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Impact of resonant excitation parameters on the intra-complex gas phase HDX within small non-covalent systems

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OVERVIEW

Objective

Exploring unexpected H/D exchanges (<HDX>) between the partners of small sodiated non-covalent complex (NCC) anions constituted by fructose 6-phosphate (F6P) and arginine (R) for distinguishing between their solvated salt (SS) and hydrogen bonded (HB) forms.

Methods

Negative ESI MS and MSⁿ experiments (resonant, CID vs. non-resonant, HCD) on deuterated sodiated NCC anions F6P/R/Na as function of excitation time (ExcTime) and normalized collision energy (NCE).

Main observations

Increase in degree of complementary enrichment(+D)/depletion(-D) HDX in the partners of NCC under CID conditions by increasing excitation parameter values (ExcTime, ExcQ and NCE) in contrast to HCD characterized by approximately the same HDX_{unexp}/HDX_{exp} ratio likely due to unusual hydride/deuteride exchanges within SS form of NCC..

INTRODUCTION

Recently, the relative contribution of hydrogen bonded (HB) and salt bridged (SB) forms of deprotonated binary complexes (with HexP and R as partners in NCC) was shown depending on the "in source" desolvation conditions [1].

- HB under CID → mainly [HexP-H]⁻ (loss of R)
- SB under CID → covalent bond cleavages (CBC)

For cationized NCC anions, quantum calculations suggested formation of solvated salt (SS) rather than SB form.

- SS forms → [HexP-H]⁻ (as HB forms) and CBC at a lesser extent

For distinguishing the SS and HB forms of F6P/R/Na, dissociations of multideuterated NCC anions after complete conventional in-solution HDX of F6P and R were explored.

- Expected product ion (from HB form): mostly [F6P_{d6}-D]⁻ (because of higher acidity of F6P than R or R/Na)
- Experimental product ion: **expected** [F6P_{d6}-D]⁻ and **unexpected** (D enriched) [F6P_{d7}-D]⁻ and [F6P_{d8}-D]⁻ [2]

The label incorporation likely occurs during dissociation of **SS** form of [(F6P_{d6}+R_{d7}-D+Na)-D]⁻.

METHODS

Mixture of F6P and R (Sigma-Aldrich, USA) in D₂O (final concentration of 100 μM) was analysed by direct injection (7 μL/min) in ESI negative mode on an Orbitrap Elite (Thermo Fisher Scientific, Courtaboeuf, France). The inter-(with residual water in linear trap) and intra-complex (between partners of ion-dipole complex) HDX for completely exchanged parent ion [(F6P_{d6}+R_{d7}-D+Na)-D]⁻ were explored by resonant (CID in LTQ) and non-resonant (HCD in ion routing multipole) excitations using variable ExcT and NCE values for CID and HCD and variable ExcQ for CID [Fig.1]. Ion spray (IS) was set at -3.5 kV, resolution was set at 60,000.

RESULTS

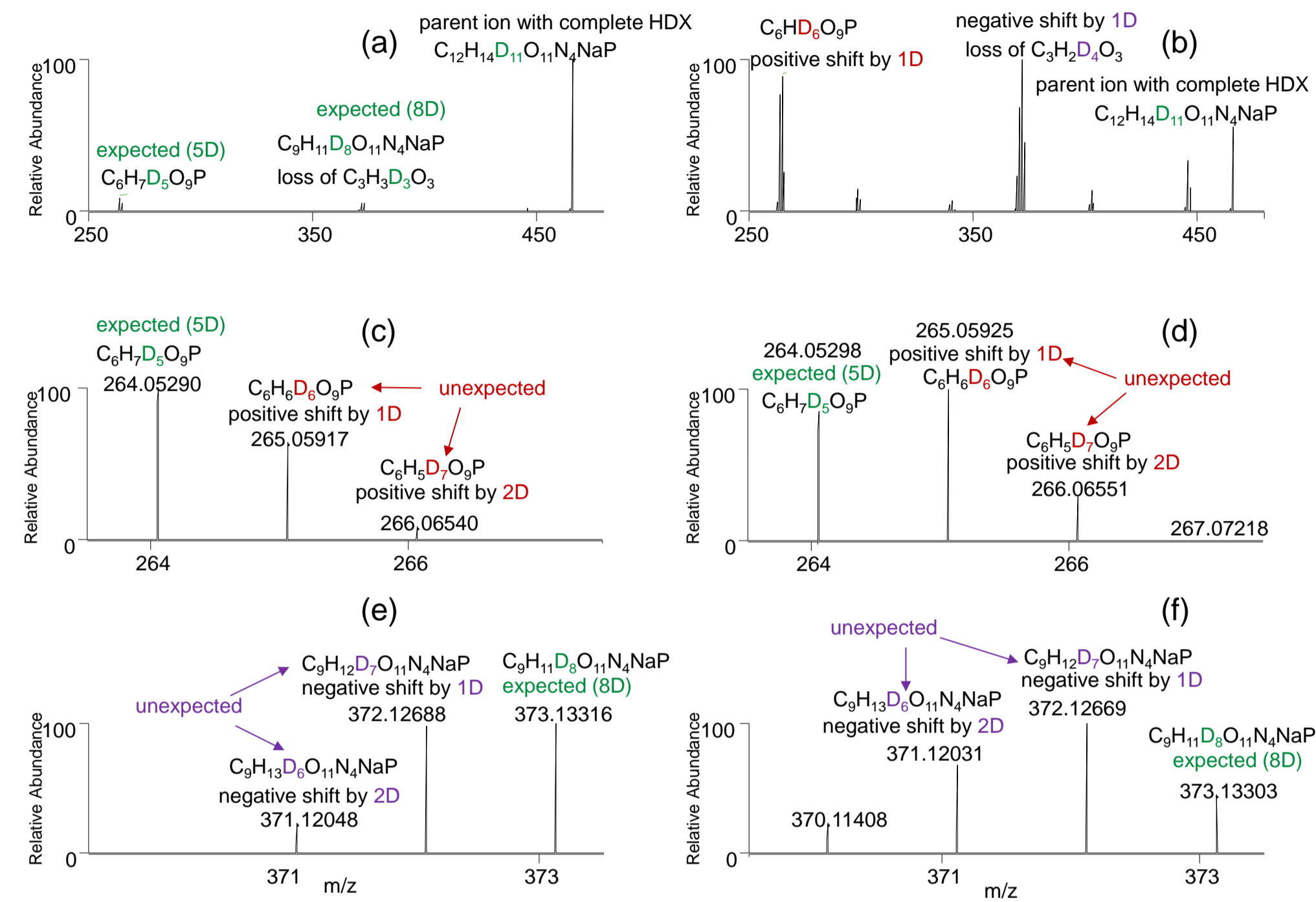


Fig. 2 Evolution of CID spectra by increasing slow heating in the LTQ cell: full CID spectra at (a) ExcTime = 500 ms and (b) ExcTime = 3000 ms; (c, d, e, f) – zoom on complementary HDX, (c) F6P and (e) R+sugar part at ExcTime = 500ms; (d) F6P and (f) R+sugar part at ExcTime = 3000 ms

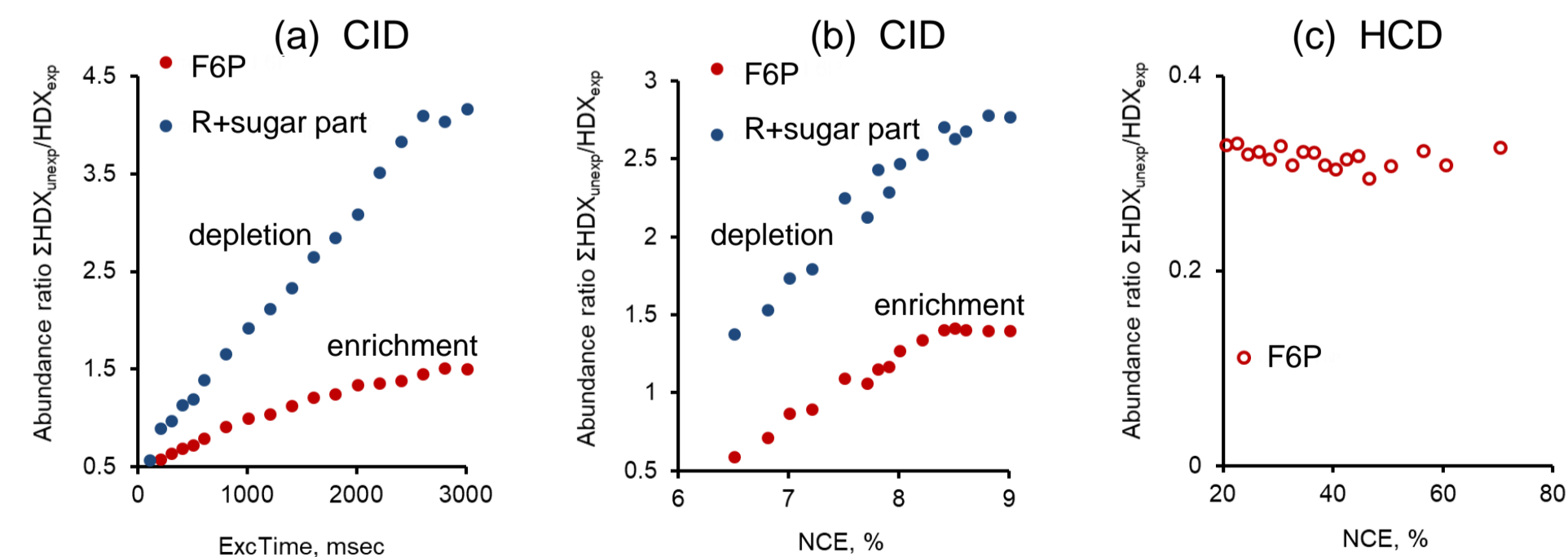


Fig. 3 Impact of excitation parameters on the evolution of the unexpected versus expected HDX between F6P and R within sodiated NCC (a) – Excitation Time at NCE=8% and (b) – NCE at ExcTime=1600ms under CID, (c) – NCE under HCD

$$\frac{\sum HDX_{unexp}}{HDX_{exp}} \text{ for F6P} = \frac{[F6P_{d6}^{265}] + [F6P_{d7}^{266}]}{[F6P_{d5}^{264}]}, \frac{\sum HDX_{unexp}}{HDX_{exp}} \text{ for [R+sugar part]} = \frac{[Frag_{d7}^{372}] + [Frag_{d6}^{371}]}{[Frag_{d8}^{373}]}$$



CID conditions:

Longer ExcT under CID conditions (*slow heating*) → higher degree of unexpected HDX (HDX_{unexp}) between the interacting partners [Figs.2 and 3a, 3b]. Enhanced exchange reactions can take place via a stepwise isomerization through hexose ring opening prior to complete NCC dissociation due to a longer ExcT value [Fig. 4]. The decrease in the depth of pseudo potential well of precursor ion storage (varying the q_z value from 0.25 to 0.15) → no dramatic changes of <HDX> processes but the enhanced storage of product ions at lower q_z and thus, their detection.

HCD conditions

Longer ExcT under HCD conditions (*fast heating*) → mainly constant ΣHDX_{unexp}/Σ HDX_{exp} ratio. In the RF multipole, the dissociation is faster than the HDX [Fig. 3c]. Total dissociation in the RF multipole is faster than the isomerization by ring opening and hydride/deuteride exchanges and takes place when the first collision transfers enough internal energy to promote it before a second consecutive collision occurs.

MS³ experiments

Sequential MS³ experiment on the most abundant product ions (HexP and complementary R containing fragment ions) and on the remained survivor precursor ion (i.e., completely exchanged NCC) → only the loss of deuterons by reverse D/H exchanges due to intermolecular collision with the residual water presented in LTQ)

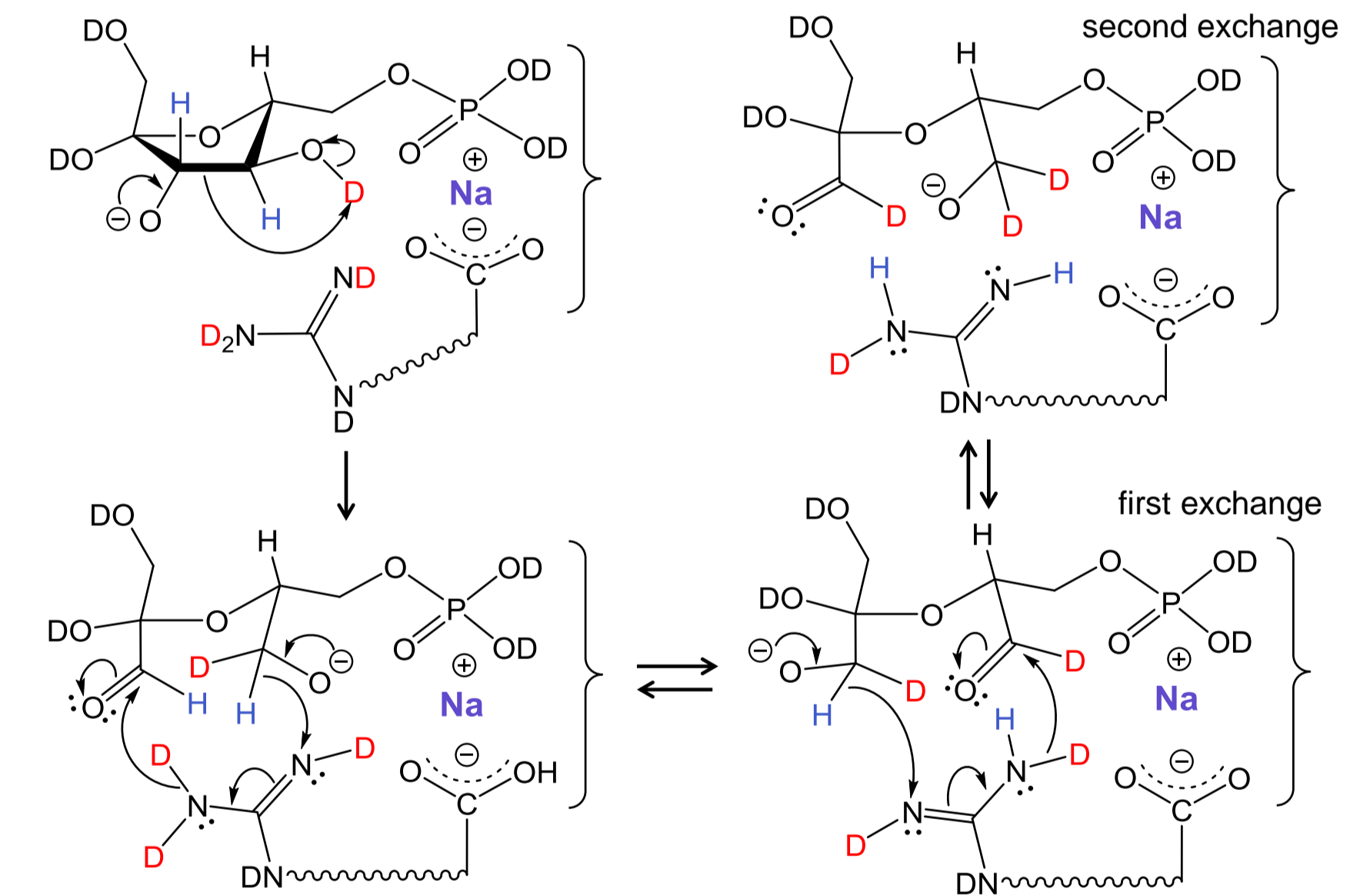


Fig. 4 Proposed mechanism involving deuteride-hydride transfer for fragmentation of cationized NCC anion with completely exchanged mobile protons

CONCLUSIONS

- Complementary enrichment(+D)/depletion(-D) detected in diagnostic product ions related to each partner (intact or not) favored under resonant excitation conditions
 - Generation of the main F6P product ion after F6P ring opening and reversible <HDX> rather than directly from intact NCC
 - Absence of non-specific proton/deuteron exchanges with residual water (or external agent) leading to labeling depletion for the product ions in MS² experiments.
 - Suggested stepwise process involving hydride/deuteride transfer from specific carbon atom to another (e.g. nitrogen) atom rather than proton/deuteron exchanges
- Calculation in progress in order to evidence these considerations.

References

- [1]. Darii E, Alves S, Gimbert Y, Perret A, Tabet JC. J Chromatogr B 1047 (2017) 45-58
- [2]. Darii E, Alves S, Gimbert Y, Perret A, Tabet JC. Poster ASMS 2017

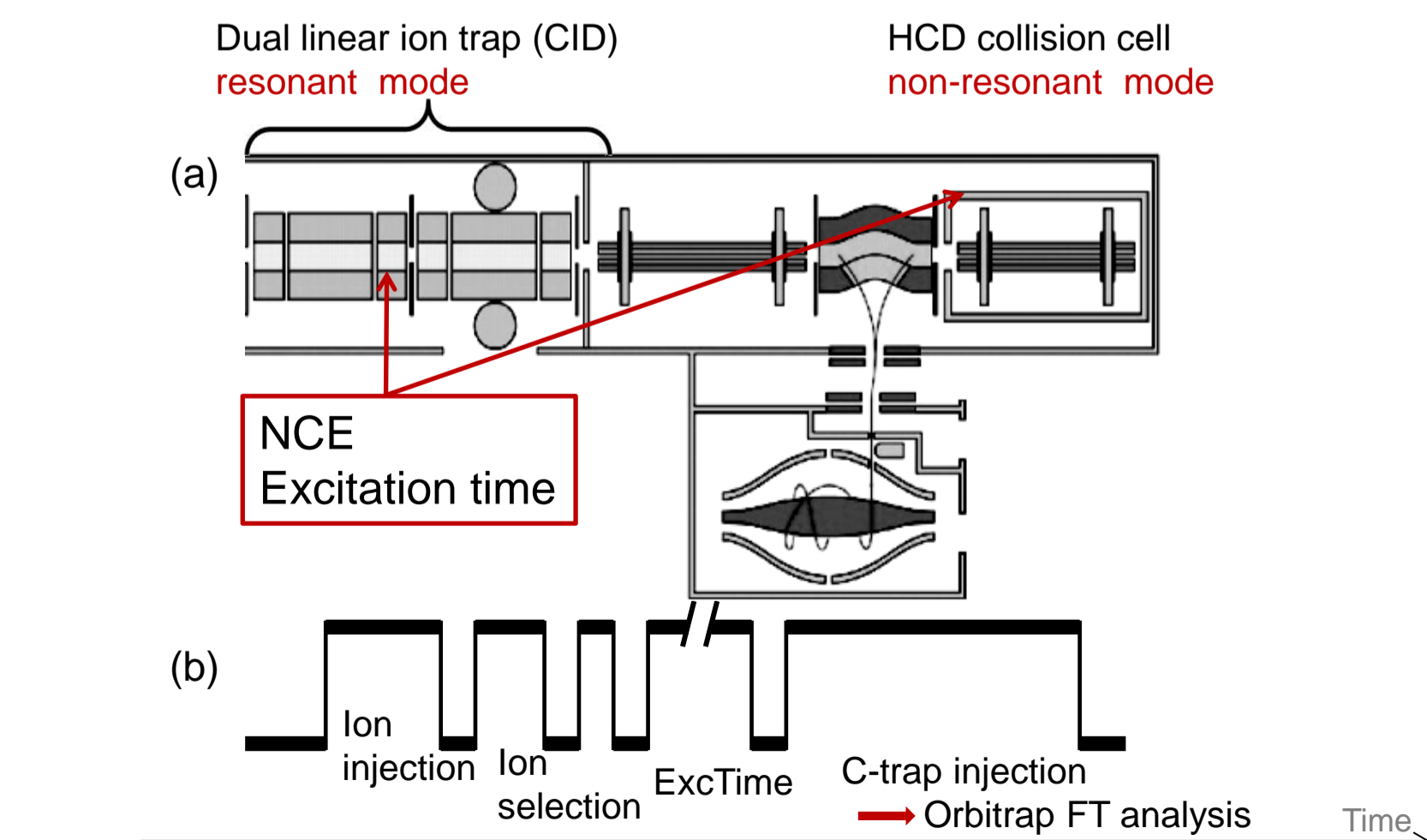


Fig. 1 (a) – Linear ion trap and HCD collision cell in an Orbitrap Elite mass-spectrometer (b) – Time-sequence for variation of Excitation Time in CID and HCD