Loss of benzaldehyde in the fragmentation of protonated benzoylamines: Benzoyl cation as a hydride acceptor in the gas phase

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Abstract

In electrospray ionization tandem mass spectrometry of protonated 1-benzoylamines (1-benzoylpiperadine, 1-benzoylmorpholine, and 1-benzoyl-4-methylpiperazine), the dominant fragmentation pathway was amide bond cleavage to form benzoyl cation and neutral amine. Meanwhile, in their fragmentations, an interesting loss of benzaldehyde (106 Da) was observed and identified to derive from hydride transfer reaction between the benzoyl cation and amine. A stepwise mechanism for loss of 106 Da (benzene and CO) could be excluded with the aid of deuterium labeling experiment. Theoretical calculations indicated that hydride transfers from amines (piperadine, morpholine and 1-methylpiperazine) to benzoyl cation were thermodynamically permitted and 1-methylpiperazine was the best hydride donor among the three amines. The mass spectrometric experimental results were consistent with the computational results. The relative abundance of the iminium cation (relative to the benzoyl cation) in the fragmentation of protonated 1-benzoyl-4-methylpiperazine was higher than that in the fragmentation of the other two protonated 1-benzoylamines. By comparing the fragmentations of protonated 1-benzyl-4-methylpiperazine and protonated 1-benzoyl-4-methylpiperazine and the energetics of their hydride transfer reactions, this study revealed that benzoyl cation was a hydride acceptor in the gas phase, but which was weaker than benzyl cation.

Keywords: Hydride transfer, Benzoyl cation, Hydride acceptor, Fragmentation mechanism, Loss of benzaldehyde

Introduction

Mass spectrometer is not only versatile in analytical chemistry but also serves as a useful tool in physical organic chemistry. Benefit from the development of electrospray ionization (ESI) and other soft ionization methods, various interesting ions can be prepared and stored in the gas phase. Researches on unimolecular or bimolecular reactions of theses ions have attracted a lot of interest in recent years because of the requirements from not only mass spectrometry itself but also other disciplines such as biochemistry and organic chemistry. Although the gas-phase ion chemistry is not equivalent to the chemistry of ions in solution and sometimes they are quite different, the results obtained from gas phase often can provide valuable even crucial information for chemical reactions in solution.[1-3] Furthermore, mass spectrometry can provide convincing experimental evidence to uncover the intrinsic reactivity of a wide range of species which cannot be probed by other techniques.[4,5]

Hydride transfer is a fundamental reaction in organic and enzymatic reactions.[6-9] Studying the properties of donor and acceptor in a hydride transfer reaction is necessary but difficult to tackle in condensed phase interfered by ion pairing, solvation and aggregation effects. Gas-phase study is an effective access to characterize the intrinsic properties of hydride transfer reaction. Proton transfer is quite popular in gas-phase reactions, but hydride transfer is much less common since the occurrence of such reaction needs proper hydride donor and acceptor. Carbocation is an important class of hydride acceptor, however, in many cases, it reacts as a proton donor so that the hydride transfer is usually inhibited by the proton transfer in the gas phase. The typical hydride-abstracting agents are *tert*-butyl cation and benzyl cation in the gas phase. The hydride transfer reaction involving these two hydride acceptors has been extensively studied by mass spectrometric methods.[10-22] Otherwise, combining mass spectrometry and theoretical calculation, the significant hydride acceptor properties of benzaldehyde[23], 1,3,5-triazine[24] and phenylisocyanate[25] have be revealed. The carbonyl group is a hydride acceptor in the reduction of aldehydes and ketones which is of fundamental importance in chemistry and biochemistry.[26,27] The hydride affinities of aldehydes and ketones can be determined by experimental method and theoretical

calculation.[28,29] Acyl cations are reactive species in the gas phase,[30-33] but hydride abstraction by a bare acyl cation was rarely reported. In solution reaction, an expected hydride transfer reaction of cycloheptatriene with benzoyl cation was not really observed in experiment.[34] Only in the gas-phase ion/molecule reactions between benzoyl cation and alcohols (butan-2-ol or cyclohexanol), the hydride abstraction (neutral benzaldehyde formation) was observed.[35,36] However, in similar gas-phase ion/molecule reactions between benzoyl cation and amines, hydride abstraction was not observed.[37-39] The alkanoyl cation is unstable in the gas phase which usually undergoes loss of CO or intramolecular cyclization and it is a much better proton donor than hydride acceptor if it contains α-H.[39-41] The benzoyl cation possesses considerable stability in the gas phase and it is not a proton donor. Although the hydride abstraction ability of benzoyl cation seems to be apparent, this issue has not yet been clarified so far. In the present work, the fragmentation reactions of selected protonated 1-benzoylamines were studied in tandem mass spectrometry. Loss of benzaldehyde from protonated 1-benzoylamines was identified and proposed to undergo a hydride transfer process in the fragmentation reaction. To understand the reaction mechanism, a combination of experimental and theoretical study was carried out herein.

Experimental

Mass Spectrometry

Accurate mass measurements for 1-benzoyl-4-methylpiperazine (compound **3**) were performed on a LTQ-Orbitrap XL mass spectrometer (Thermo Fisher Scientific, San Jose, CA, USA) equipped with an electrospray ion source. Nitrogen was used as the sheath gas and auxiliary gas. The spray voltage was set at 3.5 kV. The resolution was set at 100000 and the capillary temperature was set at 270 °C. The analyte was introduced into the ion source as a solution in methanol or methanol-d_4 at a concentration of approximately 1 μg mL^{-1}. The $[M + H]^+$ or $[M + D]^+$ ions of compound **3** were selected as parent ions and their MS/MS spectra were acquired with helium as the collision gas at a normalized collision energy (NCE) of 25%. The isolation window was 1 m/z. The mass accuracy was calibrated immediately before measurements according to manufacturer's instructions in the positive mode. All spectra were

analyzed and evaluated using Xcalibur 2.0.

The MS/MS experiments for compounds **1-4** were performed using flow inject analyses (FIA) on a hybrid quadrupole-orbitrap mass spectrometer coupled with a heated electrospray ion source (ThermoFischer Scientific, Bremen, Germany). The mobile phase was composed of 50% A and 50% B at a flow rate of 0.2 mL min^{-1}. A was 0.1% formic acid, and B was methanol. 3 μL of the sample (1 μg mL^{-1}) was injected into the ESI-MS through FIA. The MS parameters were as follows: spray voltage 3.5 kV in positive mode, sheath gas (N_2) flow 40 arb, auxiliary gas (N_2) flow 15 arb, heated capillary temperature 375 °C, auxiliary gas heater temperature 250 °C, S-lens radio frequency (RF) level 60. The MS/MS spectra were obtained with nitrogen as the collision gas after isolation of the desired precursor ion. The isolation window was 1 m/z. A 30% normalized collision energy (NCE) was employed for fragmentation of the $[M + H]^+$ precursor ions. Data processing was performed with Xcalibur 3.0 software.

Theoretical Calculations

All theoretical calculations were carried out using the Gaussian 03 suit of programs [42]. The structures of species studied were optimized using density functional theory (DFT) method with B3LYP/6-311++G(2d,p) and B3LYP/6-31++G(d,p) basis sets. Minima (no imaginary frequencies) or transition states (one imaginary frequency) were determined by frequency calculations at the same theoretical level. The minima connected by a given transition structure were confirmed by intrinsic reaction coordinate (IRC) calculations. In calculations, the temperature was 298.15 K and the pressure was 1.0 atm. The energies discussed here were the sum of electronic and thermal energies.

General Synthesis

Synthesis of benzoylamines: Benzoyl chloride (2 mmol), amine (2 mmol) and potassium carbonate (2.5 mmol) were stirred in acetonitrile (2 ml) at room temperature. After the completion of the reaction, the solvent was evaporated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford the product. The structures

were confirmed by ^{1}H NMR spectroscopy and mass spectrometry.

1-benzoyl piperadine (**1**). ^{1}HNMR: (500 MHz, $CDCl_3$): δ (ppm) = 7.39 (m, 5H), 3.72 (t, 2H), 3.35 (t, 2H), 1.68 (t, 4H), 1.52 (t, 2H).

1-benzoyl morpholine (**2**). ^{1}HNMR: (500 MHz, $CDCl_3$): δ (ppm) = 7.42 (m, 5H), 3.46-3.79 (br, 8H).

1-benzoyl-4-methylpiperazine (**3**). ^{1}HNMR: (500 MHz, $CDCl_3$): δ (ppm) = 7.40 (m, 5H), 3.81 (t, 2H), 3.45 (t, 2H), 2.50 (t, 2H), 2.35 (t, 2H), 2.33 (s, 3H).

Synthesis of 1-benzyl-4-methylpiperazine: 1-Methylpiperazine (2 mmol) and potassium carbonate (2.5 mmol) were dissolved in 3 ml tetrahydrofuran and stirred at room temperature. Benzyl bromide (2 mmol) in tetrahydrofuran was added dropwise. After the completion of the reaction, the solvent was evaporated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford the product. The structures were confirmed by ^{1}H NMR spectroscopy and mass spectrometry.

1-benzyl-4-methylpiperazine (4). ^{1}HNMR: (500 MHz, $CDCl_3$): δ (ppm) = 7.19-7.25 (m, 5H), 3.44 (s, 2H), 2.40 (br, 8H), 2.22 (s, 3H).

Results and Discussion

Some 1-benzoylamines (**1-3**) and 1-benzyl-4-methylpiperazine (**4**) were selected as model compounds (Scheme 1). Table 1 summarizes the concerned product ions generated from the fragmentation of protonated compounds **1-4**, and the related MS/MS spectra are given in Figure 1. In the fragmentation of the $[M + H]^+$ ion of compounds **1-3**, amide bond cleavage leads to the formation of the dominant product ion, benzoyl cation ($C_7H_5O^+$, *m/z* 105), which is usually one of the main reactions in the fragmentation of protonated amide compounds.[43-45] The corresponding iminium cations ($C_5H_{10}N^+$, *m/z* 84, $C_4H_8NO^+$, *m/z* 86 and $C_5H_{11}N_2^+$, *m/z* 99) can be observed, though their relative abundances are low. The formation of these iminium cations is interesting and the mechanism is probably hydride transfer at first glance.

In view of the relatively highest abundance of the iminium cation in the fragmentation of protonated **3** among the three 1-benzoylamines, compound **3** was selected as a model compound to study the formation mechanism of the iminium cation. The high-resolution MS/MS spectra of protonated **3** (*m/z* 205) and deuterated **3** (*m/z* 206) are shown in Figure 2. The elemental compositions of the product ions in the fragmentation of protonated **3** (*m/z* 205) are listed in Table 2, and the relative errors between the measured mass and the theoretical mass are all less than 4 ppm. In the fragmentation of protonated **3**, protonation at the methylated N leads to the piperazine ring cracking to generate the product ions *m/z* 148, 162 and 174. Further fragmentations of these three product ions do not produce *m/z* 99 (the MS^3 spectra are given in Figure S1 in the supporting information). There are two possible routes to produce the iminium cation (*m/z* 99) as shown in Scheme 2. Isotope labeling method is very helpful in mass spectrometry to figure out the fragmentation pathway. For the fragmentation of the $[M + D]^+$ ion of **3**, the hydride transfer mechanism gives rise to the iminium cation containing a deuteron atom (*m/z* 100). In the other possible route, the sequential losses of benzene-d_1 and CO lead to the formation of the iminium cation containing no deuteron atom (*m/z* 99). In the fragmentation of protonated **1** and **2**, loss of benzene takes place (*m/z* 112 and 114), but in the fragmentation of protonated **3**, no loss of benzene is observed (Figure 1). In the fragmentation of deuterated **3**, the iminium cation ($C_5H_{10}DN_2^+$, *m/z* 100.0976) is formed through losing C_6H_5CHO and no product ion ($C_5H_{11}N_2^+$, *m/z* 99.0913) is formed from losses of C_6H_5D and CO (Figure 2). Therefore, the sequential losses of benzene and CO to form the iminium ion can be excluded with the aid of H/D exchange experiment.

The benzoyl cation can be described in terms of the resonance hybrid contributions (Scheme 3), which had been elucidated using NMR spectroscopic methods and theoretical calculations.[46-48] In a hydride transfer reaction, the hydride ion may be released to three positions of the benzoyl cation, including the carbonyl carbon, the *ortho* positions of the phenyl ring, and the *para* position of the phenyl ring. Among these three positions, the carbonyl carbon should have the highest hydride affinity because it forms an aromatic product, benzaldehyde. When the hydride is added to the phenyl ring, the products are much

less stable than the benzaldehyde (Scheme 4). Consequently, in the fragmentation of protonated 1-benzoylamines (**1-3**), the neutral counterpart of the iminium cation should be benzaldehyde.

Secondary aliphatic amines had been shown to be good hydride donors in the gas phase when benzyl cation was the hydride acceptor in previous studies.[18,22] Removal of a hydride ion from the methylene group adjacent to the nitrogen of an amine gives rise to a very stable iminium cation. DFT calculations were performed to evaluate the energy requirement of hydride transfer reaction between secondary aliphatic amines and benzoyl cation and the results are listed in Table 3. Piperadine, morpholine and 1-methylpiperazine are the corresponding hydride donors. Hydride transfer from these N-containing heterocycles to the benzoyl cation is thermodynamically allowed. 1-Methylpiperazine is the best hydride donor among them because all its alkyl hydrogens are hydride sources and the methylene groups adjacent to the N of tertiary amine exhibit the highest reactivity. In the mass spectrometric experiments, the iminium cation derived from 1-methylpiperazine has the highest relative abundance (relative to the benzoyl cation) compared with other two iminium cations. Thus, the experimental and computational results are consistent with each other. The iminium cation *m/z* 99 may contains three isomers as shown in Table 3, but **p3-2** is the preferred isomer in terms of energy. The formation of **p3-1** and **p3-3** in hydride transfer reaction is even less favored than that of **p1**. Consequently, **p3-2** is probably the main isomer of *m/z* 99 and it is used in the following discussions.

Fragmentation of protonated **4** can generate iminium cation *m/z* 99 and benzyl cation ($C_7H_7^+$, *m/z* 91), as shown in Figure 1. The formation of iminium cations in the fragmentation of *N*-benzylated cations is a hydride transfer mechanism between the benzyl cation and the neutral amine, which has been extensively studied in very recent years.[16-23] DFT calculation indicates that the hydride transfer reaction between benzyl cation and 1-methylpiperazine is highly exothermic ($\Delta E = -192.1$ kJ mol^{-1}, Table 3). The ΔE of hydride transfer reaction between benzoyl cation and 1-methylpiperazine is -133.3 kJ mol^{-1} (Table 1). Theoretical calculation indicates that benzyl cation is a stronger hydride acceptor than benzoyl cation, which is also consistent with the mass spectrometric experiments. In the

fragmentation of protonated 1-benzyl-4-methylpiperazine (compound **4**), the relative abundance of the product ion *m/z* 99 is much higher than that in the fragmentation of protonated 1-benzoylamines (Table 1).

To further understand the energetics of the fragmentation of protonated **3**, a schematic potential energy diagram of the fragmentation of protonated **3** is given in Figure 3. The proton affinity (PA) of tertiary amine is usually higher than that of carbonyl compounds. For example, the PA of $(CH_3)(C_2H_5)_2N$ (971.0 kJ mol^{-1}) is higher than that of $C_6H_5CON(CH_3)_2$ (932.7 kJ mol^{-1}).[49] According to computational results, the energy of the *N*-protonated **3** is 25.6 kJ mol^{-1} lower than that of the *O*-protonated **3**. For compound **3**, the preferred initial protonation site should be the methylated N. The chair-conformation of compound 3 can switch to the boat-conformation with low energy barrier (TS-S1). And then the added proton can migrate from the methylated N to the amide N through a boat-conformation of piperazine ring. After amide bond cleavage, the benzoyl cation (*m/z* 105) is generated directly and the iminium cation (*m/z* 99) is formed via hydride transfer reaction. The formation of product ion **p3-2** is preferred than that of product ion **p3-1** due to the lower energy barrier and product energy. The energy threshold for the formation of iminium cation **p3-2** is lower than that for the formation of benzoyl cation, but the relative abundance of benzoyl cation is much higher than that of **p3-2** in the CID experiment. Similar phenomenon was also observed in the fragmentation of protonated *N*-benzylpiperidine which produces a benzyl cation and an iminium cation via hydride transfer.[18] A proposed explanation is that a simple bond cleavage is faster than the hydride transfer reaction. In the transition states (**TS-2** and **TS-3**), the amide bond is completely broken and a benzoyl cation is formed (see optimized structures in Figure 3), therefore the hydride transfer reaction here is analogues to a bimolecular reaction and it reveals the reactivity of a benzoyl cation. Actually, an ion/neutral complex can be considered to be involved in this hydride transfer reaction. Benzoyl cation transfer via ion/neutral complex has been reported in the fragmentation of drug molecules containing both benzoyl and carboxymethyl groups on an aromatic heterocyclic core.[50,51]

Conclusions

In mass spectrometry, fragmentation of protonated 1-benzoylamines initially produces benzoyl cation and amine. Hydride transfer between benzoyl cation and amine leads to the formation of iminium cation by the loss of benzaldehyde. The theoretically predicted hydride transfer reactivity of benzoyl cation and amines is in good agreement with the observed mass spectra. Tertiary amines are better hydride donors than secondary amines and benzoyl cation is a weaker hydride acceptor than benzyl cation. This study provides a new characterization of the fundamental benzoyl cation in the gas phase. The hydride transfer mechanism can be used to interpret the loss of benzaldehyde in the fragmentation of ions containing benzoyl group.

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References

1. D. Schröder. Applications of electrospray ionization mass spectrometry in mechanistic studies and catalysis research. *Acc. Chem. Res.* **2012**, *45*, 1521–1532.
2. F. Coelho, M. N. Eberlin. The bridge connecting gas-phase and solution chemistries. *Angew. Chem. Int. Ed.* **2011**, *50*, 5261–5263.
3. L. S. Santos. Online mechanistic investigations of catalyzed reactions by electrospray ionization mass spectrometry: a tool to intercept transient species in solution. *Eur. J. Org. Chem.* **2008**, 235–253.
4. S. Gronert. Mass spectrometric studies of organic ion/molecule reactions. *Chem. Rev.* **2001**, *101*, 329–360.
5. S. Gronert. Quadrupole ion trap studies of fundamental organic reactions. *Mass Spectrom. Rev.* **2005**, *24*, 100–120.
6. S. E. Clapham, A. Hadzovic, R. H. Morris. Mechanisms of the H_2-hydrogenation and transfer hydrogenation of polar bonds catalyzed by ruthenium hydride complexes. *Coord. Chem. Rev.* **2004**, *248*, 2201–2237.
7. Z. D. Nagel, J. P. Klinman. Tunneling and dynamics in enzymatic hydride transfer. *Chem. Rev.* **2006**, *106*, 3095–3118.
8. R. H. D. Lyngdoh, H. F. Schaefer III. Elementary lesions in DNA subunits: electron, hydrogen atom, proton, and hydride transfers. *Acc. Chem. Res.* **2009**, *42*, 563–572.
9. C. Zheng, S.-L. You. Transfer hydrogenation with Hantzsch esters and related organic hydride donors. *Chem. Soc. Rev.* **2012**, *41*, 2498–2518.
10. C. Matthias, D. Kuck. Gaseous [$C_nH_{2n+1}^+$ . . . 1,3-diphenylpropane] ion/neutral complexes containing alkyl cations of different acidities and hydride ion affinities. *Croat. Chem. Acta* **2009**, *82*, 7–19.
11. C. Matthias, A. Cartoni, D. Kuck. Ion/neutral complexes generated during unimolecular fragmentation: intra-complex hydride abstraction by *tert*-butyl cations from electron-rich and electronpoor 1,3-diphenylpropanes. *Int. J. Mass Spectrom.* **2006**, *255/256*, 195–212.
12. D. Kuck, C. Matthias. Formation of gaseous π and ion-neutral complexes as probed by

interannular *tert*-butyl cation transfer in protonated *tert*-butyl-substituted diphenylalkanes. *J. Am. Chem. Soc.* **1992**, *114*, 1901–1903.

13. C. Matthias, S. Anlauf, K.Weniger, D. Kuck. Gaseous [*t*-$C_4H_9^+$ α,ω-diphenylalkane] complexes: methyl substituent effects on the intracomplex proton transfer and regioselective hydride abstraction. *Int. J. Mass Spectrom.* **2000**, *199*, 155–187.
14. C. Matthias, B. Bredenkötter, D. Kuck. Proton-induced intra-complex hydride transfer involving bicyclo[2.2.2]octane units as a rigid spacer and as a carbocation precursor. *Int. J. Mass Spectrom.* **2003**, *228*, 321–339.
15. H. E. Audier, F. Dahhani, A. Milliet, D. Kuck. Hydride and proton transfer reactions in gaseous ion-molecular complexes [PhCH2$^+$ $HOCH_2CH_2OH$]. *Chem. Commun.* **1997**, 429–430.
16. D. Kuck, C. Matthias, D. Barth, M. C. Letzel. Isomerization of the constituents of ion/neutral complexes during the fragmentation of protonated dialkyl-substituted 1,3-diphenylpropanes. *Int. J. Mass Spectrom.* **2011**, *306*, 167–174.
17. D. Kuck. Concomitant hydride and proton transfer: an essay on competing and consecutive key reactions occurring in gaseous ion/neutral complexes. *Eur. J. Mass Spectrom.* **2012**, *18*, 161–181.
18. Y. Chai, K. Jiang, Y. Pan. Hydride transfer reactions via ion-neutral complex: Fragmentation of protonated *N*-benzylpiperadines and proprotonated *N*-benzylpiperazines in mass spectrometry. *J. Mass Spectrom.* **2010**, *45*, 496–503.
19. D. Kuck, H.-F. Grützmacher, D. Barth, S. Heitkamp, M. C. Letzel. The role of ion/neutral complexes in the fragmentation of *N*-benzyl-(alkylpyridinium) ions. *Int. J. Mass Spectrom.* **2011**, *306*, 159–166.
20. F. Li, X. Zhang, H. Zhang, K. Jiang. Gas-phase fragmentation of the protonated benzyl ester of proline: intramolecular electrophilic substitution versus hydride transfer. *J. Mass Spectrom.* **2013**, *48*, 423–429.
21. Y. Chai, K. Jiang, C. Sun, Y. Pan. Gas-phase nucleophilic aromatic substitution between piperazine and halobenzyl cation: Reactivity of the methylene arenium form of benzyl cation. *Chem. Eur. J.* **2011**, *17*, 10820–10824.
22. Y. Chai, L. Wang, L. Wang. How does a C=C double bond cleave in the gas phase?

Fragmentation of protonated ketotifen in mass spectrometry. *J. Mass Spectrom.* **2016**, *51*, 1105–1110.

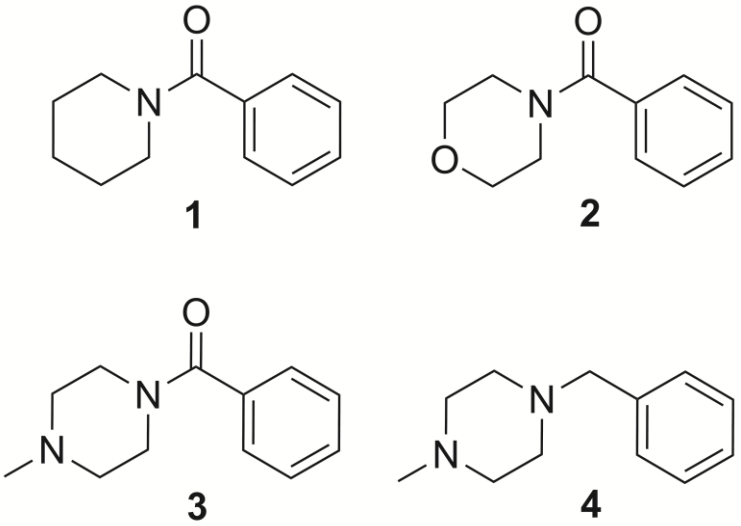
23. J. C. Sheldon, J. H. Bowie, S. Dua. The gas-phase Cannizzaro disproportionation reactions of benzaldehyde and pivaldehyde. *J. Org. Chem.* **1997**, *62*, 3931–3937.
24. J. M. Garver, Z. Yang, S. Kato, S. W. Wren, K. M. Vogelhuber, W. C. Lineberger, V. M. Bierbaum. Gas phase reactions of 1,3,5-triazine: proton transfer, hydride transfer, and anionic σ-adduct formation. *J. Am. Soc. Mass Spectrom.* **2011**, *22*, 1260–1272.
25. L. Yao, Y. Chai, C. Sun, Y. Pan. Competitive proton and hydride transfer reactions via ion-neutral complexes: fragmentation of deprotonated benzyl *N*-phenylcarbamates in mass spectrometry. *J. Mass Spectrom.* **2015**, *50*, 364–370.
26. J. C. Moore, D. J. Pollard, B. Kosjek, P. N. Devine. Advances in the enzymatic reduction of ketones. *Acc. Chem. Res.* **2007**, *40*, 1412–1419.
27. B. T. Cho. Recent development and improvement for boron hydride-based catalytic asymmetric reduction of unsymmetrical ketones. *Chem. Soc. Rev.* **2009**, *38*, 443–452.
28. S. Gronert, J. R. Keeffe. Identify hydride-ion transfer from C-H donors to C acceptor sites. Enthalpies of hydride addition and enthalpies of activation. Comparison with C···H···C proton transfer. An ab initio study. *J. Am. Chem. Soc.* **2005**, *127*, 2324–2333.
29. X.-Q. Zhu, X. Chen, L.-R. Mei. Determination of hydride affinities of various aldehydes and ketones in acetonitrile. *Org. Lett.* **2011**, *13*, 2456–2459.
30. L. A. B. Moraes, M. N. Eberlin. Structurally diagnostic ion–molecule reactions: acylium ions with α-, β- and γ-hydroxy ketones. *J. Mass Spectrom.* **2002**, *37*, 162–168.
31. E. C. Meurer, M. N. Eberlin. Mono and double polar [4 + 2^+] Diels–Alder cycloaddition of acylium ions with *O*-heterodienes. *J. Mass Spectrom.* **2002**, *37*, 146–154.
32. L. A. B. Moraes, T. Kotiaho, M. N. Eberlin. Gas-phase chemistry of acylium ions. Seven-to-five ring contraction of 1,3-dioxepane and 1,3-dioxep-5-ene. *J. Mass Spectrom.* **1999**, *34*, 670–676.
33. E. C. Meurer, L. A. B. Moraes, M. N. Eberlin. Cyclization of acylium ions with nitriles: gas-phase synthesis and characterization of 1,3,5-oxadiazinium ions. *Int. J. Mass Spectrom.* **2001**, *212*, 445–454.
34. J. A. Blair, G. P. McLaughlin, J. Paslawski. The reaction of cycloheptatriene with

benzoylium fluoroborate. *Chem. Commun*. **1967**, 12–13.

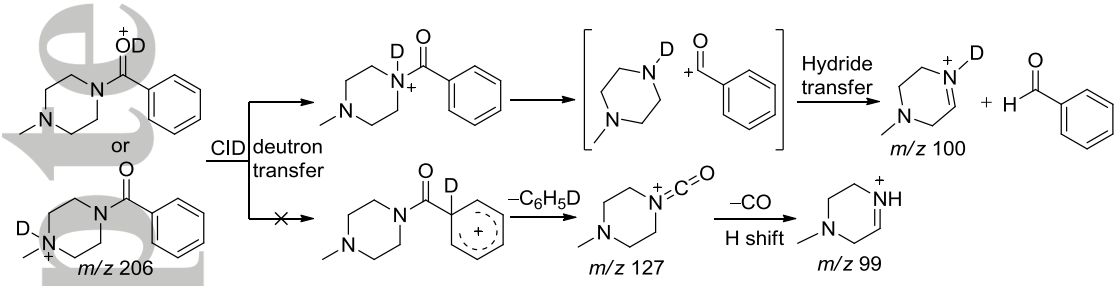
35. C. S. Creaser, B. L. Williamson. Selective gas-phase ion-molecule reactions of the benzoyl ion. *J. Chem. Soc., Chem. Commun.* **1994**, 1677–1678.
36. C. S. Creaser, B. L. Williamson. Ion-molecule reactions of benzoyl ions in a quadrupole ion trap mass spectrometer. *J. Chem. Soc., Perkin Trans. 2* **1995**, 427–433.
37. A. P. Bruins, N. M. M. Nibbering. ICR study on benzoylation reactions in gas-phase. *Tetrahedron Lett.* **1975**, 4491–4494.
38. B. L. Williamson, C. S. Creaser. Letter: ion–molecule reactions of the benzoyl ion $[C_6H_5CO]^+$ with compounds containing the amine functional group in a quadrupole ion trap. *Eur. Mass Spectrom.* **1998**, *4*, 103–106.
39. G. E. Reid, S. E. Tichy, J. Pérez, R. A. J. O'Hair, R. J. Simpson, H. I. Kenttämaa. *N*-Terminal derivatization and fragmentation of neutral peptides via ion-molecule reactions with acylium ions: toward gas-phase Edman degradation? *J. Am. Chem. Soc.* **2001**, *123*, 1184–1192.
40. Y.-P. Tu. Dissociative protonation sites: reactive centers in protonated molecules leading to fragmentation in mass spectrometry. *J. Org. Chem.* **2006**, *71*, 5482–5488.
41. Y.-P. Tu, A. G. Harrison. Fragmentation of protonated amides through intermediate ion–neutral complexes: neighboring group participation. *J. Am. Soc. Mass Spectrom.* **1998**, *9*, 454–462.
42. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A.

Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople. Gaussian 03, Gaussian, Inc., Pittsburgh PA, 2003

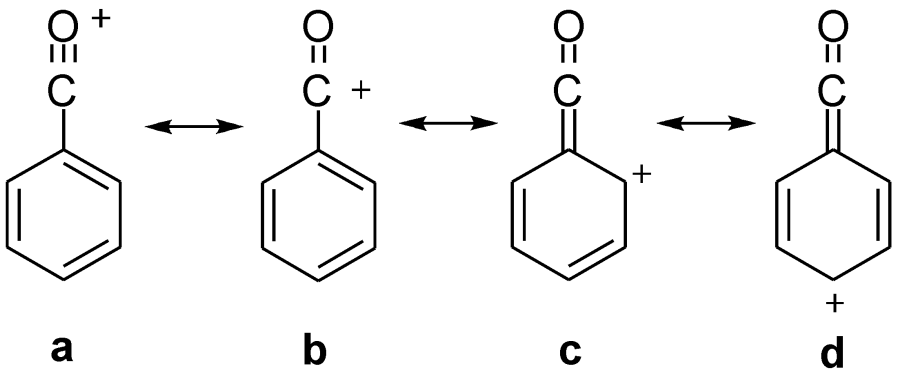
43. Y.-P. Tu. Fragmentation of conjugated amides at the C–C(O) bond in electrospray mass spectrometry: a proton-bound dimeric intermediate identified by the kinetic method. *Rapid Commun. Mass Spectrom.* **2004**, *18*, 1345–1351.
44. H.-Y. Lin, D. P. Ridge, E. Uggerud, T. Vulpius. Unimolecular chemistry of protonated formamide. Mass spectrometry and ab initio quantum chemical calculations. *J. Am. Chem. Soc.* **1994**, *116*, 2996–3004.
45. R. Boyd, Á. Somogyi. The mobile proton hypothesis in fragmentation of protonated peptides: a perspective. *J. Am. Soc. Mass Spectrom.* **2010**, *21*, 1275–1278.
46. G. A. Olah, P. W. Westerman. Stable carbocations. CXLIV. The structure of benzoyl cations based on their carbon-13 nuclear magnetic resonance spectroscopic study. The importance of delocalized, "ketene-like" carbenium ion resonance forms. *J. Am. Chem. Soc.* **1973**, *95*, 3706–3709.
47. C. U. Pittman, B. Kim, Q. Y. Ng, L. D. Kispert. Theoretical study of charge distribution in the benzoyl and alkynoyl cations. *J. Chem. Soc., Perkin Trans. 2* **1976**, 621–623.
48. J. Oomens, J. M. Bakker, B. G. Sartakov, G. Meijer, G. von Helden. The infrared spectrum of the benzoyl cation. *Chem. Phys. Lett.* **2003**, *367*, 576–580.
49. E. P. L. Hunter, S. G. Lias. Evaluated gas phase basicities and proton affinities of molecules: an update. *J. Phys. Chem. Ref. Data* **1998**, *27*, 413–656.
50. Y.-P. Tu, Y. Huang, C. Atsriku, Y. You, J. Cunniff. Intramolecular transacylation: fragmentation of protonated molecules via ion-neutral complexes in mass spectrometry. *Rapid Commun. Mass Spectrom.* **2009**, *23*, 1970–1976.
51. Y.-P. Tu. Dissociative protonation and fragmentation: retro-Friedel–Crafts reactions of heterocyclic drug and metabolite molecules in mass spectrometry. *Int. J. Mass Spectrom.* **2012**, *316-318*, 40–46.



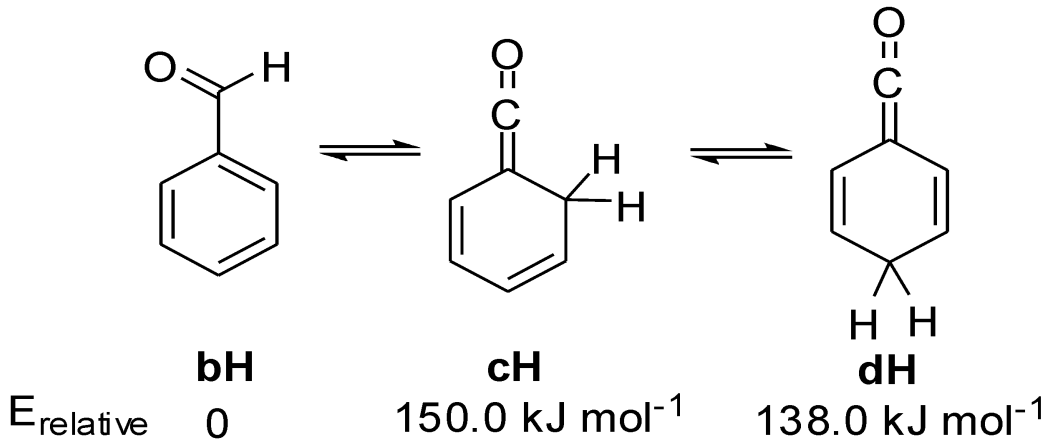
Scheme 1. The structures of compounds studied.



Scheme 2. The proposed fragmentation mechanism of the $[M + D]^+$ ion of 1-benzoyl-4-methylpiperazine (*m/z* 206)



Scheme 3. The resonance of benzoyl cation.



Scheme 4. The computed relative energies of isomers of $C_7H_6O^+$ using DFT method at B3LYP/6-311++G(2d,p) theoretical level.

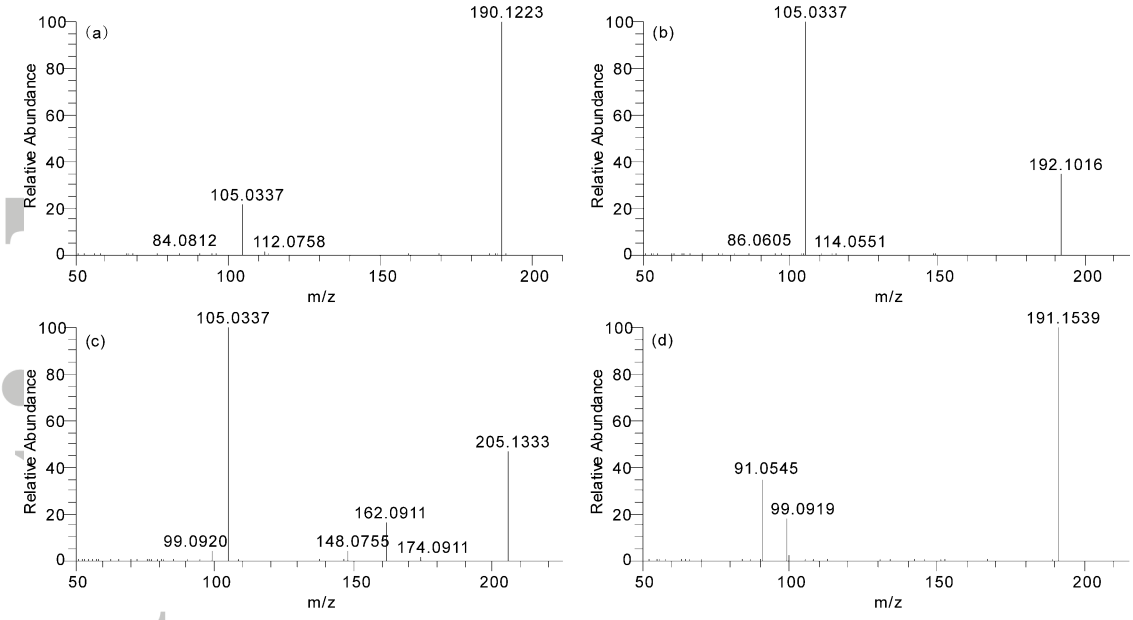


Figure 1. The MS/MS spectra of the $[M + H]^+$ ion of (a) 1-benzoyl piperadine (*m/z* 190.1223), (b) 1-benzoyl morpholine (*m/z* 192.1016), (c) 1-benzoyl-4-methylpiperazine (*m/z* 205.1333), and (d) 1-benzyl-4-methylpiperazine (*m/z* 191.1539) using a Q-orbitrap mass spectrometer (NCE 30%).

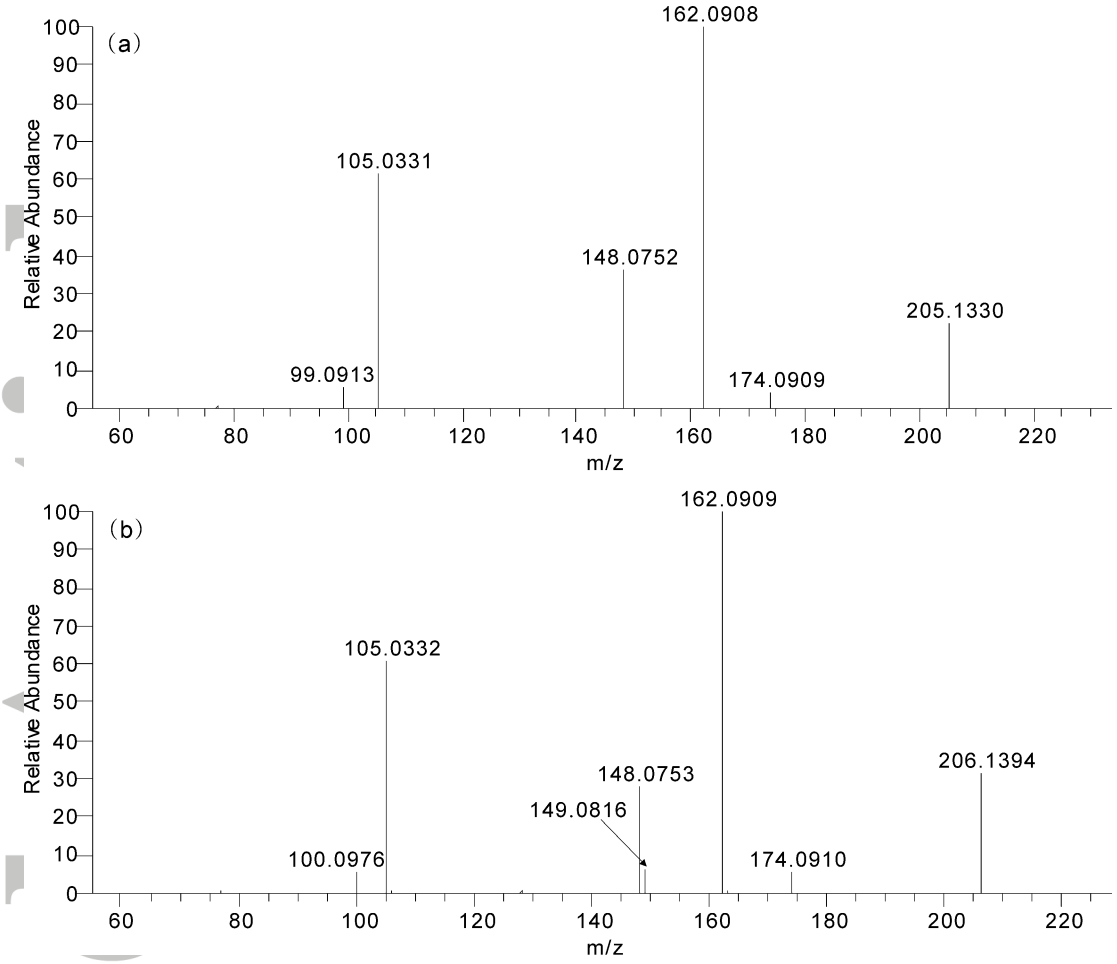


Figure 2. The MS/MS spectra of (a) $[M + H]^+$ ion of 1-benzoyl-4-methylpiperazine (*m/z* 205.1330) and (b) $[M + D]^+$ ion of 1-benzoyl-4-methylpiperazine (*m/z* 206.1394) using a LTQ-orbitrap mass spectrometer. The measured *m/z* value of each product ion is consistent with the theoretical one.

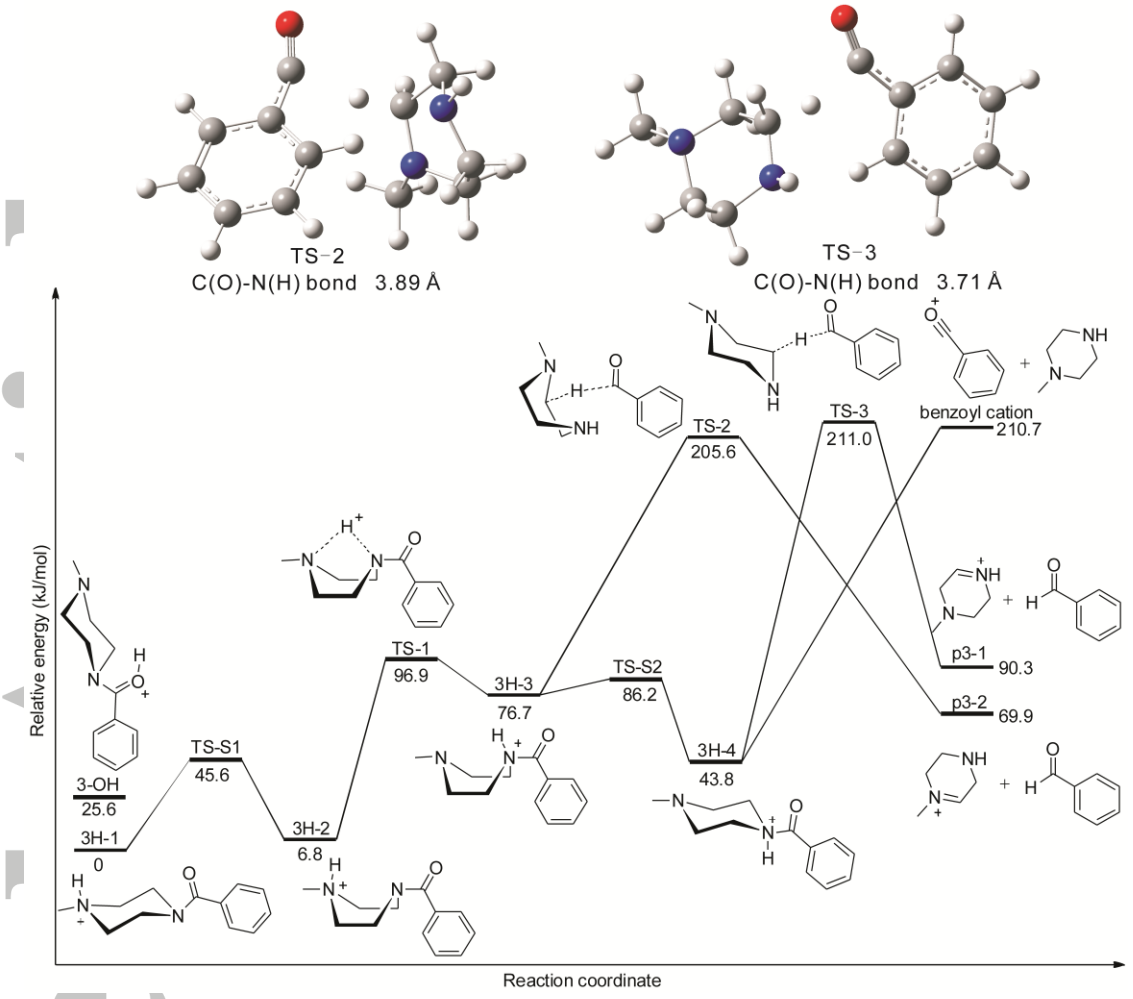


Figure 3. Potential energy surface (PES) of the fragmentation of protonated 1-benzoyl-4-methylpiperazine using DFT at the B3LYP level of theory with the 6-31++G(d,p) basis set. Relative energies are given in kJ mol^{-1}. The optimized structures of TS-2 and TS-3 are shown above the PES.

Table 1. Product ions generated in the fragmentation of protonated compounds **1-4** (NCE 30%).

Precursor ion	Product ions			
	Benzoyl cation	Benzyl cation	Iminium cation	Ratio [a]
[**1** + H]$^+$	105 (21.2) [b]	-	84 (0.37)	1.8
[**2** + H]$^+$	105 (100)	-	86 (0.22)	0.2
[**3** + H]$^+$	105 (100)	-	99 (3.86)	3.9
[**4** + H]$^+$	-	91 (34.81)	99 (17.61)	50.6

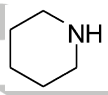
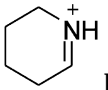
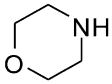
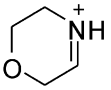
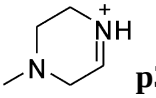
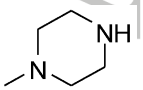
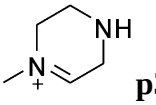
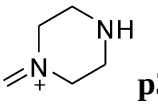
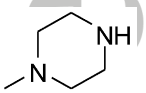
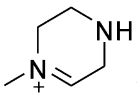
[a] the ratio of the abundance of iminium cation to that of benzoyl cation or benzyl cation

[b] *m/z* (relative abundance %)

Table 2. Accurate masses and elemental compositions of the product ions in the fragmentation of protonated 1-benzoyl-4-methylpiperazine (*m/z* 205.1330).

Measured mass	Elemental composition	Theoretical mass	Error (ppm)
99.0913	$C_5H_{11}N_2^+$	99.0917	-4.0
105.0331	$C_7H_5O^+$	105.0335	-3.8
148.0752	$C_9H_{10}NO^+$	148.0757	-3.4
162.0908	$C_{10}H_{12}NO^+$	162.0913	-3.1
174.0909	$C_{11}H_{12}NO^+$	174.0913	-2.3

Table 3. The relative energies of hydride transfer reactions between benzoyl cation/benzyl cation and selected secondary amines using DFT method at B3LYP/6-311++G(2d,p) theoretical level.

Amine	Cation	Iminium cation	Neutral species	$\Delta E_{relative}$ (kJ mol^{-1})
	Benzoyl cation	 **p1**	Benzaldehyde	−121.6
	Benzoyl cation	 **p2**	Benzaldehyde	−84.2
		 **p3-1**	Benzaldehyde	−112.3
	Benzoyl cation	 **p3-2**	Benzaldehyde	−133.3
		 **p3-3**	Benzaldehyde	−100.9
	Benzyl cation	 **p4**	Toluene	−192.1