Tetrahedron 73 (2017) 2977–2983

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Gas-phase C^{α}=C^{β} double bond cleavage in the dissociation of protonated 2-benzylidenecyclopentanones: Dissociative proton transfer and intramolecular proton-transport catalysis

Shanshan Shen [a], Yunfeng Chai [b], Lingzi Dai [a], Chang Li [b], Yuanjiang Pan [a, *]

[a] Department of Chemistry, Zhejiang University, Hangzhou 310027, China
[b] College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China

ARTICLE INFO

Article history:
Received 24 February 2017
Received in revised form
5 April 2017
Accepted 8 April 2017
Available online 11 April 2017

Keywords:
Dissociative proton transfer
Proton-transport catalysis
C=C bond cleavage
Tandem mass spectrometry

ABSTRACT

Among gas-phase dissociation reactions, double bond cleavage reaction appears to happen extremely rare, especially in the case of C=C double bond. In the dissociation reaction of protonated 2-benzylidenecyclopentanones in tandem mass spectrometry, the formation of benzyl cations was observed, resulting from the cleavage of C^{α}=C^{β} double bonds, which is different from the general cleavage route seen in most α, β-unsaturated ketone cases. A combined experimental and theoretical investigation on intramolecular hydrogen transfers was carried out to illustrate the mechanisms. The external proton is initially localized on the carbonyl oxygen (the thermodynamically-preferred protonation site). Upon collisional activation, the mobile proton stepwise migrates to the C^{α} position to achieve the reduction and subsequent cleavage of the C^{α}=C^{β} double bond. The stepwise proton transfer is achieved via intramolecular proton-transport catalysis with the assistance of the phenyl ring. The *ortho* position of the phenyl accepts the proton from the carbonyl oxygen via a 1,6-H shift, and then donates it to the C^{α} stepwise. The conventional 1,3-H shift from the carbonyl oxygen to the C^{α} position can be excluded in this case due to its significant energy barrier. Further isotope-labeling experiments are applied to confirming the reaction mechanism. Last but not least, the scope-expansion experiments indicates that the aromatic and cycloalkanonyl moieties play a crucial roles in the cleavage reaction of C^{α}=C^{β} double bond.

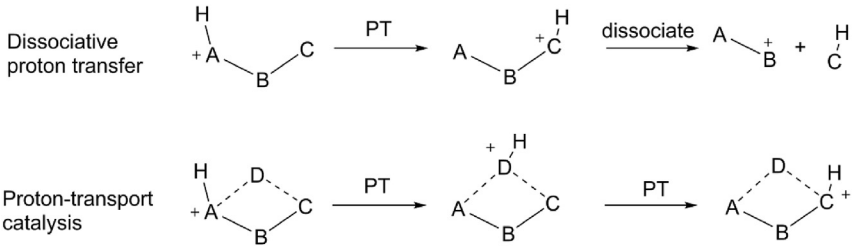
1. Introduction

The development of improved capabilities for electrospray ionization mass spectrometry (ESI-MS) based study of gas-phase chemistry is one of the focal points in scientific research. Attributing to the high vacuum environment, ESI-MS readies compounds by isolation and storing them with no complicating interferences by solvent effects, aggregation phenomena, *etc.*, which provides us a deep understanding of the intrinsic mechanism in organic reaction.[1–4]

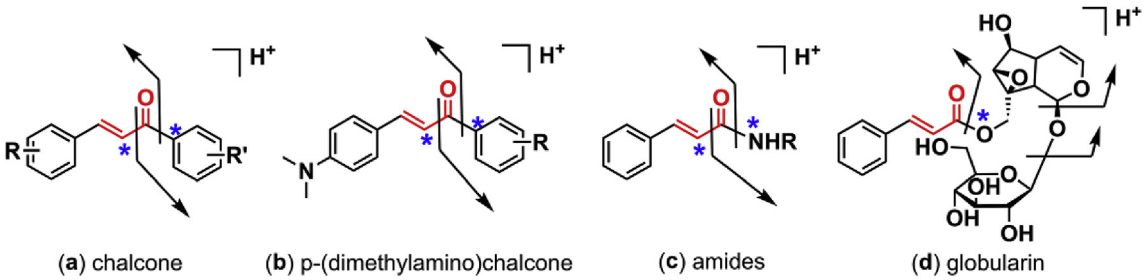
At the initial stage of a typical ESI-MS experiment, molecules are protonated at the ionization process, which usually triggers subsequent dissociation reactions under collision-induced dissociation (CID) conditions.[5] Generally, there are two major fragmentation pathways that lead to the ion formation under CID, which are charge-remote and charge-driven fragmentation.[6,7] Charge-remote fragmentation refers to a type of covalent bond breaking that occurs in a gas phase ion in which the cleaved bond is not adjacent to the location of the charge.[8,9] As for the charge-driven fragmentation, the positive charge brought in by protonation is commonly the driving force for the dissociation reactions of a protonated molecule ($[M+H]^+$), *i.e.*, so-called dissociative proton attachment.[10–12] Nevertheless, in most cases, *no* fragmentation reaction takes place when the external proton is predominantly attached to the thermodynamically-favored site; in contrast, the major fragmentation reactions occur when the proton transfers (PT) to some protonation-unfavorable sites. The very sites were known as the dissociative protonation sites that are reactive centers in ESI-MS^n.[13] The fragmentation triggered by dissociative proton transfer,[14–16] from the basic center to the reactive center, are sometimes hindered by high energy barrier or steric hindrance. Under such

* Corresponding author. Department of Chemistry, Zhejiang University, 38 Zheda Road, Hangzhou 310027, China.
E-mail address: panyuanjiang@zju.edu.cn (Y. Pan).

http://dx.doi.org/10.1016/j.tet.2017.04.010
0040-4020/



Scheme 1. Schematic diagrams for the dissociative proton transfer and proton-transport catalysis.



Scheme 2. Chemical structures of selective α, β-unsaturated ketones and its analogues. The dissociative protonation sites are marked with asterisks, and the dissociated bonds are marked with arrows.

circumstances, it may take advantage of solvent assistance or neighboring group participation to promote proton transfer.[17–19] That is, the energy barrier of the proton transfer can be reduced to some extent due to the interaction with an external molecule or an internal moiety. Such catalytic effect was described as proton-transport catalysis (Scheme 1).[20–22]

Many α, β-unsaturated ketones, of the type R–C═C–C(O)-R′, are found in nature as components of odor and flavor volatiles and are important industrial chemicals.[23–27] α, β-unsaturated ketones have also been reported as environmental pollutants, for example, in cigarette smoke and workplace and urban air.[28–30] On the other hand, from the point of view of gas-phase chemistry, α, β-unsaturated ketones have also been chosen as an ideal model to explore the exquisite gas-phase ion dissociation behavior. Chalcones, for example, possessing a basic structure Ph-CH═CH–CO-Ph', loss of a benzene and a styrene were observed as the major fragmentation reactions of the protonated molecules in ESI(+)-MS/MS (Scheme 2(a)). The carbonyl oxygen was the most favorable site for protonation (which is, however, not dissociative) and subsequent 1,3-proton transfer (1,3-PT) to the two α-carbons (marked with asterisks) was a regulator of the overall reactions. Once the labile proton attaches to the dissociative sites, the two adjacent C(O)–C bonds directly cleave induced by the positive charge.[31] Consistently, the fragmentation mechanism of protonated *p*-(dimethylamino)chalcone by ESI(+)-MS/MS undergoes similar pattern that the prominent product ions are generated by dissociative 1,3-PT to the two α-carbons (Scheme 2(b)).[32] For the α, β-unsaturated amides (R–CH═CH–CO–NH-R′), it is found to undergo protonation more favorable at the oxygen as well, similar to α, β-unsaturated ketones.[33] However, dominant fragmentation reactions prevail that the 1,3-PT from the initial site to the carbon atom or nitrogen (marked with asterisks) next to the carbonyl is expected to occur prior to the fragmentation reaction (Scheme 2(c)).[34] When it comes to α, β-unsaturated esters (Ph-CH═CH–CO–O–R), the C–CO and CO–O bonds were found inclined to cleave as the consequence of 1,3-PT under collisional activation. Take globularin for instance: in addition to the glycosidic fission and ring cleavage of both aglycone and sugar moieties, the loss of cinnamoyl was also observed during CID, corresponding to the cleavage of the ester bond (Scheme 2(d)).[35] Overall, α, β-unsaturated ketones are known to be protonated preferentially at the carbonyl oxygen due to its higher proton affinity, and isomerization of the O-protonated species to the dissociative species take place prior to loss of the certain neutral moiety. In most cases, as abovementioned, the dissociative species are usually limited to the α-position-protonated molecules as the result of the 1,3-PT, and the *single* bond adjacent to the carbonyl group cleavage is peculiar to take place in a concerted fashion. However, as far as we know, quite few papers have reported the cleavage probability of the $C^{\alpha}=C^{\beta}$ *double* bond of α, β-unsaturated ketones, which we are interested in.

The cleavage reaction of *double* bond, especially the C═C double bond, is much less explored. This is partly due to the higher bond order and stronger bond energy of C═C double bond (611 kJ mol^{-1} for C═C bond *versus* 347 kJ mol^{-1} for C–C bond).[36] On the other hand, unlike C═X (X = O, NH) double bonds, C═C bond is hardly to be protonated because of its low proton affinity (PA).[37] Therefore, more often than not, the cleavage of C═C bond is lack of charge driving force.

In the fragmentation of protonated 2-benzylidenecyclo pentanones in ESI(+)-MS/MS, we observed that the cleavage reaction of $C^{\alpha}=C^{\beta}$ *double* bond instead of the C(O)–C *single* bonds. Our results from detailed isotopic-labeled experiments show that the incipient proton that attaches to the carbonyl oxygen is mobile, and it ambulates to the phenyl ring before migrates to the cyclopentanone moiety, in which the phenyl *ortho*-carbon plays a role as a proton-transport catalyst to achieve the fission of the double bond. Additionally, theoretical computation and scope-expanding experiments were used to follow the proton-ambulation mechanism.

2. Results and discussion

In the CID experiments of a series of protonated 2-benzylidenecyclopentanones (Table 1), one particular species of the identifiable product ions, benzyl cations ($RC_6H_4CH_2^+$), as envisaged resulting from the $C^{\alpha}=C^{\beta}$ double bonds cleavage, were