

Mass Spectrometric Differentiation of Topological Isomers of Macrocyclic Compounds

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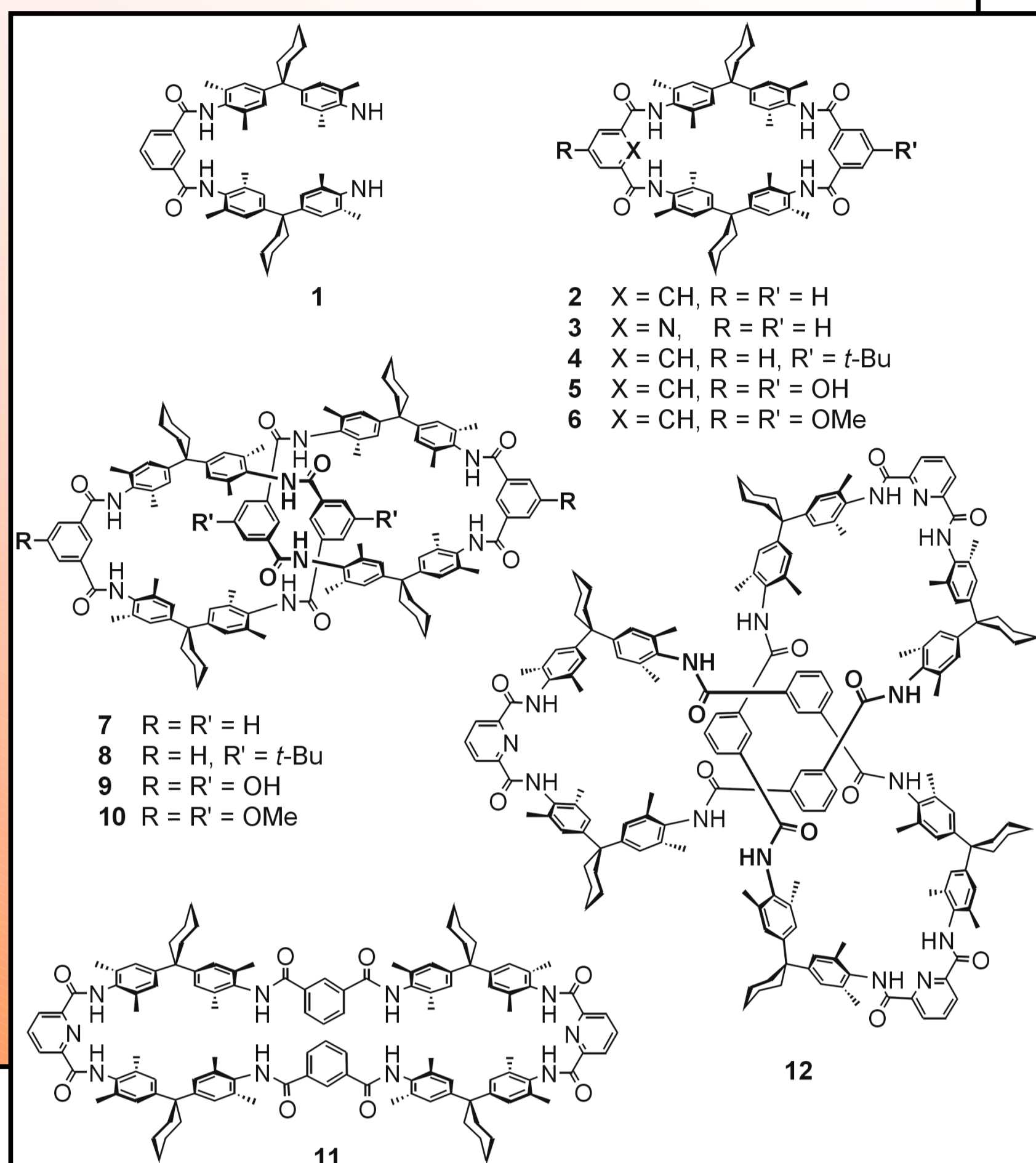
I. The Problem: Distinguishing Topologies

Macrocycles, catenanes, and knots are formed from the same building blocks during synthesis

Due to often complex spectra, NMR analysis is of limited help in distinguishing interlocked from non-interlocked topologies; small differences exist, but are not always easy to analyze

A rapid and simple method to solve this problem would be invaluable for the synthetic chemist, when new variants of such macrocyclic species are prepared

Mass spectrometry provides access to the fragmentation pattern in tandem MS experiments, which permit the collisional activation of the complexes under study

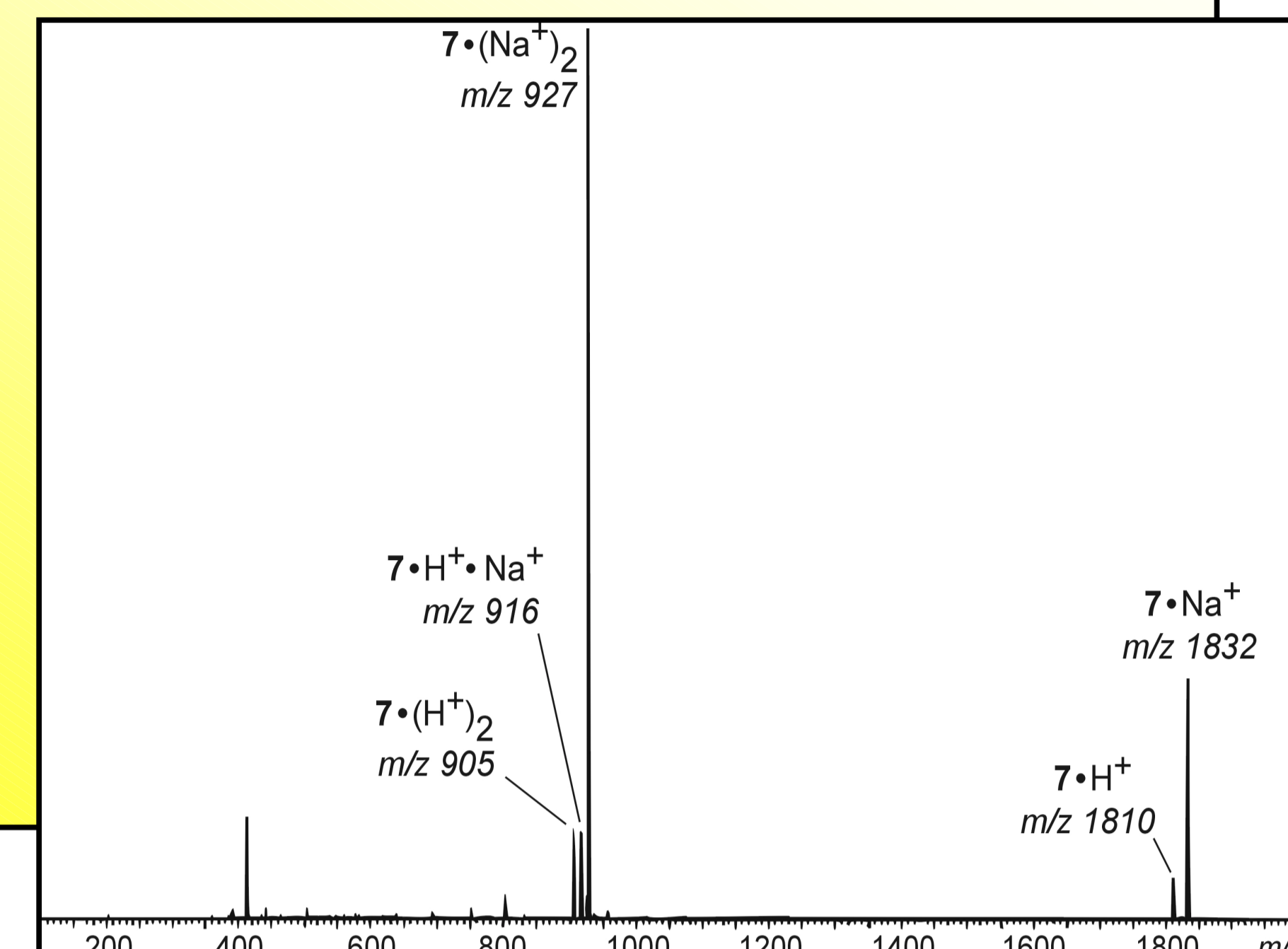


II. Typical Nanospray Ionization Mass Spectrum

Typically, tetralactam macrocycles **2 - 6** yield predominantly singly charged (protonated, sodiated) ions; larger species such as catenanes **7 - 10** also give rise to pronounced signals for doubly charged ions

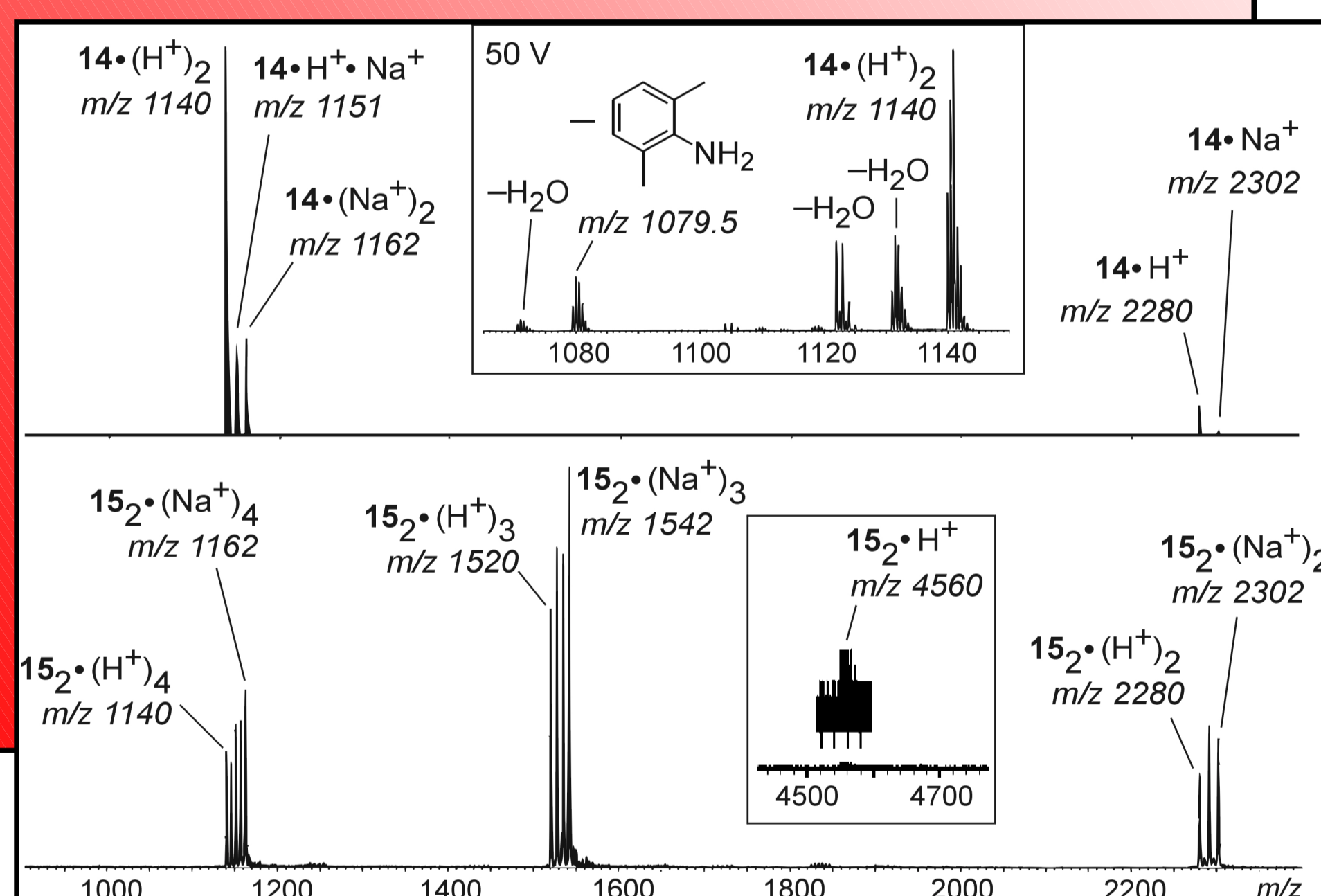
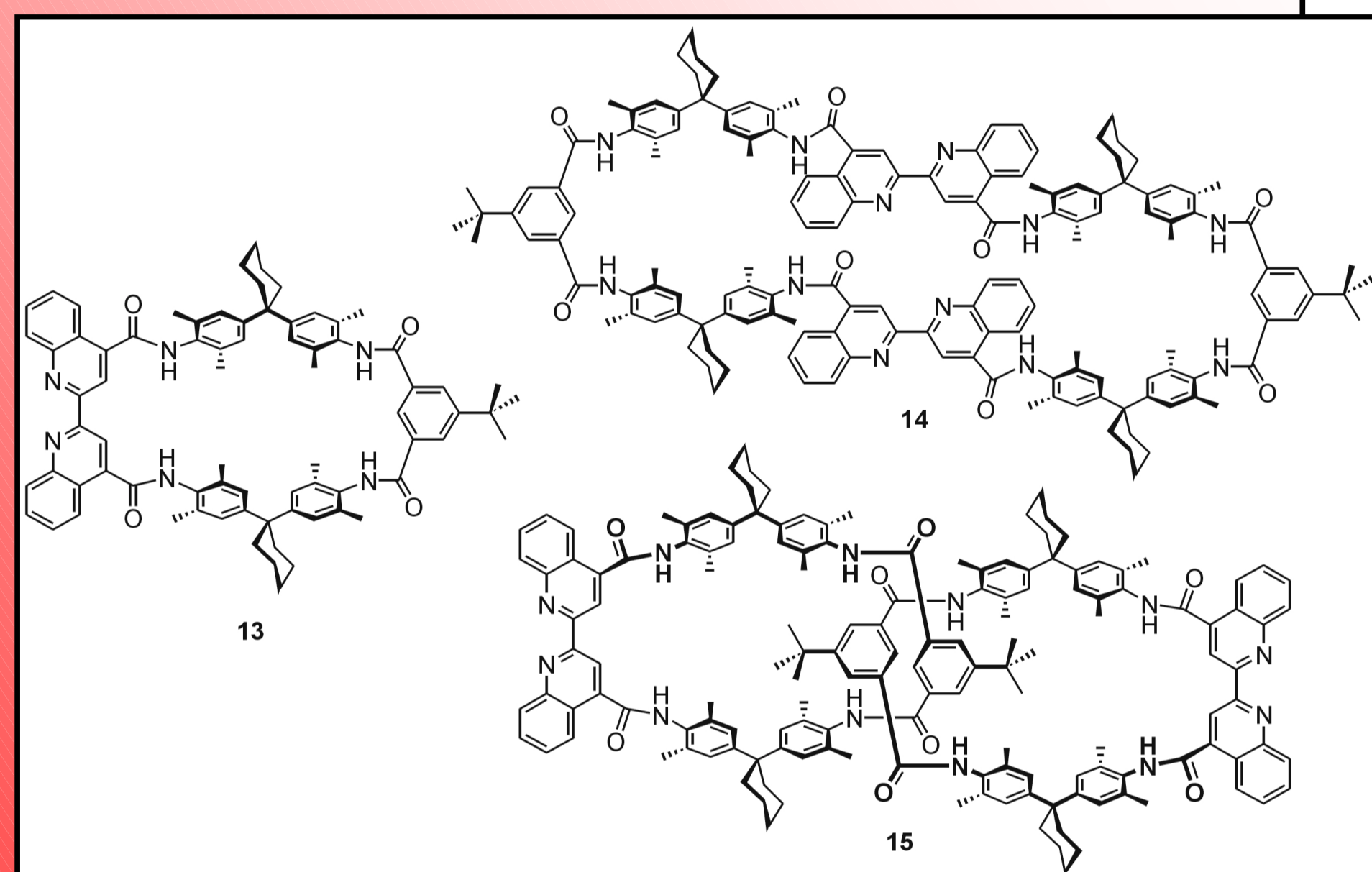
Relative abundances of singly and doubly charged ions, however, depend much on the exact experimental conditions

For most compounds, differentiation of different topologies is thus impossible through the ESI mass spectra alone



III. Bisquinoline-Substituted Catenane and Macrocycle

While macrocycle **14** is ionized as singly and doubly charged monomers, catenane **15** dimerizes and yields doubly to triply charged ions upon ESI-MS: Differentiation possible here!



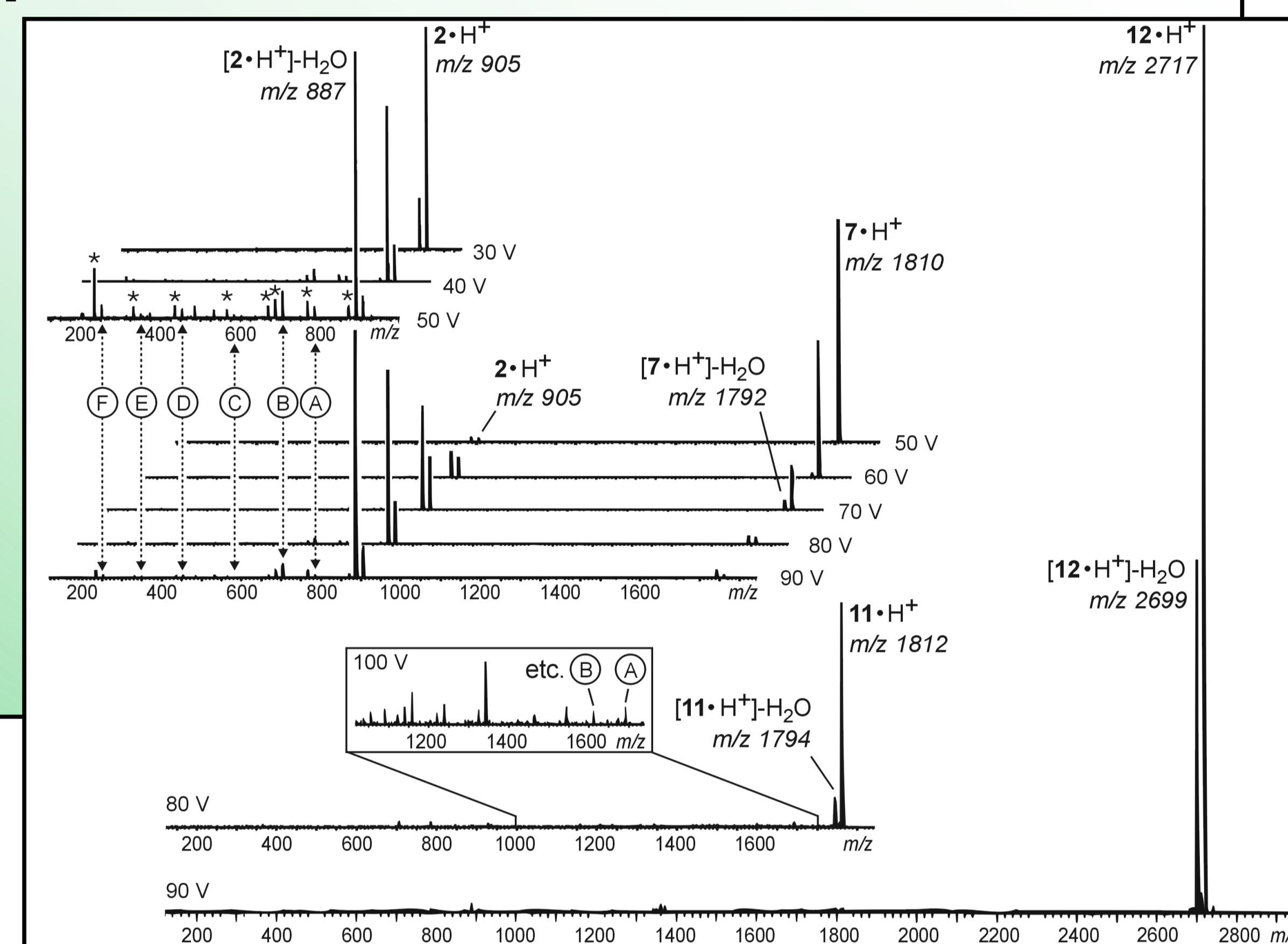
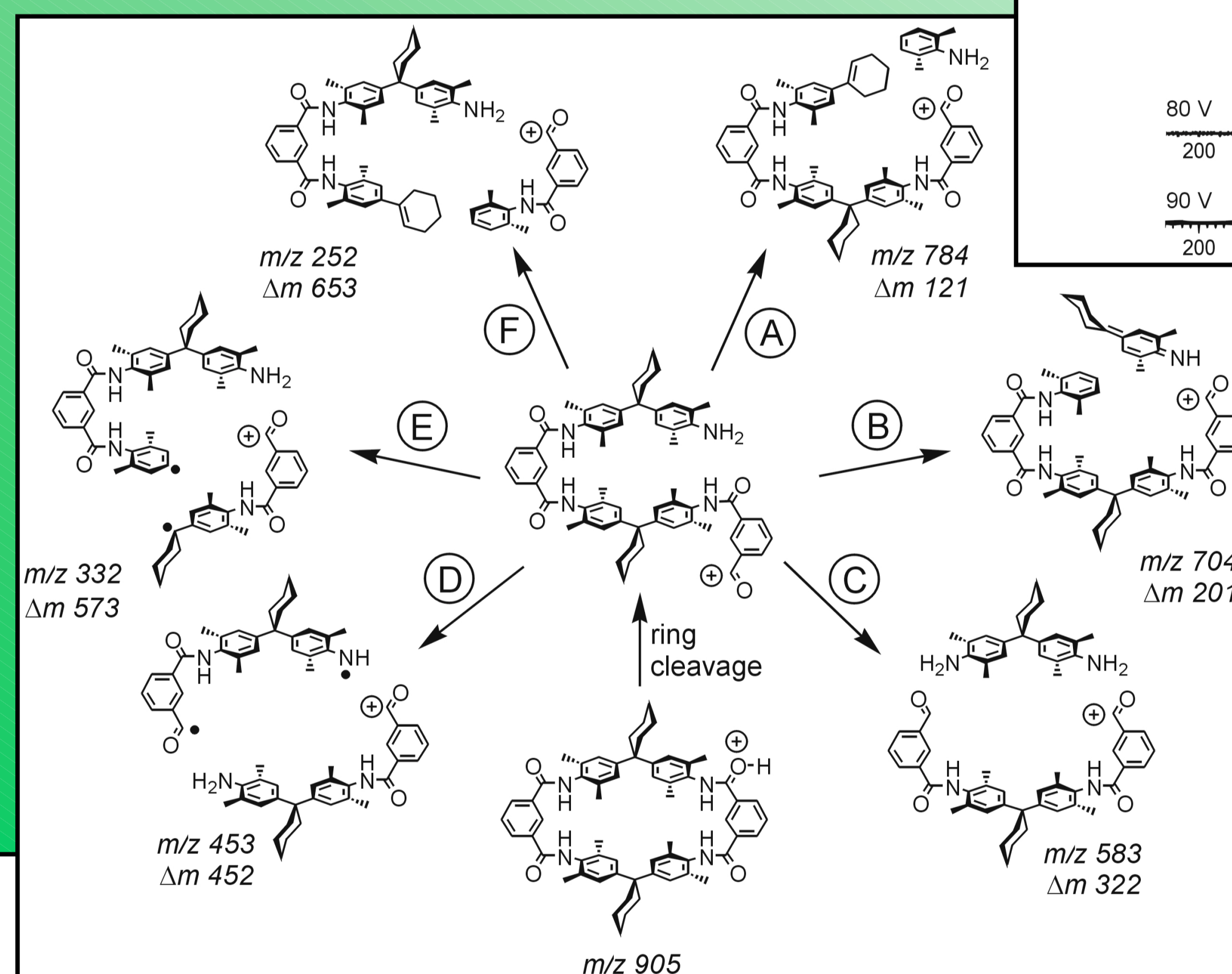
IV. Tandem Mass Spectrometry: Fragmentation Patterns

Collisional activation of singly protonated species allows us to distinguish mono-macrocycles from catenated topologies

The fragmentation channel of lowest energy is water loss from the protonated amide group for all monocyclic species

The catenanes instead undergo ring cleavage followed by deslippage of the second wheel; loss of half the catenane is then followed by water loss

At higher collision energies, fragmentation of further benzylic and amide bonds are observed (fragmentation channels A-F) from ring-opened species

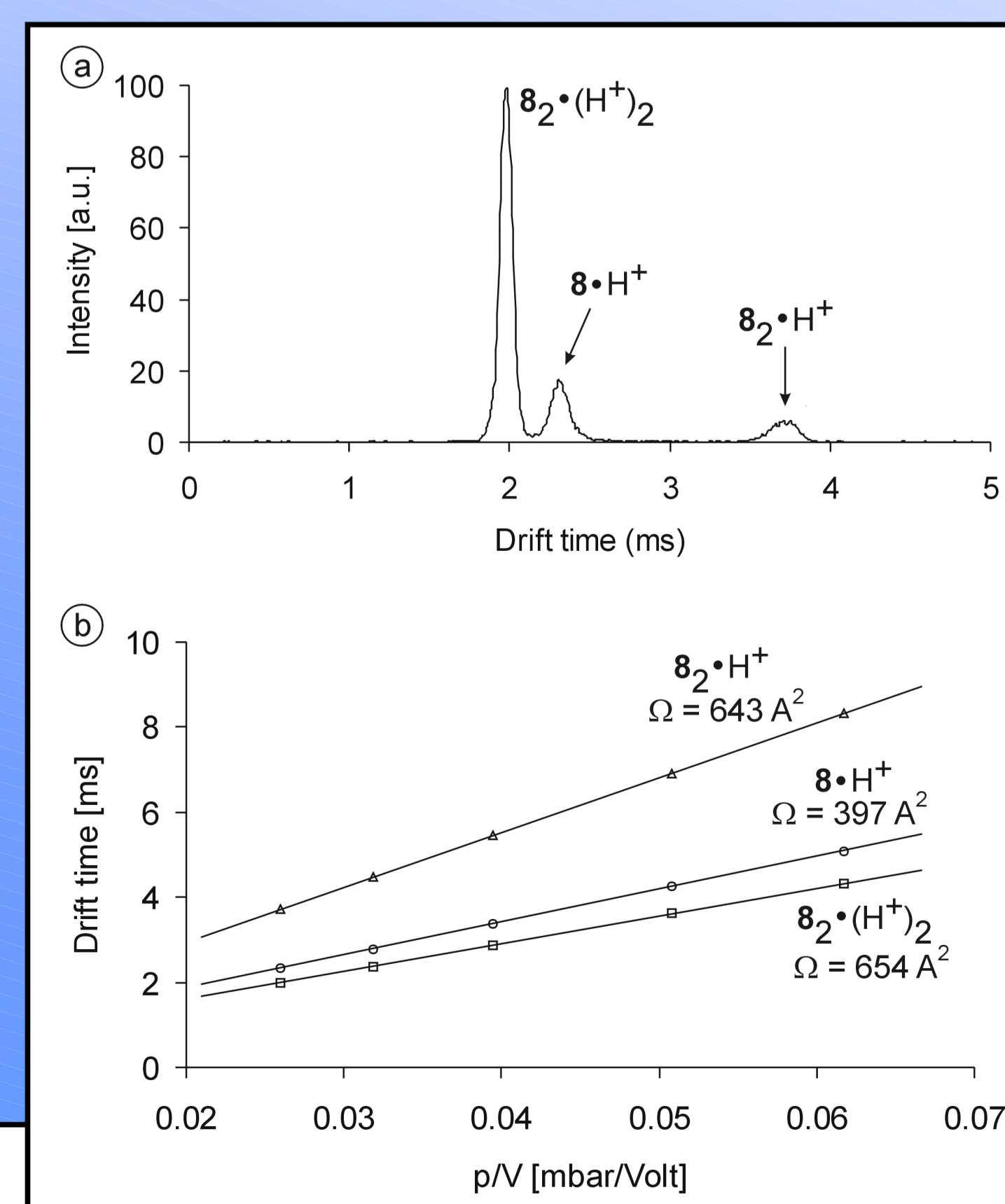


Catenanes do not show any of these fragmentations occurring directly from the parent ion; they appear only after loss of one of the macrocycles

Octalactam macrocycle, however, reveals analogous fragmentation processes of the parent ion itself

While protonated catenane **7H+** is almost completely destroyed at 80V acceleration voltage, macrocycle **11H+** is still abundant: More energy is needed for the cleavage of two covalent bonds here

V. Ion Mobility Experiments: Distinguishing Knot and Unknot?



The problem remains, how the knot and the unknot (non-intertwined dodecalactam macrocycle) can be distinguished by mass spectrometry; both are mono-macrocycles and thus should show rather similar fragmentation patterns, in particular since both would produce the same ion after ring cleavage

Ion mobility experiments permit the determination of collision cross sections for the ions under study through arrival time measurements in a helium-filled drift tube

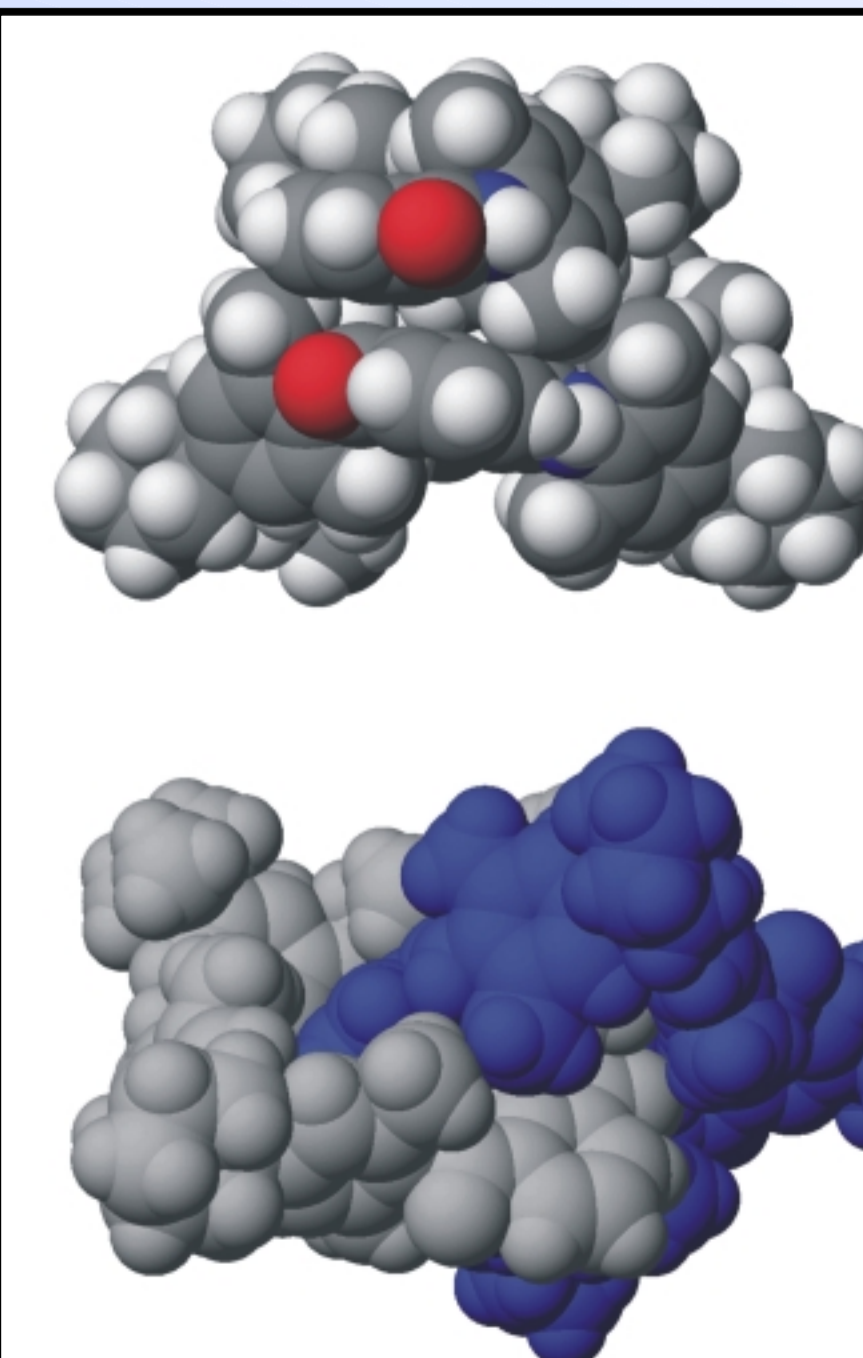
Comparison of these collision cross sections with those determined from molecular dynamics simulations of the macrocycles, catenanes, and knots shows good agreement between experiment and theory

Due to self-solvation in the gas phase, octalactam macrocycle **11** forms a quite densely packed structure; its collision cross section does not differ much from that of the intertwined catenane **7**

Catenanes and macrocycles can thus better be distinguished by their fragmentation patterns rather than ion mobility experiments

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substance	formula	exp. collision cross section	theor. collision cross section
tetralactam macrocycles			
unsubst.	C ₆₀ H ₆₄ N ₄ O ₄ -H ⁺	225 Å ²	231 Å ²
pyridine	C ₅₉ H ₆₃ N ₅ O ₄ -H ⁺	227 Å ²	230 Å ²
t-butyl	C ₆₄ H ₇₂ N ₄ O ₄ -H ⁺	244 Å ²	248 Å ²
(OH) ₂	C ₆₂ H ₆₈ N ₄ O ₆ -H ⁺	249 Å ²	245 Å ²
catenanes			
unsubst.	C ₁₂₀ H ₁₂₈ N ₈ O ₈ -H ⁺	371 Å ²	364 Å ²
t-butyl	C ₁₂₈ H ₁₄₄ N ₈ O ₈ -H ⁺	397 Å ²	400 Å ²
(OH) ₄	C ₁₂₄ H ₁₃₆ N ₈ O ₁₂ -H ⁺	391 Å ²	385 Å ²
octalactam macrocycle			
pyridine	C ₁₁₈ H ₁₂₆ N ₁₀ O ₈ -H ⁺	362 Å ²	381 Å ²
knotted and non-knotted dodecalactam macrocycles			
knot	C ₁₇₇ H ₁₈₉ N ₁₅ O ₁₂ -H ⁺	497 Å ²	499 Å ²
unknot	C ₁₇₇ H ₁₈₉ N ₁₅ O ₁₂ -H ⁺	-	541 Å ²

The calculated cross sections for knot and unknot are however significantly different; thus, it should be possible to distinguish these two topological isomers by ion mobility experiments

Unfortunately, the synthesis of the unknot has not been successful so far, so that no experimental data can be given here