[\alpha\text{-CD}\cdot 3\text{-OHBA}]^-$, respectively. Green dashed lines represent hydrogen-bonding interactions.

with the experimentally determined gas-phase stability order of their adducts with $\alpha$-CD (see above).

**Comparison with Solution-State Data.** When we compare our gas-phase results with published solution-state data for host−guest complexes[6] of $\alpha$-CD with benzoic acid derivatives, the impact of the environment becomes clear. In our MS experiments, appreciable fragmentation of $[\alpha\text{-CD}\cdot\text{BA}]^-$ requires collision energies that are more than an order of magnitude bigger than its stability in solution of only 1.4 kcal mol$^{-1}$.[55] The aqueous neutral complexes of $\alpha$-CD with substituted benzoic acids are more strongly bound with Gibbs free energies of association $-\Delta G^0$ = 3.4−4.1 (BA),[56,57] 3.3−3.7 (3-OHBA),[57,58] and 3.3 kcal mol$^{-1}$ (3-MeBA).[56] Thus, the solution-state thermodynamic stability trend of these neutral host−guest complexes is governed by the steric influence of the meta substitution and differs from the kinetic trend that we observe for their deprotonated counterparts in the gas phase.

It is difficult to obtain a more detailed understanding of the effects of the surrounding medium as mass spectrometric experiments alone do not provide information on the structures of, and hence, the specific interactions in these host−guest complexes. However, the high-vacuum environment of a mass spectrometer allows a direct comparison with theoretical studies without the need to model solvent influences. Quantum-chemical calculations, combined with classical characterization techniques in the gas phase such as ESI−MS, thus enable us to derive gas-phase structural details and dissociation energies of the studied complexes, which help to clarify fundamental aspects of the interactions involved and can be useful for the experimentalist's interpretations. The intrinsic properties in the gas phase can then be compared with those in the condensed phase, as influenced by the surrounding solvent, to afford a better understanding of the solvent effects. Therefore, DFT calculations were performed.

**Calculated Gas-Phase Conformations.** One would expect that, in the gas phase, a structure with the largest number of hydrogen bonds is the most stable. Accordingly, a relatively rigid hydrogen-bonded conformation was found as the global energy

minimum of α-CD.[59−61] The substituted benzoate guests can adopt two general orientations, having the carboxylate pointing either in the same ("head") or the opposite direction ("tail") as the taper of the conical α-CD. PM3 searches for either orientation[40,43,44] of host−guest complexes $[\alpha\text{-CD}\cdot\text{3-MeBA}]^-$, $[\alpha\text{-CD}\cdot\text{BA}]^-$, and $[\alpha\text{-CD}\cdot\text{3-OHBA}]^-$ afforded minimum-energy conformations that all had in common that the largest hydrogen-bonding network was formed between α-CD and the benzoate derivative. These geometries were refined by DFT calculations at the M06-L/6-31+G(d,p) level of theory (Figure 5). For the head orientation, so-called inclusion conformations are favored having the guest's aryl group inside the cavity of α-CD, whereas we found nonspecific complexes with the aryl group outside α-CD's cavity as the preferred conformations for the tail orientation. It is worth noting that the conformations for the head orientation (A, B, and C) found by the DFT calculations are similar to crystal structures for analogous host−guest complexes.[62] For instance, in the solid state the guest molecules are hosted by the cavity of α-CD, and the carboxylate or nitro group is usually more or less in the plane of the small rim, just as in our calculations. In contrast, the hydroxyl groups of α-CD point outward to form hydrogen bonds with neighboring solvent or host molecules in the condensed phase, while our gas-phase conformations feature multiple hydrogen bonds of hydroxyl groups on the narrower rim with the guest's carboxylate group as shown in Figure 5. These structural differences reflect the fact that in general, a more delocalized electron density is energetically favorable. Since in the gas phase there is no solvent to interact with the polar groups such as the hydroxyls, the intra- and intermolecular hydrogen bonds with which the negative charge is efficiently distributed are believed to constitute the primary interaction in our system.

**Host−Guest Bonding Energies.** We calculated reaction energies for the dissociation of hydrogen-bonded complexes $[\alpha\text{-CD}\cdot\text{RBA}]^-$ into either deprotonated $[\alpha\text{-CD}]^-$ anion and neutral RBA (Scheme 2, pathway 1) or neutral α-CD and benzoate $[\text{RBA}]^-$ (Scheme 2, pathway 2). The first pathway is that observed in our gas-phase experiments, whereas the second pathway is analogous to the reversible host−guest complexation in solution according to the $pK_a$ values of α-CD and $[\text{RBA}]^-$.

For either pathway, we calculated larger dissociation energies for the complexes with head orientation of the substituted benzoate than for the corresponding tail conformations (Table 2, e.g., $[\alpha\text{-CD}\cdot\text{3-MeBA}]^-$, 40.59 versus 31.92 kcal mol$^{-1}$ for pathway 1). As illustrated in Scheme 2, this reflects the fact that the head conformations are more stable than the tail conformations by 8.67, 9.66, and 1.57 kcal mol$^{-1}$ for the complexes with 3-MeBA, BA, and 3-OHBA as the guest, respectively. For $[\alpha\text{-CD}\cdot\text{3-OHBA}]^-$ the tail conformation is not as much disfavored because it features an additional hydrogen bond between the meta hydroxyl group of the guest and a primary hydroxyl on the small rim of the host (Figure 5F), whereas in the head orientation (C) a glycosidic oxygen atom is involved, providing weaker hydrogen bonding. In the electrospray process, the host−guest complexes should be able to adjust their structure during the transition to the gas phase; our calculations thus suggest that the detected $[\alpha\text{-CD}\cdot\text{RBA}]^-$ ions would preferentially adopt a head conformation.

As shown in Table 2, the M06-2X//M06-L dissociation energies required for pathway 1 are smaller than for pathway 2 for all the studied complexes ($[\alpha\text{-CD}\cdot\text{3-MeBA}]^-$ $\Delta\Delta E$ = 8.18; $[\alpha\text{-CD}\cdot\text{BA}]^-$ 7.23; $[\alpha\text{-CD}\cdot\text{3-OHBA}]^-$ 5.26 kcal mol$^{-1}$). This preference for pathway 1 is in agreement with our CID experiments that afforded only $[\alpha\text{-CD}]^-$ anion and in which no benzoate $[\text{RBA}]^-$ was observable. As the two pathways produce the same species as are involved in the (hypothetical) proton-transfer reaction between $[\alpha\text{-CD}]^-$ and $[\text{RBA}]^-$, the difference in dissociation energies $\Delta\Delta E$ should correspond approximately to the difference in gas-phase basicities of $[\alpha\text{-CD}]^-$ and $[\text{RBA}]^-$, assuming that the Gibbs free energy contributions and any systematic errors largely cancel. Combining the data in Tables 1 and 2, we can thus estimate the average gas-phase basicity of $[\alpha\text{-CD}]^-$ to be $\Delta G^0$ = 325−327 kcal mol$^{-1}$. No experimental value has been reported yet, and the common methods[63,64] to determine gas-phase basicities have limitations that particularly apply to measuring the gas-phase basicity of $[\alpha\text{-CD}]^-$. The widely used equilibrium method is based on the determination of the equilibrium constant for the proton-exchange reaction in the gas phase and is therefore obviously restricted to volatile compounds, whereas the kinetic method should be used with care for polyfunctional molecules. However, Kralj et al.[35] stated that the gas-phase basicity of $[\alpha\text{-CD}]^-$ should be close to that of *p*-nitrophenolate (321 kcal mol$^{-1}$)[65] as fragmentation of the corresponding host−guest complex produces both anions, with which our estimate is in acceptable agreement.

**Scheme 2. Potential Energy Diagram for the Two Possible Dissociation Pathways of $[\alpha\text{-CD}\cdot\text{RBA}]^-$ Conformations**

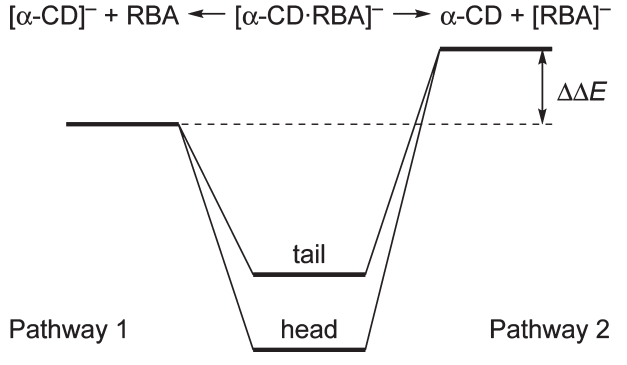


**Table 2. Calculated M06-2X//M06-L/6-31+G(d,p) Dissociation Energies (kcal mol$^{-1}$), Including BSSE Corrections**

| | head | | tail | | |
|---|---|---|---|---|---|
| complex | $[\alpha\text{-CD}]^-$ + RBA | α-CD + $[\text{RBA}]^-$ | $[\alpha\text{-CD}]^-$ + RBA | α-CD + $[\text{RBA}]^-$ | $\Delta\Delta E^a$ |
| $[\alpha\text{-CD}\cdot\text{3-MeBA}]^-$ | 40.59 | 48.77 | 31.92 | 39.56 | 8.18 |
| $[\alpha\text{-CD}\cdot\text{BA}]^-$ | 40.71 | 47.94 | 31.05 | 38.07 | 7.23 |
| $[\alpha\text{-CD}\cdot\text{3-OHBA}]^-$ | 43.95 | 49.21 | 42.38 | 47.28 | 5.26 |

[a] Energy difference between pathways 1 and 2 for the head conformations.


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Table 3. M06-2X//M06-L/6-31+G(d,p) Bond Lengths (Å) and Angles (deg) and NBO Donor−Acceptor Interaction Energies $E(2)$ (kcal mol$^{-1}$) for Intermolecular Hydrogen Bonds in $[\alpha\text{-CD}\cdot\text{RBA}]^-$ Complexes[a]

| | head conformation | | | | tail conformation | | |
|---|---|---|---|---|---|---|---|
| hydrogen bond | $R_{O\cdots O}$ | ∠O−H···O | $E(2)$ | hydrogen bond | $R_{O\cdots O}$ | ∠O−H···O | $E(2)$ |
| (A) $[\alpha\text{-CD}\cdot\text{3-MeBA}]^-$ | | | | (D) $[\alpha\text{-CD}\cdot\text{3-MeBA}]^-$ | | | |
| $O6^aH\cdots O$ | 2.721 | 156.24 | 20.6 | $O6^aH\cdots O$ | 2.713 | 174.06 | 30.1 |
| $O6^bH\cdots O$ | 2.891 | 148.96 | 8.4 | $O6^bH\cdots O$ | 2.790 | 167.50 | 20.2 |
| $O6^dH\cdots O'$ | 2.731 | 157.63 | 20.3 | $O6^dH\cdots O'$ | 2.714 | 173.28 | 29.6 |
| $O6^eH\cdots O'$ | 2.904 | 147.57 | 7.5 | $O6^eH\cdots O'$ | 2.778 | 166.44 | 20.6 |
| | | | Σ 56.8 | | | | Σ 100.5 |
| (B) $[\alpha\text{-CD}\cdot\text{BA}]^-$ | | | | (E) $[\alpha\text{-CD}\cdot\text{BA}]^-$ | | | |
| $O6^aH\cdots O$ | 2.827 | 155.76 | 12.3 | $O6^aH\cdots O$ | 2.732 | 169.49 | 24.4 |
| $O6^bH\cdots O$ | 2.968 | 139.67 | 4.2 | $O6^bH\cdots O$ | 2.779 | 166.60 | 22.1 |
| $O6^dH\cdots O'$ | 2.827 | 155.79 | 12.2 | $O6^dH\cdots O'$ | 2.745 | 169.33 | 23.3 |
| $O6^eH\cdots O'$ | 2.969 | 139.77 | 3.6 | $O6^eH\cdots O'$ | 2.785 | 168.81 | 22.1 |
| | | | Σ 32.3 | | | | Σ 91.9 |
| (C) $[\alpha\text{-CD}\cdot\text{3-OHBA}]^-$ | | | | (F) $[\alpha\text{-CD}\cdot\text{3-OHBA}]^-$ | | | |
| $O6^aH\cdots O$ | 2.847 | 155.35 | 11.1 | $O6^aH\cdots O$ | 2.683 | 167.69 | 13.2 |
| $O6^bH\cdots O$ | 2.939 | 143.22 | 5.3 | $O6^bH\cdots O$ | 2.811 | 168.16 | 23.2 |
| $O6^dH\cdots O'$ | 2.852 | 154.84 | 10.5 | $O6^cH\cdots O'$ | 2.784 | 161.98 | 15.8 |
| $O6^eH\cdots O'$ | 2.938 | 142.48 | 5.2 | $O6^dH\cdots O'$ | 2.754 | 168.81 | 33.6 |
| $O1^b\cdots HO^m$ | 3.359 | 164.32 | 2.1 | $O6^f\cdots HO^m$ | 2.785 | 167.49 | 21.1 |
| | | | Σ 34.2 | | | | Σ 106.9 |

[a] $O6^{a-f}$ are the oxygen atoms connected to C6 of the six glucose units a−f in $\alpha$-CD, with $O1^b$ connecting units b and c; O and O′ are the RBA carboxylate oxygen atoms and $O^m$ is the hydroxyl oxygen atom of 3-OHBA.

The experimentally observed trend in gas-phase kinetic stabilities $[\alpha\text{-CD}\cdot\text{3-MeBA}]^- < [\alpha\text{-CD}\cdot\text{BA}]^- < [\alpha\text{-CD}\cdot\text{3-OHBA}]^-$ is reproduced by the calculated dissociation energies of 40.59 < 40.71 < 43.95 kcal mol$^{-1}$, respectively (Table 2), although we must note that the first two energies are very similar. The results will still be slightly affected by the Gibbs free energy contributions, which we cannot take into account here because the effective temperature of the ions in our experiments is not known. One may expect that the dissociation of $[\alpha\text{-CD}\cdot\text{BA}]^-$ is entropically somewhat less favorable than of the host−guest complexes with substituted benzoates, as for the latter the constraints by the host's cavity on the rotations and vibrations of the substituent are relieved. This effect is probably largest for the complex of 3-OHBA as our calculations suggest that the hydroxyl substituent undergoes hydrogen bonding with the host. These entropic contributions may thus slightly change the differences, but not the trend, in dissociation energies of the studied host−guest complexes. However, such variations likely fall within the accuracy of the computational method used.

**Hydrogen-Bonding Interactions.** The observation of proton-transfer dissociation and the DFT calculations clearly indicate that hydrogen bonding plays a decisive role in the gas-phase conformation and kinetic stability of the $[\alpha\text{-CD}\cdot\text{RBA}]^-$ complexes. Therefore, we investigated these interactions in more detail by natural bond orbital (NBO) analysis[66] at the M06-2X//M06-L/6-31+G(d,p) level of theory. Hydrogen bonding is often described as an electrostatic dipole−dipole interaction. However, it also has some features of covalent bonding: it usually involves a limited number of interaction partners and is directional. Within NBO theory, the second-order perturbation energies $E(2)$ are associated with donor−acceptor delocalization corrections to the idealized Lewis structure, in which the carboxylate moiety is described as the single-bonded resonance extreme $ArC^+(O^-)_2$ with three lone pairs on each oxygen atom. These lone pairs are primarily delocalized into the O−H antibonds of $\alpha$-CD, and the sums of their interaction energies with each hydroxyl group reflect the host−guest hydrogen-bonding strengths.[67−69] In geometries A−C in Figure 5, the RBA anion is completely surrounded by $\alpha$-CD and therefore the orientation of the carboxylate group is restricted, which may affect the hydrogen bonding. On the other hand, geometries D−F have the RBA anion outside of the $\alpha$-CD cavity, so that its carboxylate group has more freedom to attain a suitable position to engage in strong hydrogen bonding. Thus, the hydrogen bonding in geometries A−C is expected to be weaker than in D−F. This is corroborated by the hydrogen bond parameters listed in Table 3, featuring longer O···O distances and more bent O—H···O arrangements for geometries A−C than for D−F, and accordingly smaller interaction energies $E(2)$. As a result, the total hydrogen-bonding interaction is markedly weaker for the head conformations A−C than for the corresponding tail conformations D−F. One should keep in mind, though, that the interaction energies $E(2)$ are relative to the reference Lewis-like descriptions chosen by the NBO analyses, which are not exactly identical for the different complexes; i.e., their bonds, lone pairs, and antibonds have slightly different electron occupations. Consequently, these results can only serve for a semiquantitative comparison and cannot be combined with the calculated overall relative energies to accurately estimate the magnitude of the residual host−guest interactions that stabilize the head over the tail conformations. Such interactions may include unconventional hydrogen bonds (C—H···O),[70] C—H···$\pi$ interactions,[71] C—H···anion interactions,[72] and van der Waals forces.[24] We are currently developing a computational strategy to quantify these bonding


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contributions. Furthermore, we are performing energy-resolved CID experiments to determine the absolute gas-phase dissociation energies for these complexes, which will serve to validate the computational level.

## CONCLUSIONS

The anionic host−guest complexes of $\alpha$-cyclodextrin with substituted benzoates $RBA^-$ were studied by ESI−MS and their 1:1 composition was confirmed by the unit-mass spacing of their isotope patterns. The correlation of the gas-phase kinetic stabilities of these complexes, as disclosed by CID experiments, with the basicities of the host and guests involved sheds light on the intrinsic properties of the gas-phase noncovalent complexes. The gas-phase basicity of deprotonated $\alpha$-CD was found to be lower than that of all investigated benzoate guests ($RBA^-$) as concluded from the dissociation of the $[\alpha\text{-CD}\cdot RBA]^-$ complexes into $[\alpha\text{-CD}]^-$ and the neutral benzoic acid derivative. This proton-transfer reaction signifies the existence of hydrogen bonding between host and guest in the gas phase and indicates that the basicity order of deprotonated $\alpha$-CD vs the benzoates is reversed as compared to solution state. A comparison of the ratios between reactant and product intensities under identical collision conditions with the gas-phase basicities of the used benzoates establishes that the complex is kinetically more stable when the difference in gas-phase basicities of host and guest anions is smaller. The noncovalently bound species of the $[\alpha\text{-CD}\cdot RBA]^-$ complexes formed in solution are unlikely to retain the same conformation in the gas phase. DFT calculations show a preference for the largest number of hydrogen bonds involved in the $[\alpha\text{-CD}\cdot RBA]^-$ complexes, in agreement with our experimental results. The calculated dissociation energies suggest that the inclusion complexes are favored over the nonspecific complexes in the gas phase, although the hydrogen bonding is weaker in the former conformations. The combination of experimental and computational results provides an estimate for the gas-phase basicity of $[\alpha\text{-CD}]^-$ of 325−327 kcal $mol^{-1}$, which is useful for a better understanding of the properties of gas-phase cyclodextrin complexes.

## ASSOCIATED CONTENT

**Supporting Information.** Results of the PM3 conformational searches, and absolute energies and optimized geometries at the M06-L/6-31+G(d,p) level of theory for all studied species. This material is available free of charge via the Internet at http://pubs.acs.org.

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