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1 **Probing topology of supramolecular complexes between cy-**
2 **clodextrins and alkali metals by ion mobility-mass spectrom-**
3 **etry**

4 Cédric Przybylski^{a,*} Véronique Bonnet^b

5 ^a Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire, IPCM, 4 Place Jussieu, 75005 Paris, France.

6 E-mail: cedric.przybylski@sorbonne-universite.fr

7

8 ^b Université de Picardie Jules Verne, Laboratoire de Glycochimie, des Antimicrobiens et des Agroressources, LG2A,

9 CNRS, 33 rue Saint Leu, 80039 Amiens, France.

10 **ABSTRACT**

11 In this study, the size and shape of supramolecular assemblies between cyclo-oligosaccharides
12 and proton, ammonium or a series of alkali metals by electrospray coupled to trapped ion mobil-
13 ity-mass spectrometry (ESI-TIMS) have investigated. Native cyclodextrins (CD) were selected as
14 models, and collision cross section (CCS) values were deducted for the main positive singly and
15 doubly charged species. Experimental CCS values were in good agreement with those obtained
16 from molecular modeling. Due to the high mobility resolving power and resolution, it was possi-
17 ble to highlight the presence of various conformers. Also, TIMS allowed to discriminate and esti-
18 mate the content of various orientations from non-covalent nanotubes-based CD, involving sec-
19 ondary/secondary rim hydroxyl groups (head-to head), primary/secondary rim (head-to-tail) hy-
20 droxyl groups or primary/primary rim (tail-to-tail) hydroxyl groups interactions. Such results pave
21 the way for a better knowledge of the topology of cyclo-oligosaccharides based supramolecular
22 complexes, demonstrating that TIMS can be a particularly attractive molecular descriptor.

23

24

25 **Keywords:** Cyclo-oligosaccharides; Cyclodextrins; Supramolecular assembly; Conformers; Ion-
26 mobility; Mass spectrometry.

27

28 1. INTRODUCTION

29 Starch is among the most abundant polysaccharides present in the plant kingdom. It is
30 composed of numerous glucose (Glc) units predominantly linked by α -(1→4) glycosidic
31 bonds and occasionally branched by α -(1→6) moderately long chains.(Tester et al., 2004)
32 The combined action of enzymes such as α -amylase and cyclodextrin glycosyltransferase,
33 has attracted major interest from industry due to their unique capacity to catalyse the
34 formation of α -(1→4) malto-oligosaccharides as linear (maltodextrins) or cyclic ones (cy-
35 clodextrins; CDs) all with possible branching in α -(1→6).(Ao et al., 2007; French et al., 1965;
36 Taniguchi & Honnda, 2009; Terada et al., 1997) On the basis of the number of residues, com-
37 mercially available CDs are torus-shaped cyclic oligosaccharides composed of 6, 7 and 8
38 α -(1→4) linked D-glucopyranose units for α -CD, β -CD, and γ -CD, respectively.(Szejtli, 1998)
39 CDs form a hydrophobic cavity able to encapsulate several organic molecules,(Kfoury et
40 al., 2018; Song et al., 2009) and exhibit peripherally hydrophilic features forming intra- and
41 inter-molecular networks thanks to hydrogen bonds.(Loftsson et al., 2005) Such particular
42 properties is abundantly exploited to form various inclusion complexes in many industrial
43 and research fields like food, flavours, cosmetics, drug delivery, catalyst or chiral selectors
44 amongst other.(Davis & Brewster, 2004; Singh et al., 2002; Szejtli, 1998; Szente & Szemán, 2013)
45 Also, the non-bonding electron pairs of the glycosidic oxygen bridge directed towards the
46 inside of the cavity lead to a high electron density which lends CDs some Lewis base char-
47 acter.(Saenger, 1980; Szejtli, 1998; Wenz, 1994) Moreover, the 6-hydroxyl group of the pri-
48 mary rim can constitute very good attachment sites for various metals.(S. Angelova et al.,

49 2017; S. E. Angelova et al., 2017; Dossmann et al., 2021; Przybylski et al., 2015) One of the cen-
50 tral concepts of molecular recognition is the issue of “selectivity”, i.e. the preferential
51 binding of one guest over another by the host. In this sense, one of the elusive structural
52 characteristics when studying CD complexation is how the cavity shape changes upon
53 complexation. Hence, the determination of effective complexation, as well as size and
54 shape of host with and without any guest at a molecular level are mandatory conditions.
55 In a common way, such piece of information was commonly accessed using NMR based
56 diffusion experiments,(Schneider et al., 1998) X-ray diffraction analysis(Steiner & Koellner,
57 1994) and molecular modeling.(Quevedo & Zoppi, 2018)
58 Nonetheless, the introduction of a new technology, named ion mobility coupled to mass
59 spectrometry (IM-MS), offers a promising complementary tool to reach aforementioned
60 objectives. IM-MS have successfully been applied to the gas-phase ion separation of a
61 large range of (bio)molecules based isomers such as peptides/proteins, oligonucleotides,
62 lipids, glycans, synthetic polymers or complexes.(Ben-Nissan & Sharon, 2018; Butcher et al.,
63 2018; Charles et al., 2020; Dodds & Baker, 2019; Gray et al., 2016; Kalenius et al., 2019; Li et al.,
64 2020; Zheng et al., 2018) Unfortunately, its potentiality in supramolecular assemblies inves-
65 tigation remains still underestimated.(Kalenius et al., 2019; Polewski et al., 2021) Such dis-
66 crimination based on structural differences can be characterized by determination of their
67 collision cross section (CCS) values in a given gas. Of special interest, IM-MS has been pre-
68 viously applied to CDs analysis using different instrumental configurations such as matrix-
69 assisted laser desorption or electrospray coupled to drift-tube ion mobility spectrometry
70 (ESI-DTIMS). (Liu & Clemmer, 1997; Klein et al., 2018;Fenn & McLean, 2011; S. Lee et al., 1997)

71 ESI with Traveling-Wave Ion Mobility Spectrometry (ESI-TWIMS) was used to study nega-
72 tively charged mono- to trimeric β -CD(Berland et al., 2014), or positively charged complexes
73 like amino- β -CD/sesamins,(Sugahara et al., 2015) α - and β -CD with o-, m- and p-coumaric
74 acids,(Kralj et al., 2009) with piperine/curcumin, (Nag et al., 2018) or with amino acids. (S.-
75 S. Lee et al., 2018; Chen et al., 2018). Unfortunately, the aforementioned studies with com-
76 plexes involving at least two molecules reported a quite low/medium mobility resolution.
77 A high resolution IM-MS prototype using serpentine ultra-long path was described for α -
78 CD with bile acids analysis in negative and positive mode .(Chouinard et al., 2018)
79 Very recently, a high resolution IM-MS instrument named trapped ion mobility spectrometry
80 (TIMS) was commercially introduced.(Michelmann et al., 2015) TIMS operates at low elec-
81 tric field, preventing ion heating and exhibiting very high resolution.(Jeanne Dit Fouque &
82 Fernandez-Lima, 2019; Ridgeway et al., 2018, 2019) Nevertheless, its application to carbohy-
83 drates analysis is still in infancy, although it was successfully applied for the analysis of
84 glycosaminoglycan,(Wei et al., 2019) permethylated lacto-N-tetrasaccharides,(Pu et al., 2016)
85 or separation of 13 isomeric trisaccharides.(Przybylski & Bonnet, 2021) In the study herein, we
86 hypothesize that TIMS can be a useful analytical tool to both probe the influence of alkali metals
87 on cyclo-oligosaccharides conformational modification (size/shape) in complexes, as well as to
88 identify the sub-units orientation in supramolecular hierarchical assemblies and estimate the rel-
89 ative content of these last ones.

90 **2. MATERIALS AND METHODS**

91 **2.1. Chemicals and Materials**

92 α -, β - and γ -Cyclodextrin (α -, β - and γ -CD, respectively) were kindly supplied by Wacker Chimie
93 S.A.S. (Lyon, France). LiCl, NaCl, KCl, RbCl and CsCl alkali salts were purchased from Sigma-Aldrich
94 (Saint-Quentin Fallavier, France).

95 **2.2 Solvents**

96 Methanol used for sample preparation was of MS grade and was purchased from VWR (West
97 Chester, PA, USA). Water was of ultrapure quality (18.2 M Ω).

98 **2.3 Samples**

99 Stock solutions were made at 1 mM in water and then diluted to 1 μ M in methanol/water (1:1
100 v/v) with or without salts (0.3 μ M) for further analysis.

101 **2.4 TimsTOF™ Experiments.**

102 We used ESI-timsTOF™ (Bruker Daltonics, Bremen, Germany) operating with oTOF control v5.0
103 software. The source temperature was hold at 200°C, and the drying and nebulizing gas (N₂) op-
104 erate at a flow rate of 3 L. min⁻¹ and at a pressure of 0.3 bar. The instrument was calibrated using
105 Tuning Mix G24221 (Agilent Technologies, Les Ulis, France). Applied voltages were +4 kV and -0.5
106 kV for capillary and endplate offset, respectively. Acquisition was achieved in the m/z 400-4000
107 range with a centre at m/z 500. TIMS separation depends on the gas flow velocity (v_g), elution
108 voltage ($V_{elution}$), ramp time (t_{ramp}), base voltage (V_{out}) and the electric field (\vec{E}). The reduced
109 mobility, K_0 , can be calculated as follows:

110
$$K_0 = \frac{v_g}{\vec{E}} = \frac{A}{(V_{elution} - V_{out})} \text{ (Eq. 1)}$$

111 The mobility calibration constant A was determined using known reduced mobilities of tuning
112 mix components. The resolving power (R) and resolution (r) are defined as $R = (1/K_0)/w$ and
113 $r = 1.18 \times [(1/K_0)_2 - (1/K_0)_1]/(w_1 + w_2)$, where w is the full peak width at half-maximum.
114 To improve separation efficiency, scan rate ($Sr = \Delta V_{ramp}/t_{ramp}$) was tuned thanks to imeX™ tech-
115 nology. For this, t_{ramp} is automatically set as function of manually adjusted ΔV_{ramp} . N₂ was used
116 as buffer gas at funnel temperature ($T = 305$ K) with v_g set by the pressure difference of 1.69
117 mbar. A potential of 350 Vpp was applied to radially confine the trapped ion cloud. The measured
118 inverse reduced mobilities were converted into collision cross sections (CCS) using the Mason-
119 Schamp equation:

$$120 \quad \Omega = \frac{(18\pi)^{1/2}}{16} \times \frac{q}{(k_B \times T)^{1/2}} \times \left[\frac{1}{m_i} + \frac{1}{m_g} \right]^{1/2} \times \frac{1}{N} \times \frac{1}{K_0} \text{ (Eq. 2)}$$

121 where q is the ion charge, k_B is the Boltzmann constant, N is the gas number density, m_i is the
122 ion mass, and m_g is the gas molecule mass. TIMS-MS spectra and mobilograms were analysed
123 using Compass Data Analysis 5.1 (Bruker).

124

125 **2.6 ESI-TIMS-MS analysis of the cyclo-oligosaccharides**

126 Throughout this study, all cyclo-oligosaccharides were analysed in the positive ion mode with or
127 without salt doping. All samples were continuously infused at 3 $\mu\text{L}\cdot\text{min}^{-1}$ via a 250 mL syringe.

128

129 **2.7 Theoretical Collision Cross Section Calculations**

130 All initial geometry relaxations were performed using the Merck molecular force field (MMFF94)
131 implemented in Avogadro (v1.95.1). Geometry optimization was finalized using density functional
132 theory (DFT) as previously described (Dossmann et al., 2021) and calculations with NWChem
133 (v7.0). Theoretical CCS calculations were carried out in IMoS (v.1.10)(Larriba & Hogan, 2013) using
134 the average of ten processes by Elastic/Diffuse Hard Sphere Scattering or Trajectory method Dif-
135 fuse Hard Sphere Scattering.⁴⁶

136

137 **3. RESULTS AND DISCUSSION**

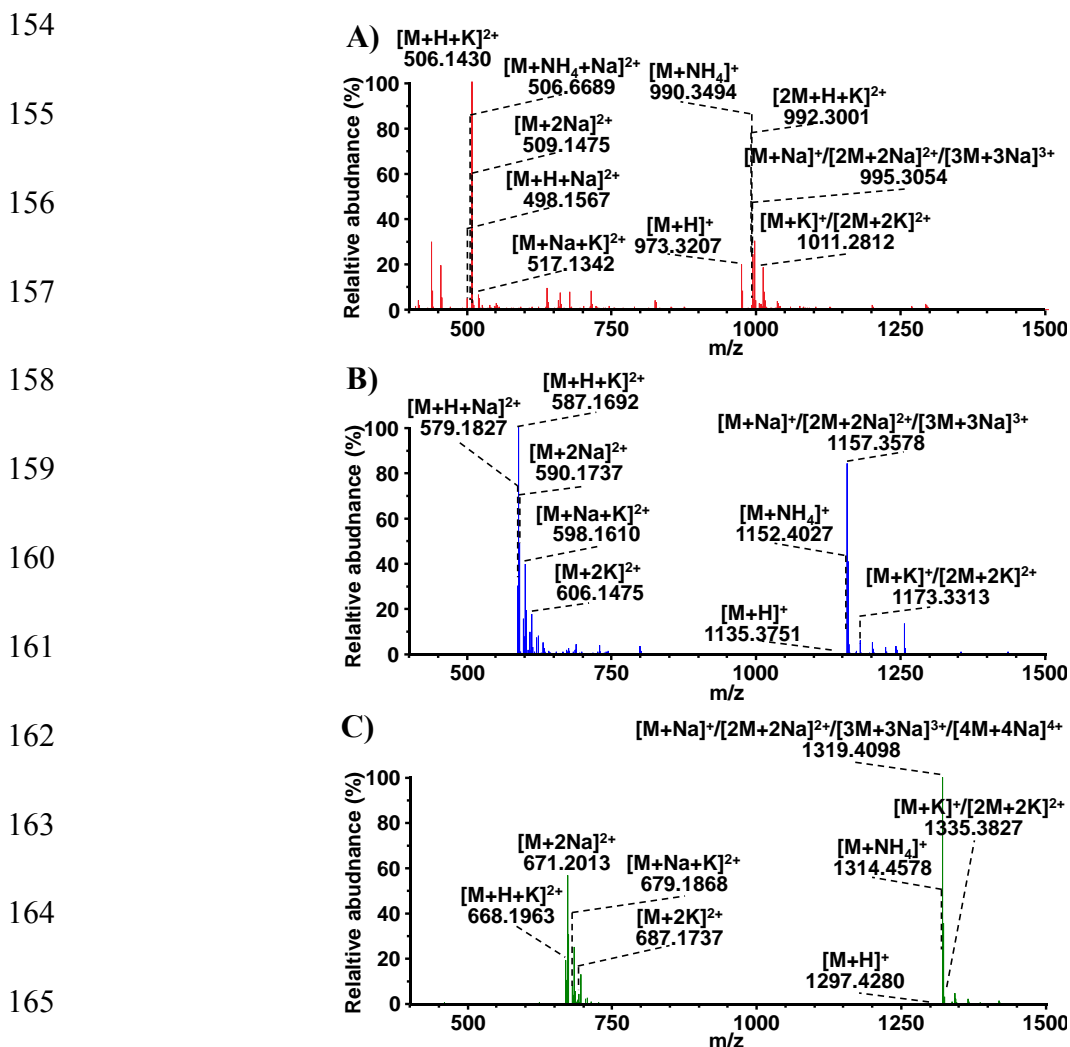
138 As all neutral carbohydrates molecules, cyclodextrins exhibit intrinsically a strong affinity towards
139 usual alkali metals.(Frański et al., 2005; Metzger et al., 1991; Przybylski et al., 2015; Przybylski &
140 Bonnet, 2013; Reale et al., 2005) We have previously demonstrated that a solution containing an
141 equimolar mixtures of β -CD and LiCl, NaCl and KCl allowed to determine apparent solution selec-
142 tivity and the relative affinity of various complexes.(Przybylski et al., 2015) However, here we
143 only aimed to study size and conformation of the complexes by IM-MS, and not the abundance.
144 In this sense, as glassware provides enough source of Na^+ and K^+ , we have directly acquired a first
145 series of spectra with separate α -, β - and γ -CD without any addition. In a second series, α -, β - or
146 γ -CD was mixed with each alkali metals.

147 **3.1 Mobility of singly charged monomers**

148 ***3.1.1 Protonated and ammoniated native cyclodextrins***

149 Cyclodextrins present a lower affinity for H^+/NH_4^+ as compare to usual alkali metals. However,
150 the gas phase basicity of glucose is reported to be $188\pm 3 \text{ kcal.mol}^{-1}$.(Jebber et al., 1996) Hence,

151 even without any doping, ESI full spectra reveal the presence of such adducts coupled as singly
 152 ions at m/z 973.3207/990.3494, 1135.3751/1152.4027 and 1297.4280/1314.4578 for α -, β - and
 153 γ -CD, respectively (Fig. 1).

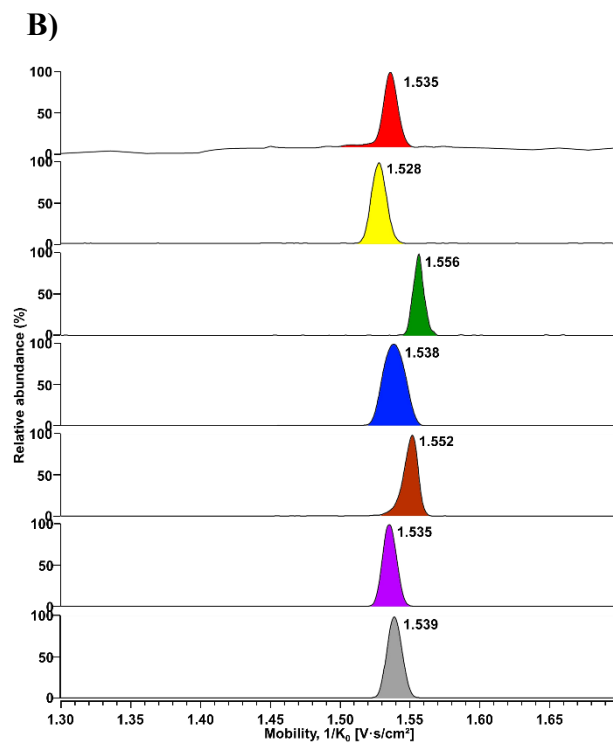
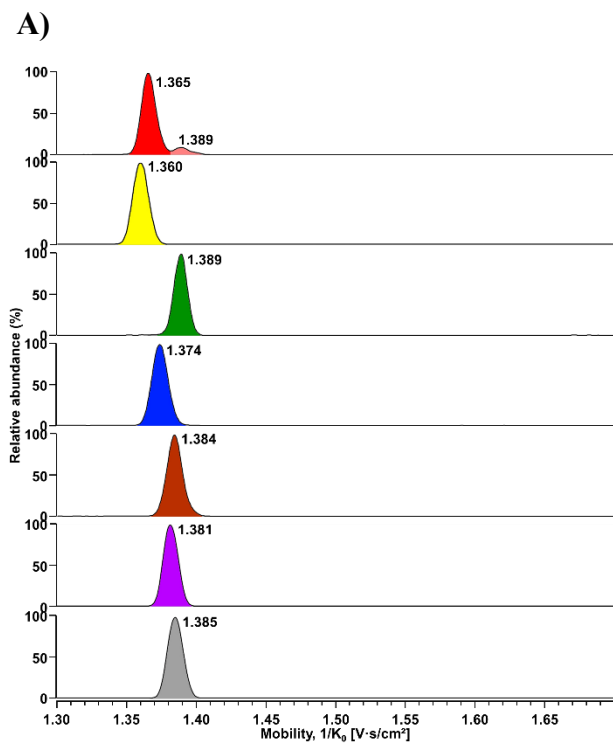


166 **Fig. 1.** Full MS spectra of α -CD (A), β -CD (B) and γ -CD (C) without salt doping.

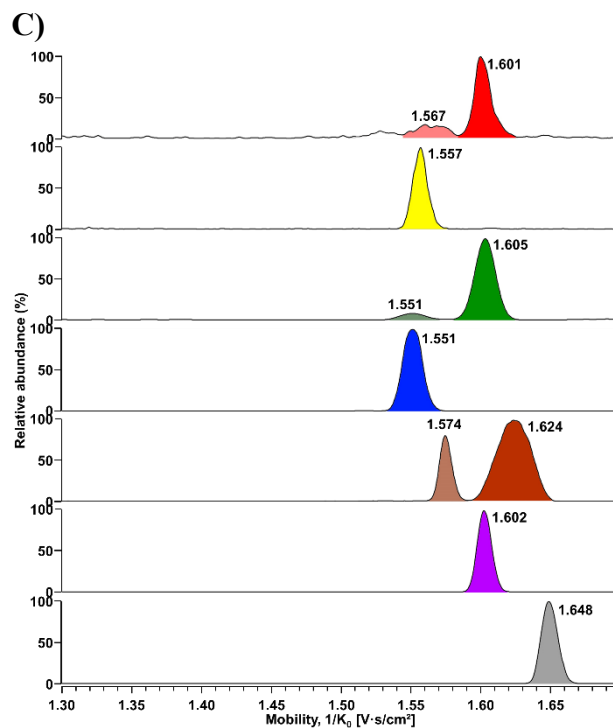
167

168 Examination of the respective extracted mobilograms leads to a couple of prominent/minor mo-
 169 bility peaks for α -CD and γ -CD with $1/K_0$ values of 1.365/1.389 and 1.601/1.567 V.s/cm², respec-
 170 tively (Fig. 2).

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189 **Fig. 2.** TIMS based mobilograms for singly charged ions [CD+X]⁺ of A) α -CD, B) β -CD and C) γ -CD.

190 Color coding for X: H (red), Li (yellow), NH₄⁺ (green), Na (blue), K (brown), Rb (violet) and Cs (grey).

191 Conversely, β -CD presents a single mobility peak at 1.535 V.s/cm² reflecting a unique stabilized
192 location of the proton. Regarding ammoniated adducts, α -/ β -CD present a single peak with $1/K_0$
193 values equal to 1.389 and 1556 V.s/cm², respectively, while for γ -CD, a couple of values at
194 1.605/1.551 V.s/cm² were observed (Fig. 2). Such result may be explained by a more pronounced
195 flexibility leading to two distinct complexes $[\gamma\text{-CD}+\text{NH}_4]^+$.

196 **3.1.2 Native cyclodextrins with alkali metals (Li, Na, K, Rb and Cs)**

197 Native CDs exhibit lone pairs which greatly favours the attachment and stabilization of alkali met-
198 als. Mobility values of singly charged α -CD gradually increase from lithium to sodium (1.360 to
199 1.374 V.s/cm²), and again with potassium (1.384 V.s/cm²), and then slightly decrease for rubid-
200 ium (1.381 V.s/cm²) before to be barely higher with cesium (1.385 V.s/cm²) (Fig. 2). As expected,
201 higher mobility values for β -CD than α -CD were measured with all alkali metals. Moreover, the
202 same increasing trend was observed for lithium, sodium and potassium (1.528, 1.538 and 1.552
203 V.s/cm², respectively). Conversely, lower values than potassium were measured with rubidium
204 and cesium (1.535 and 1.539 V.s/cm², respectively). Regarding γ -CD, except higher values than β -
205 CD, it can be noted a significant difference in the evolution of mobility values that the two previ-
206 ous CDs. If $[\gamma\text{-CD}+\text{Li}]^+$ and $[\gamma\text{-CD}+\text{Na}]^+$ are quasi-similar (1.557 and 1.551 V.s/cm², respectively), at
207 least two distinct peaks at higher mobility values were observed for $[\gamma\text{-CD}+\text{K}]^+$ (1.624/1.539
208 V.s/cm², with the latter detected as a twofold lower abundance). Similarly to α -CD and as com-
209 pared to main $[\gamma\text{-CD}+\text{K}]^+$ value, mobility peak of $[\gamma\text{-CD}+\text{Rb}]^+$ is lower (1.602 V.s/cm²) whereas that
210 of $[\gamma\text{-CD}+\text{Cs}]^+$ is the highest (1.648 V.s/cm²). From these data, and except for $[\gamma\text{-CD}+\text{K}]^+$, a single
211 mobility peak is systematically obtained for singly charged species, presumably corresponding to
212 a unique and stable complex.

213 3.2 Mobility of doubly charged monomers

214 The $[\alpha\text{-CD+H+Na}]^{2+}$ and $[\alpha\text{-CD+H+K}]^{2+}$ ions lead to a close mobility value of 0.798 and 0.791
215 V.s/cm²), respectively. With lithiated complexes ($[\alpha\text{-CD+Li+X}]^{2+}$), mobility values were lower at
216 0.747, 0.763 and 0.759 V.s/cm², for X = Li, Na and K, respectively. Interestingly for both $[\alpha\text{-}$
217 $\text{CD+2Na}]^{2+}$ or $[\alpha\text{-CD+Na+K}]^{2+}$, two couples of mobility peak were detected at 0.803/0.795 and
218 0.790/0.810 V.s/cm², respectively. Such observation suggests the existence of two distinct ter-
219 nary complexes for each ion. None doubly charged species based $\alpha\text{-CD}$ involving two potassium
220 or even one/two rubidium and cesium was detected. This is presumably due to higher ionic radii
221 ($r_i = 137, 152$ and 167 pm for K^+, Rb^+ and Cs^+ , respectively)(Haymes, Lide & Bruno, 2016) impairing
222 a good matching, with the coordination sites from this cyclo-oligosaccharide template. As ex-
223 pected, the mobility values $[\beta\text{-CD+H+X}]^{2+}$ with X = Na and K are higher than for $\alpha\text{-CD}$. Neverthe-
224 less, no significant differences occurs for the two herein $\beta\text{-CD}$ species with 0.854 and 0.855
225 V.s/cm², respectively. Such results show that $[\beta\text{-CD+H+K}]^{2+}$ as compact as $[\beta\text{-CD+H+Na}]^{2+}$ suggest-
226 ing similar coordination sites and/or flexibility of the CD. Introduction of lithium in ternary com-
227 plex leads to a single mobility peak at 0.801, 0.814 and 0.830 V.s/cm², for $[\beta\text{-CD+2Li}]^{2+}$, $[\beta\text{-}$
228 $\text{CD+Li+Na}]^{2+}$ and $[\beta\text{-CD+Li+K}]^{2+}$, respectively. Similarly, to $\alpha\text{-CD}$, for adducts with 2Na and 1Na+K,
229 two couples of mobility peaks were observed at 0.852/0.820 and 0.828/0.851 V.s/cm², respec-
230 tively. Interestingly, the $\beta\text{-CD}$ allows the formation of both $[\beta\text{-CD+2X}]^{2+}$ with X = K or Rb exhibiting
231 two distinct mobility values (0.869/0.839 V.s/cm²) for the former and a unique for the latter
232 (0.876 V.s/cm²). Concerning $\gamma\text{-CD}$, as for $\beta\text{-CD}$, only a single peak was observed for $[\gamma\text{-CD+2Li}]^{2+}$,
233 $[\gamma\text{-CD+Li+Na}]^{2+}$, $[\gamma\text{-CD+Li+K}]^{2+}$, $[\gamma\text{-CD+Na+Rb}]^{2+}$ and $[\gamma\text{-CD+2Rb}]^{2+}$ at 0.826, 0.852, 0.873, 0.900 and
234 0.878 V.s/cm², respectively. Nonetheless, instead of a unique peak for $\beta\text{-CD}$, $[\gamma\text{-CD+H+Na}]^{2+}$ and

235 $[\gamma\text{-CD} + \text{K} + \text{Rb}]^{2+}$, showed two peaks at 0.903/0.879 and 0.892/0.915 V.s/cm², respectively. As re-
236 gards other doubly charged species, very different behaviours were quoted out for γ -CD compare
237 to both α - and β - ones. Indeed, three distinct peaks were detected for $[\gamma\text{-CD} + \text{X} + \text{K}]^{2+}$ with $X = \text{H}$ or
238 K at 0.873/0.907/0.847 and 0.897/0.855/0.876 respectively. For $[\gamma\text{-CD} + \text{Na} + \text{X}]^{2+}$ with $X = \text{Na}$ or K,
239 only one value can be observed at 0.893 and 0.866 V.s/cm², respectively. Conversely to α -/ β -CDs,
240 complexes involving cesium have been successfully detected for γ -CD with only one value for $[\gamma$ -
241 CD + Na + Cs]²⁺ (0.901 V.s/cm²) and $[\gamma\text{-CD} + 2\text{Cs}]^{2+}$ (0.882 V.s/cm²) and three for $[\gamma\text{-CD} + \text{K} + \text{Cs}]^{2+}$
242 (0.876/0.890/0.899 V.s/cm²). These last results support the hypothesis that β -CD is the smaller
243 CD able to simultaneously attach two potassium. Also, a minimal number of 7 and 8 glucoses is
244 required to complex two simultaneous potassium and rubidium or cesium based doubly charged
245 species, respectively. Moreover, it was previously observed that the coulombic repulsion be-
246 tween two cations in the ternary complex is reduced for the larger size host. (Wang et al., 2010)
247 Furthermore, two, three and even four mobility peaks can be detected for a given doubly charged
248 ion. That strongly suggests the simultaneous occurrence of several more and less stable complex,
249 which can be estimated by area integration of mobility peaks.

250 **3.3 Scaling cyclodextrin/metals complexes using the collision cross section as molecular de-** 251 **scriptor**

252 After determination of ion mobility values of a given ion and by using Mason-Schamp equation
253 (see experimental section), its collision cross section (CCS) can be deducted. The relationship be-
254 tween structure and CCS has been widely used to offer insights into the structures of gas phase
255 species. More particularly, CCS provide precious pieces of information regarding size and shape
256 of the corresponding molecules. In the case of CDs, we used IM-MS to probe both size difference

257 informing on location of coordination site including more and less deep insertion in the cavity,
258 and on the shape feature which can be due to the existence of various conformational states
259 during cationization.

260 **3.3.1 Singly charged ions**

261 Protonated α -, β - and γ -CD have CCS_{N_2} equal to 276.8/282.2, 311.1 and 323.8/317.2 \AA^2 , respec-
262 tively. Herein values are very close to those reported in the literature (Table 1).(Klein et al., 2018;
263 May et al., 2014) Nonetheless, we noted that herein, α - and γ -CD exhibits two and three distinct
264 mobility peaks respectively, which can be putatively ascribed to different conformational states
265 or protomers. This was obtained thanks to the high resolution of TIMS while unique value was
266 extracted from DTIMS analysis.(Klein et al., 2018) Regarding ammonium adducts, an increase of
267 CCS according to size was observed with 282.1, 315.4 and 324.4/313.9 \AA^2 for α -, β - and γ -CD,
268 respectively. However, we noted none linearly correlation since we could expect 348.7 \AA^2 for a
269 not deformed γ -CD, but obtained values lower by ~ 24 -30 \AA^2 . From these last results, two hypoth-
270 eses can be formulated either ammonium ion can be more deeply inserted into the γ -CD cavity
271 and/or γ -CD can adopt deformed conformations due to its intrinsic flexibility. In all case, the com-
272 parison of any given ion form as a function of CD type shows an expected increase in CCS as a
273 function of increasing molecular weight and/or size (e.g. with $[M+Li]^+$, CSS is 276.1, 309.6 and
274 315.1 \AA^2 for α -, β - and γ -CD, respectively (Table 1 and Fig. S1).

275

276 **Table 1.** Characteristics of singly charged ions from α -, β - and γ -CD under alkali-metal cation com-
 277 plexes. Brackets indicate the relative content. *: large peak, ND: not detected; NC: not calculated.

Name	<i>m/z</i>		Mass accuracy (ppm)	1/ <i>K</i> ₀ (V.s.cm ⁻²)	CCS _{N₂} (Å ²)		
	Experimental	Theoretical			Experimental (n=5)	Theoretical (n=10)	Literature
[α -CD+H] ⁺	973.3207	973.3242	-3.6	1.365 /1.389 (92/8)	276.8±0.6/282.2±0.5	276.8±0.8/281.8±0.7	280.5 ^a ;285.2 ^b
[α -CD+Li] ⁺	979.3346	979.3325	2.2	1.360	276.1±0.4	276.3±0.6	
[α -CD+NH ₄] ⁺	990.3494	990.3508	-1.4	1.389	282.1±0.7	282.2±0.8	280.9 ^a
[α -CD+Na] ⁺	995.3054	995.3062	-0.8	1.374	278.9±0.4	278.8±0.5	278.2 ^a ;285.5 ^b
[α -CD+K] ⁺	1011.2812	1011.2801	1.1	1.384	281.0±0.5	280.9±0.6	280.0 ^a ;287.7 ^b
[α -CD+Rb] ⁺	1057.2269	1057.2282	-1.2	1.381	280.2±0.8	280.2±0.8	
[α -CD+Cs] ⁺	1105.2208	1105.2218	-0.9	1.385	280.8±0.9	281.2±0.8	
[β -CD+H] ⁺	1135.3751	1135.3770	-1.7	1.535	311.1±0.4	311.5±0.6	312.4 ^a ; 301.3/319.6 ^b
[β -CD+Li] ⁺	1141.3843	1141.3853	-0.9	1.528	309.6±0.6	309.9±0.8	
[β -CD+NH ₄] ⁺	1152.4027	1152.4036	-0.8	1.556	315.4±1.1	315.3±0.6	312.5 ^a
[β -CD+Na] ⁺	1157.3578	1157.3590	-1.0	1.538	311.7±0.6	311.8±0.4	309.0 ^a ;319.7 ^b
[β -CD+K] ⁺	1173.3313	1173.3329	-1.4	1.552	314.4±0.7	314.6±0.7	308.9 ^a ;320.3 ^b
[β -CD+Rb] ⁺	1219.2796	1219.2810	-1.2	1.535	310.9±0.6	311.2±1.0	
[β -CD+Cs] ⁺	1267.2733	1267.2747	-1.1	1.539	311.5±0.8	311.3±1.1	
[γ -CD+H] ⁺	1297.4280	1297.4299	-1.4	1.601/1.567 (81/19)	323.8±0.8/317.2±0.9	323.6±0.7/317.3±0.9	324.3 ^a ;322.6 ^b
[γ -CD+Li] ⁺	1303.4372	1303.4382	-0.7	1.557	315.1±0.6	314.9±0.5	317.7 ^b
[γ -CD+NH ₄] ⁺	1314.4578	1314.4564	1.1	1.605/1.551 (93/7)	324.4/313.9±0.7	324.3±0.9/314.0±1.3	324.3 ^a ;
[γ -CD+Na] ⁺	1319.4098	1319.4118	-1.5	1.551	313.9±0.8	313.8±1.0	316.0 ^a ;322.1 ^b
[γ -CD+K] ⁺	1335.3827	1335.3857	-2.3	1.624*/1.574 (77/23)	328.5±0.8/318.8±1.2	328.8±1.1/318.6±1.2	319.3 ^a ;324.8 ^b
[γ -CD+Rb] ⁺	1381.3364	1381.3383	-1.4	1.602	324.0±1.0	324.0±1.3	327.3 ^b
[γ -CD+Cs] ⁺	1429.3258	1429.3275	-1.2	1.648	333.3±1.1	333.2±1.3	338.2 ^b

278 ^a Klein et al., 2018 ^b May et al., 2014

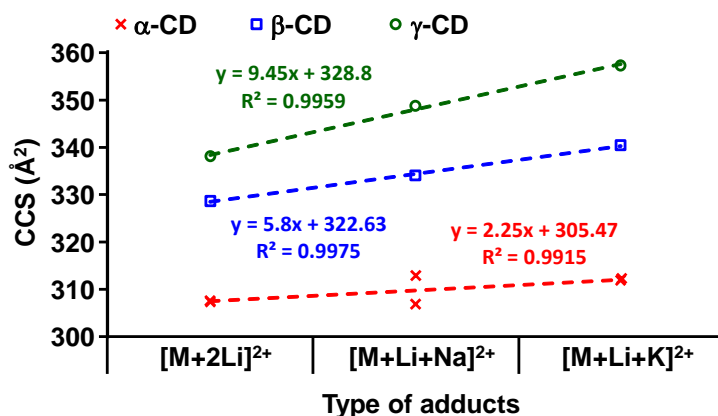
279

280 Further examination of complexes involving alkali metals, allows achievement of some observa-
 281 tions: i) with α -CD, CCS increase linearly by step of 2.8 and 2.1 Å² from Li⁺ to Na⁺ and from Na⁺ to
 282 K⁺, respectively, and then remains quite constant with Rb⁺ and Cs⁺ (Fig. S1, red star) ii) with β -CD,
 283 CCS increase linearly also by step of 2.1 and 2.7 Å² from Li⁺ to Na⁺ and from Na⁺ to K⁺, respectively,
 284 but decrease by ~3.5 Å² for Rb⁺ and drop only slightly for Cs⁺ (Fig. S1, blue square). iii) with γ -CD,
 285 measured CCS portray a completely different behaviour as a slight decrease by ~1.2 Å² occurred
 286 from Li⁺ to Na⁺ and then a drop by 4.9 or 14.6 Å² for K⁺ as two peaks were detected. Next, accord-
 287 ing to previous considered values for K⁺ a variation of -4.5/+5.2 Å² occurred for Rb⁺ and a drop by
 288 9.3 Å² from this last one to Cs⁺ (Fig. S1, green circle). Also, such a decrease in CCS observed with

289 CDs and some alkali metals compared to corresponding protonated or ammoniated forms, can
290 be tentatively explained by a greater oxophilicity - stronger coordination of the formers, as pre-
291 viously described for carbohydrates.(Fenn & McLean, 2011) In brief, CCS can be summarized as
292 a consequence of a balance between main factors: size of both cation and CD (including eventual
293 distortions) and more and less deep inclusion of the cation inside cavity (according to coordina-
294 tion features).

295 3.3.2 Doubly charged ions

296 Considering the sum of the relative intensities from all alkali metal cations-based CDs observed
297 by MS, the part of 1:2 complexes compared with 1:1 one increased constantly from α -CD to γ -
298 CD. Such trend was similar to that reported elsewhere for an increasing methylation degree on
299 β -CD.(Przybylski et al., 2015) As for singly charged species, any particular ternary complexes the
300 higher the molecular weight and/or size of CD, the higher the CCS (e.g. with $[M+2Li]^{2+}$, 307.6,
301 328.6 and 337.9 \AA^2 for α -, β - and γ -CD, respectively) (Table S1 and Fig. 3).



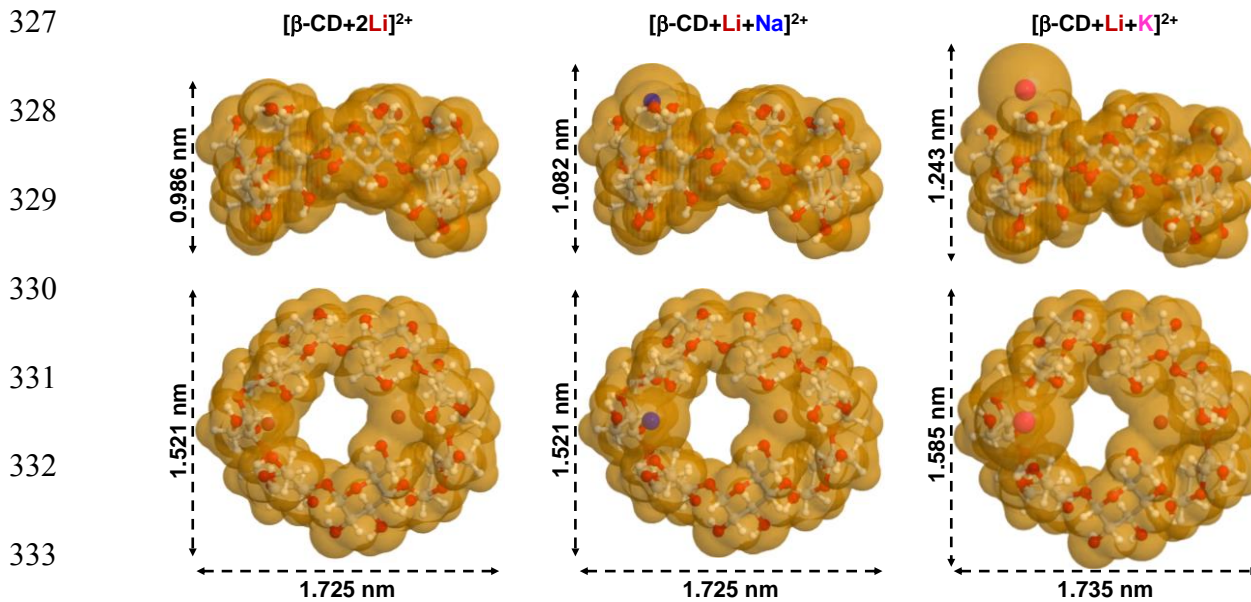
302
303 **Fig.3.** Evolution of CCS as function of doubly charged species $[CD+Li+X]^{2+}$ where X is lithium, so-
304 dium or potassium. α -CD (red cross), β -CD (blue square) and γ -CD (green circle).

305 Also, interestingly, for a given CD involving both one lithium and in the other hand an additional
306 lithium, sodium or potassium, CCS increase linearly with the size of the associated cation. Exam-
307 ination of the slope value of the resulting curve i.e. 2.25, 5.8 and 9.45 portrays a growing ampli-
308 tude in CCS drop for α -, β - and γ -CD, respectively (Fig. 3). However, such behaviour according size
309 of the cations was not obvious for all ternary complexes, even if a relative growing linearity of
310 CCS can be deducted for $[\alpha\text{-CD or } \beta\text{-CD}+\text{Na}+\text{X}]^{2+}$ and $[\alpha\text{-CD or } \beta\text{-CD}+\text{K}+\text{X}]^{2+}$ (where $X = \text{Li, Na and}$
311 K) as well as for $[\gamma\text{-CD}+\text{K}+\text{X}]^{2+}$ $[\gamma\text{-CD}+\text{Na}+\text{X}]^{2+}$ (where $X = \text{Li, Na, K and Rb}$) (Fig. S2-S5). We have
312 previously demonstrated by molecular modeling that two cations are stabilized by various coor-
313 dination sites onto the primary rim of β -CD.(Przybylski et al., 2015) For example, ternary com-
314 plexes with native β -CD including 2 Li are stabilized each one by three electron donating. Such
315 coordination landscape involves 3 oxygens of the primary rim of n , $n+1$ and $n+3$ glucose for one
316 side and $n-1$, $n-2$ and $n-3$ for the second side.(Przybylski et al., 2015) The lower bond length be-
317 tween the three proximal oxygens of doubly lithiated forms highlighted a tighter interaction of
318 the two metals than for corresponding singly charged complexes. Moreover, the coordination of
319 two cations induces a strong distortion of CDs like a spindle with cation localized at each tip.
320 Increasing CCS can be roughly visualized using Van der Waals (WDV) radii for each atom of the
321 molecule, in other words VDW surface through which the molecule might be conceived as inter-
322 acting with other ones. Examples of VDW surface were given for the three axis of $[\beta\text{-CD}+\text{Li}+\text{X}]^{2+}$
323 (where $X = \text{Li, Na or K}$) (Fig. 4).

324

325

326



334 **Fig. 4.** Van der Waals surface of $[\beta\text{-CD}+\text{Li}+\text{X}]^{2+}$ (where $\text{X} = \text{Li}, \text{Na}$ or K) from ball and stick model of
 335 optimized models of complexes with x,y axis (bottom view) and z-axis side (top view).

336

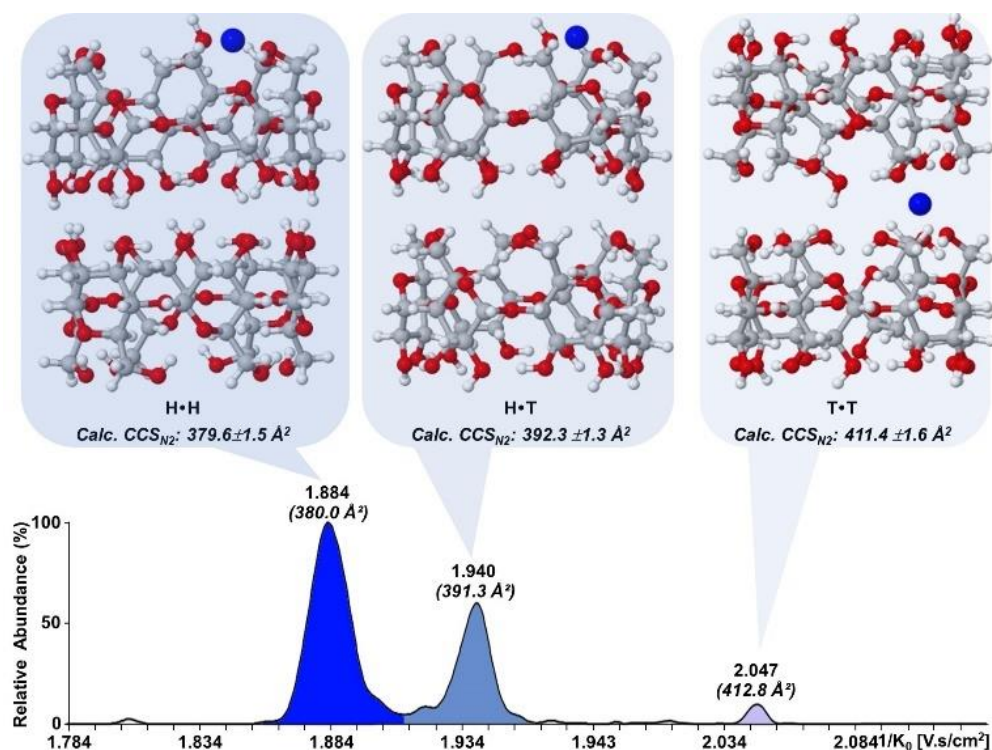
337 Such last examples depict well the possible differences portraying the linear increase of the CCS
 338 values where only length on the z axis increases while those of x, y axis remain constant from $[\beta\text{-}$
 339 $\text{CD}+\text{Li}+\text{Li}]^{2+}$ to $[\beta\text{-CD}+\text{Li}+\text{Na}]^{2+}$ and then length of the three axis enlarge from $[\beta\text{-CD}+\text{Li}+\text{Na}]^{2+}$ to
 340 $[\beta\text{-CD}+\text{Li}+\text{K}]^{2+}$.

341

342 **3.4 Study of multimeric assemblies of cyclodextrins**

343 Literature described that CD can form aggregates with various shapes but based on only 2 types
 344 of molecular arrangements: clustered cage or channel.(Saenger et al., 1998) Nevertheless, prob-
 345 ability to form disordered assemblies prevails from concentration in the millimolar

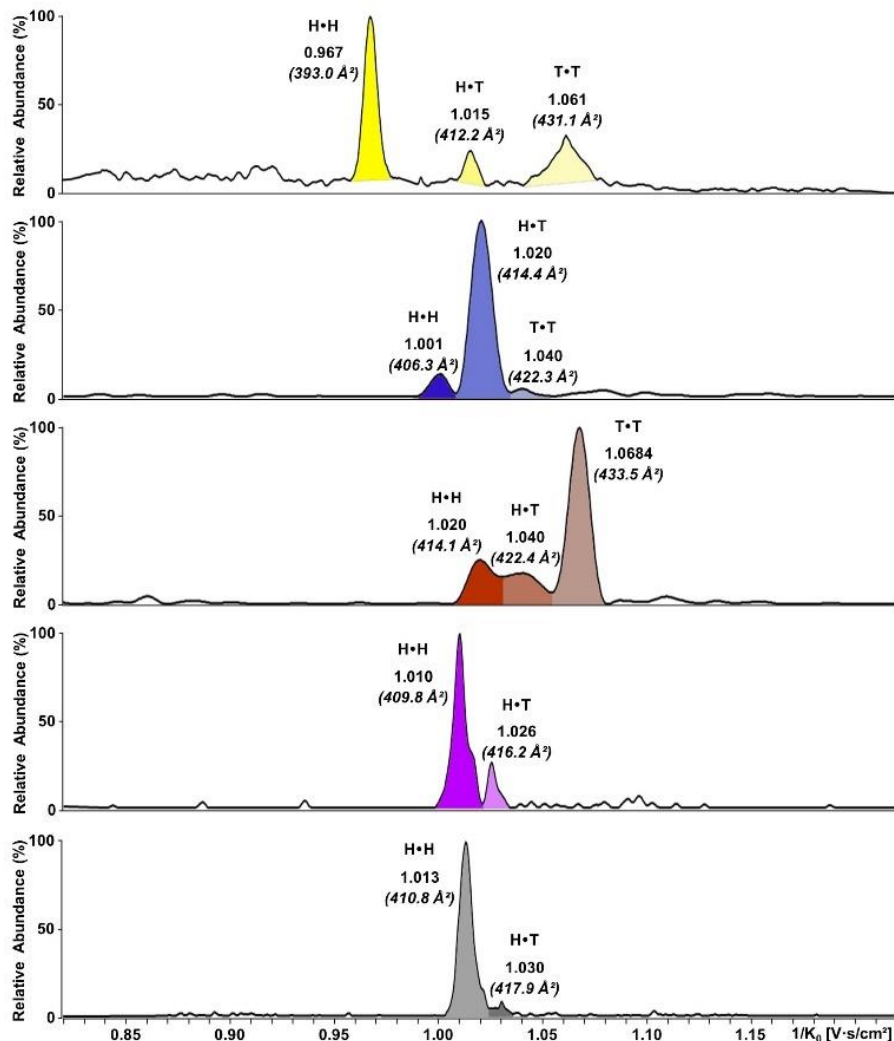
346 range.(Messner et al., 2010) Nevertheless, in our study, we used diluted solution (one micromo-
 347 lar) which must favour formation of ordered assemblies. All the CD have the shape of a basketball
 348 net, including a large (head, H) and a small (tail, T) aperture. In tubular arrangements of CDs, they
 349 can interact among themselves according to three possible orientations: Head-to-Tail (H•T),
 350 Head-to-Head (H•H) or Tail-to-Tail, (T•T).(Staelens et al., 2015) Such organization is the result of
 351 the formation of several intermolecular hydrogen bonds constituting the main driving force for
 352 holding and stabilizing two or more units together.(Nascimento et al., 2005) As example, we have
 353 investigated the ion mobility traces of the singly charged ion at m/z 1967.6199 ascribed to $[(\alpha-$
 354 $CD)_2+Na]^+$ and deduced corresponding CCS values (Fig. 5).



355
 356 **Fig. 5.** TIMS based mobilogram for the singly charged dimer of α -CD $[(\alpha\text{-CD})_2+Na]^+$ revealing the
 357 three orientations as H•H (bright k blue), H•T (steel blue) and T•T (clear blue).

358

359 Examination of the mobilogram revealed two main peaks at 380.0 and 391.3 Å² and one minor
360 one at 412.8 Å². These values are in very good agreement with theoretical CCS calculated for H•H
361 (379.6±1.5 Å²), H•T (392.3 ±1.3 Å²), and T•T (411.4±1.6 Å²) assemblies, respectively. Such results
362 demonstrated that TIMS can successfully discriminate the three possible orientations of mono
363 sodiated dimers of CDs. Efficiency of separation can be defined with resolving power (*R*) of a
364 given mobility peak and also with peak-to-peak resolution (*r*). Here, the values were equal to
365 109/141/282 and 1.8/5.1 depicting both high *R* and *r*. Also, by approximating that equal ioniza-
366 tion efficiencies take place and that relative abundance of the overall spectrum could be inter-
367 preted as a good image of the solution content, we can estimate content of mono-sodiated spe-
368 cies of H•H, H•T and T•T α-CD dimers as 59, 35 and 6%, respectively. Such content is in good
369 agreement with stability order obtained from molecular dynamics (MD) simulations (T•T < H•T <
370 H•H).(Bonnet et al., 2001) Regarding doubly charged species with the two same cations, the na-
371 ture of the cation leads to contrasted results in terms of both *r* and *R*, which rely on their ability
372 to detect and also to discriminate the different orientations as well as their respective content.
373 Results for $[(\alpha\text{-CD})_2+2X]^{2+}$ with X=Li, Na, K, Rb or Cs were given in Fig. 6.



374

375 **Fig. 6.** TIMS based mobilograms for the doubly charged dimer of α -CD ($[(\alpha\text{-CD})_2\text{X}]^{2+}$) revealing

376 the possible orientations (H•H, H•T and T•T). Color coding for X: Li (yellow), Na (blue), K (brown),

377 Rb (violet) and Cs (grey).

378

379 In details, double adduction with lithium allows to easily highlight the presence of the three pos-

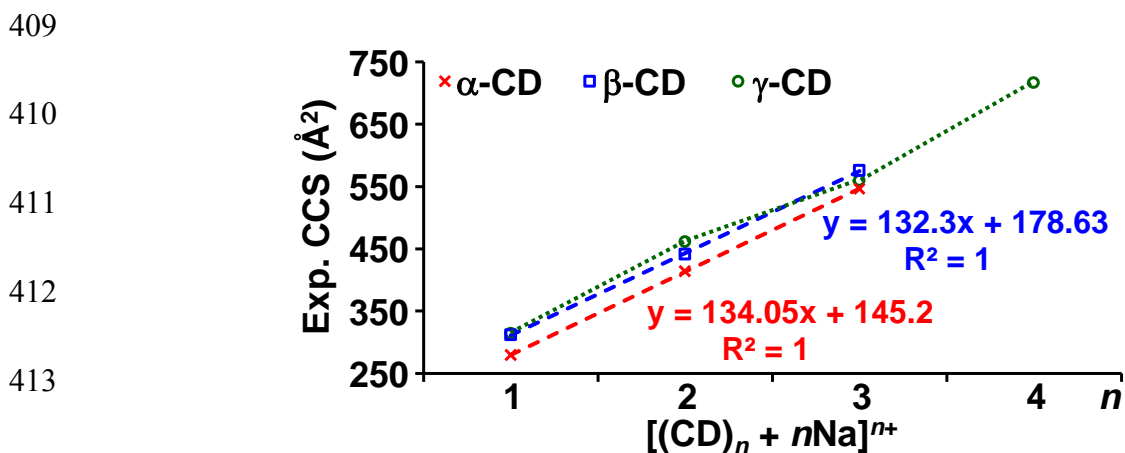
380 sible orientations (H•H, H•T and T•T) of α -CD dimer with both R equal to 138, 127 and 71, re-

381 spectively, and r of 3.2 (H•H to H•T) and 2.0 (H•T to T•T). With two sodium or two potassium, r

382 strongly decreases to 0.8/1.0 and 0.5/0.8 for H•H to H•T/H•T to T•T, respectively. The same trend

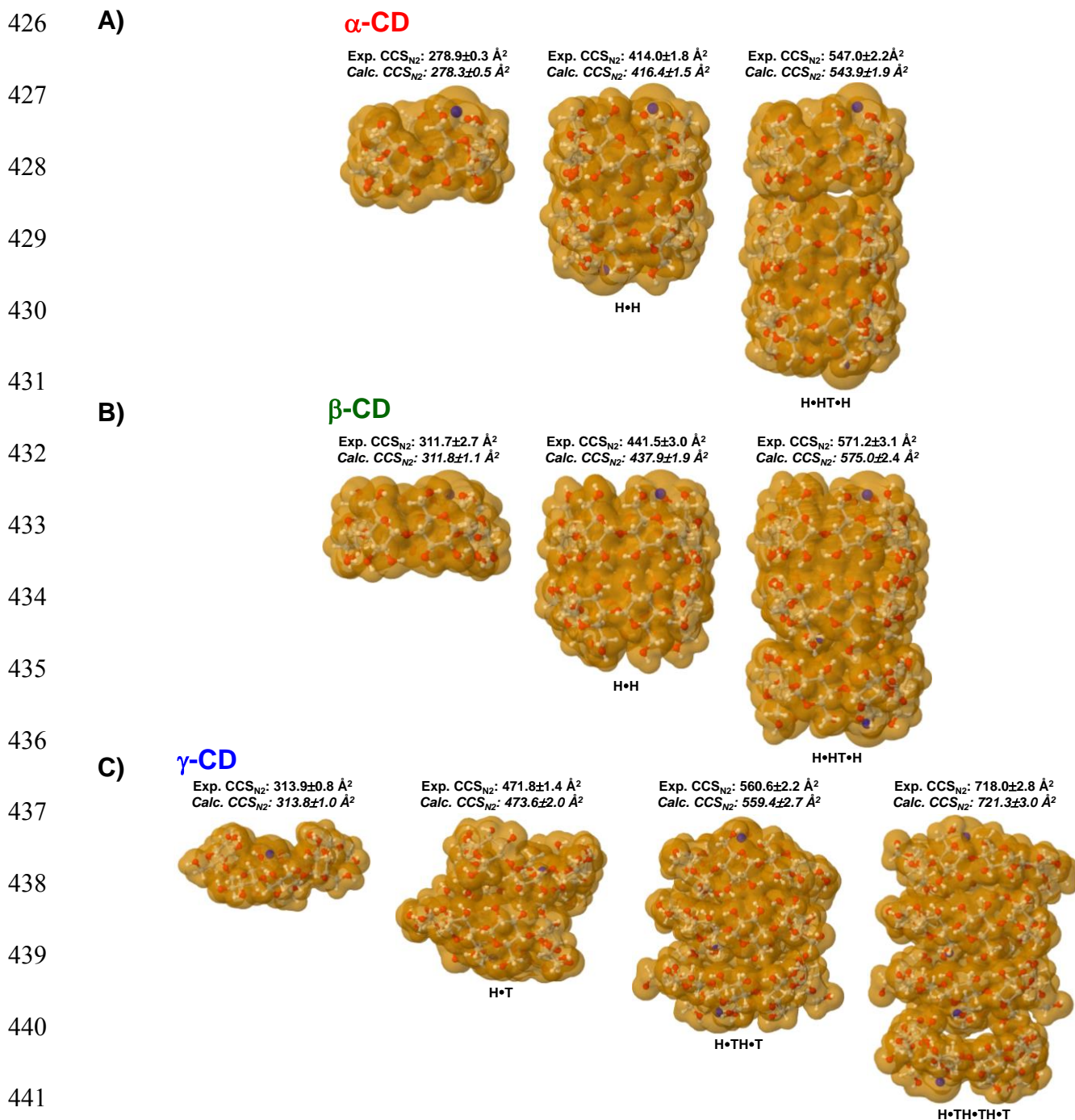
383 was noted regarding R with values for the mobility peak of the three orientations of 80/85/145
384 and 65/47/92, respectively. Introduction of rubidium lead to detection of only two orientations
385 i.e. H•H and H•T with satisfactory R (141/174) and r (1.2). Such data strongly suggest that the T•T
386 dimer of $[(\alpha\text{-CD})_2+2\text{Rb}]^{2+}$ cannot be formed and/or stabilized in the gas phase. Similar results
387 were obtained with cesium leading to the two dimers: H•H and H•T with close R (133/138) and r
388 (1.1), and a lesser content of the latter orientation as compared to Rb (9 vs 22%). Interestingly, R
389 and r from $[(\alpha\text{-CD})_2+2\text{Na}]^{2+}$ are both lower than $[(\alpha\text{-CD})_2+\text{Na}]^+$ (109/141/282 vs 80/85/145 and
390 0.8/1.0 vs 1.8/5.1). Moreover, difference in CCS of the latter vary from 11.3 Å² and 21.5 Å² for
391 H•H to H•T and H•T to T•T, respectively, while it is constant (8 Å²) for the former. Such results
392 support the hypothesis that the presence of two sodium acts as a more structuring agent than
393 only one, presumably by compacting dimer to minimize natural intrinsic difference resulting from
394 the different orientations. We have demonstrated that for a given CD, the type of adducted cat-
395 ions strongly influences the discrimination ability, but a given cation do not act with the same
396 beneficial/detrimental balance according to the studied CD. For example, the smallest alkali
397 metal studied herein, lithium led to the high-resolution during analysis of $[(\alpha\text{-CD})_2+2\text{Li}]^{2+}$ (Fig. 6),
398 while $[(\beta\text{-CD})_2+2\text{Li}]^{2+}$ and $[(\gamma\text{-CD})_2+2\text{Li}]^{2+}$ only revealed two dimers namely H•H and H•T exhibiting
399 R equal to 124/88 and 160/123, respectively, but also with r of 3.5 and 2.1, respectively (Fig. S6).
400 Conversely, with the largest studied alkali metal, cesium, $[(\alpha\text{-CD})_2+2\text{Cs}]^{2+}$ exhibits only H•H and
401 H•T dimers (R : 133/138 and r : 1.1) while the analysis of $[(\beta\text{-CD})_2+2\text{Cs}]^{2+}$ unambiguously showed
402 the presence of the three possible orientations H•H, H•T and T•T (R : 286:82/129 and r : 1.4/1.3)
403 respectively (Fig. S7). Finally, a single peak with an important tailing, leading to low R (96), was
404 obtained for $[(\gamma\text{-CD})_2+2\text{Cs}]^{2+}$. Such peak was mainly ascribed to H•T by computational methods,

405 and the tailing is presumably due to the detection and/or separation difficulty of the other di-
 406 mers, due to aforementioned high distortion ability of γ -CD and existence of several conformers.
 407 To explore the influence of the number (n) of CDs/charge state couple on the formation of small
 408 oligomers, we draw experimental CCS as function of $[(CD)_n + nNa]^{n+}$ (Fig. 7).



415 **Fig. 7.** Evolution of the experimental collision cross section as a function of $[(CD)_n + nNa]^{n+}$ ions
 416 where n is both the number of CDs, the number of adducted sodium and the charge state. α -CD
 417 (red cross), β -CD (blue square) and γ -CD (green circle).

418 In the case of a non-driven CDs aggregation, resulting CCS should be randomly distributed. Con-
 419 versely, in the case of well-ordered supramolecular assemblies with a tubular topology assimi-
 420 lated to a cylinder or a compact near-spherical nucleation, expected CCS fitting should be near a
 421 fully linear or involving a modular exponentiation. (Hanozin et al., 2019; Ruotolo et al., 2008)
 422 Herein, we obtain a linear fit for α - and β -CD for 1- to 3-mer portraying both a well-organized
 423 into a hierarchical assemblies consecutive to stacked CDs and a structuring role of sodium. Such
 424 observations were confirmed by theoretical CCS calculation of single CDs and their supramolec-
 425 ular assemblies (Fig. 8A-B).



442 **Fig. 8.** Illustration of the incremental construction of the cyclodextrins based tubular assemblies.
 443 Van der Waals surface from Ball and stick model of optimized models (A) $[(\alpha\text{-CD})_n+n\text{Na}]^{n+}$, (B) $[(\beta\text{-}$
 444 $\text{CD})_n+n\text{Na}]^{n+}$ and (C) $[(\gamma\text{-CD})_n+n\text{Na}]^{n+}$ (where $n = 1, 2, 3$ or 4 for mono-, di-, tri and tetramer). Exper-
 445 imental ($n=5$) and theoretical ($n=10$) collision cross section are indicated above structures.

446 γ -CD and its short oligomers containing until 4 units show a different behaviour. Firstly, based on
447 a semi-rigid conformation behaviour similar to α - and β -CD, expected CCS of $[\gamma\text{-CD}+\text{Na}]^+$ should
448 be $\approx 348.7 \text{ \AA}^2$, but an experimental value of $313.8 \pm 1.0 \text{ \AA}^2$ was obtained. Such discrepancy can be
449 tentatively explained by a distortion of γ -CD. Indeed, it was mentioned in literature that when
450 size of CD increase, probabilities of band flip and kinks occurrence are growing. (Jacob et al., 1999;
451 Saenger, 1980; Steiner & Saenger, 1998) In this sense, MD simulations have previously given ev-
452 idences that γ -CD exhibits two diametrically opposed glucoses (between n and $n \pm 4$ unit), which
453 are flipped by $\sim 180^\circ$, leading to elliptical and curved structures with a quite narrow, slit-like cav-
454 ity. (Bonnet et al., 2001, 2002; Suárez & Díaz, 2017) Based on the model from Bonnet *et*
455 *al.*, (Bonnet et al., 2001, 2002) three glucoses are folded toward the cavity leading to the for-
456 mation of intramolecular O6-H6 \cdots O6 by their corresponding primary hydroxyl groups. Such ori-
457 entation of some groups from the primary rim strongly supports the coordination of the sodium
458 cation (Fig. 8C). Secondary, slope between 2 and 3 CD is lower than that observed between both
459 1 to 2 and 3 to 4 CDs (Fig. 7). Similar trends were observed for $[(\text{CD})_n + nX]^{n+}$ with $X = \text{Li}, \text{K}$ and Rb
460 (Fig. S8-S10). Interestingly one exception occurred for $[(\gamma\text{-CD})_n + n\text{Cs}]^{n+}$ where a linear fit can be
461 calculated from mono to tetramer, presumably to a more structuring role of Cs during nanotubes
462 formation (Fig. S11). As previously observed, the most stable dimer was assigned to H•H assem-
463 bly whatever CD. (Bonnet et al., 2001) Differently to α - and β -CD, due to the incurved ellipsoidal
464 conformation of γ -CD, such dimer corresponds to superimposed irregular bowls with slightly dif-
465 ferent orientation of $\sim 90^\circ$ along z axis close to structure reported by Bonnet *et al.* (Bonnet et al.,
466 2001) Moreover, such structural arrangement favours a closer contact between each CD and en-
467 hances the inter-oligosaccharides van der Waals' stabilization. Furthermore, previous studies

468 have demonstrated that favourable elongation of γ -CD based tubular arrangements corresponds
469 to a decrease of the potential energy value of the tubes per CD unit as a function of the number
470 of CDs.(Staelens et al., 2015) The important flexibility of γ -CD leads to a more compressed stacked
471 assembly during the trimer formation compared to α - and β -CD where a quite more incremental
472 addition of monomer of semi-rigid structure seems to take place. Such phenomenon can explain
473 why the CCS difference between di- (H•H) and trimer (H•TH•T) is by far lower than from mono-
474 to dimer. Then starting for a compressed trimer, an additional γ -CD can be associated leading to
475 an orientated growing of the supramolecular chain by formation of a 4-mer (H•TH•TH•T). Inter-
476 estingly, slope of the curve between CCS of 3-mer and 4-mer is strictly identical than that be-
477 tween 1-mer to 2-mer suggesting a similar assembly elongation process.

478

479 **4. CONCLUSIONS**

480 It was unambiguously demonstrated in this work that hyphenation with high resolution TIMS
481 represents a powerful and suitable tool to differentiate various non covalent complexes between
482 α -, β - and γ -CD with both various alkali metals or between their self-assemblies. Indeed, cyclo-
483 oligosaccharides, as cyclodextrins, are well known to be more rigid than linear or branched ones,
484 suggesting a low probability of several stable attachment sites for the alkali cations. This
485 prompted us to think that detection of two or more mobility peaks, especially for γ -CD, can be
486 rationally ascribed to the presence of different conformers. Indeed, the distinct deducted CCS
487 portrayed well the various size and shape of the CD based complexes, which results as a conse-

488 quence of a balance between size of both cationized metal (ionic radii) and CD (including even-
489 tual distortions) and more and less deep inclusion of the cation inside CD cavity (according to
490 coordination features). Moreover, experimental data have been adequately correlated with the-
491 oretical models. In this sense, TMS can be particularly attractive to be used as a suitable molec-
492 ular descriptor to enlighten parameters affecting the recognition process, to study the first
493 sphere coordination behaviour as well as rationalization of the catalytic activities based on CD-
494 metal supramolecular assemblies. On the other hand, TMS was also particularly efficient to high-
495 light the presence and the identity of various orientations of the different constituent CD within
496 hierarchical assemblies' nanotubes as well as to estimate their relative content. According to
497 added metals, it was possible to reveal and discriminate such supramolecular edifices involving
498 secondary/secondary hydroxyl groups (head-to head, H•H), primary/secondary rim (head-to-tail,
499 H•T) hydroxyl groups or primary/primary rim (tail-to-tail, T•T) hydroxyl groups interactions. Such
500 results constitute an important milestone since, at our knowledge, it is the first experimental
501 evidences of the existence of various orientations, which until now have been only investigated
502 by theoretical approaches. The present work paves the way for a better understanding of the
503 topology from cyclo-oligosaccharides based supramolecular complexes, which could of course
504 involve both other metals *viz* transition, post-transition rare earth or noble one, but also other
505 cyclo-oligosaccharides based self-assemblies with or without any (bio)chemical modifications.

506 **CONFLICTS OF INTEREST**

507 The authors declare that they have no known competing financial interests or personal
508 relationships that could have appeared to influence the work reported in this paper.

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