

Unimolecular Fragmentation Properties of Thermometer Ions from Chemical Dynamics Simulations

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Abstract

Thermometer ions are widely used to calibrate the internal energy of the ions produced by electrospray ionization in mass spectrometry. Commonly used ions are benzyropyridinium ions with different substituents. More recently benzhydryropyridinium ions were proposed for their lower bond dissociation energies. Direct dynamics simulations using M06-2X/6-31G(d), DFTB, and PM6-D3 are performed to characterize the activation energies of two representative systems: *para*-methyl-benzyropyridinium ion (*p*-Me-BnPy⁺) and methyl,methyl-benzhydryropyridinium ion (Me,Me-BhPy⁺). The theoretical bond dissociation energies agree with the experiment. Simulation results are used to calculate rate constants for the two systems. These rate constants and their uncertainties are used to find the Arrhenius activation energies and RRK fitted threshold energies which give reasonable agreement with calculated bond dissociation energies at the same level of theory. There is only one fragmentation mechanism observed for both systems, which involves C-N bond dissociation via a loose transition state, to generate either benzylium or benzhydrylium ion and a neutral pyridine molecule. For *p*-Me-BnPy⁺ using DFTB and PM6-D3 the formation of tropylium ion, from rearrangement of benzylium ion, was observed but only at higher excitation energies and for longer simulation times. These observations suggest that there is no competition between reaction pathways that could affect the reliability of internal energy calibrations.

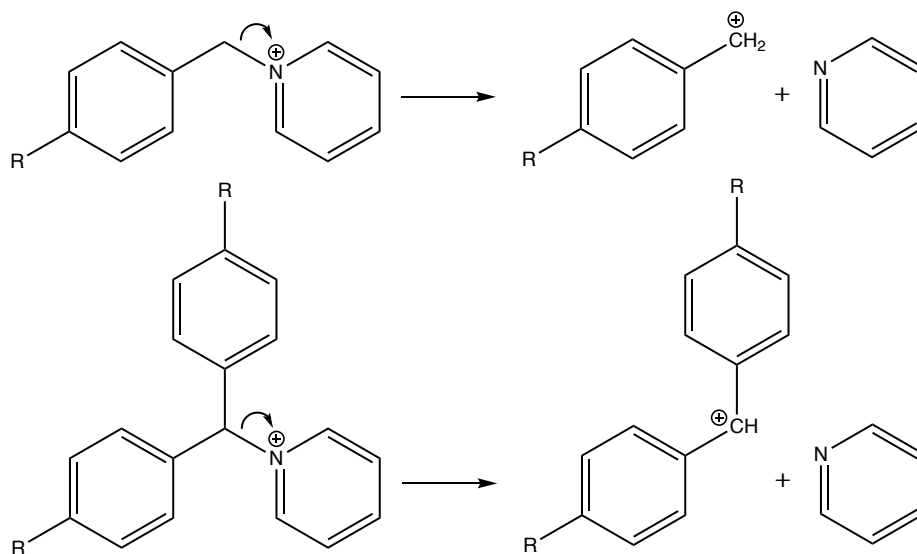
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1.Introduction

Understanding the characteristic temperature of ions produced by electrospray ionization (ESI) is of fundamental importance in mass spectrometry (MS).¹ The fragmentation yield in fact depends on the internal energy/temperature of such ions, but this quantity cannot be measured directly. At this end, the use of thermometer ions was introduced years ago: first studies by Cooks and co-workers focused on (C₂H₅)₄Si⁺, Fe(CO)₅⁺, and W(CO)₆⁺,²⁻⁴ while lately, benzyropyridinium (BnPy) ions were chosen as standard reference.^{5,6} The former ions in fact are more suited for electron ionization or photoionization while the latter for ESI, which has become in recent years the most used ionization technique to study biomolecular systems. Due to the softness of the ionization in ESI, structures are conserved, which is crucial to study peptides, sugars, proteins or other similar compounds.

To obtain internal energy distribution and thus characteristic temperature of the thermometer ions, a crucial quantity to know is the threshold energy. Quantum chemistry calculations can provide the bond dissociation energy (BDE) as the energy difference between products and reactants. This is possible in thermometer ions because they have simple one-product reactions characterized by a loose transition state (TS). Recently, a new set of thermometer ions was proposed, the benzhydrylpyridinium (BhPy) ions, which show lower activation energies than the original BnPy ions due to the addition of an extra phenyl ring that should weaken the C-N bond by stabilizing the resultant benzhydrylium ion.^{7,8} In **Scheme 1** we report the unimolecular fragmentations which characterize these two classes of thermometer ions.

Recently, chemical dynamics simulations were shown to be a useful tool to obtain unimolecular fragmentation energy thresholds.^{9,10} In particular, activation energies were obtained for fragmentation of relatively large peptides, for which it would be difficult to obtain these energies from potential energy surface scan.^{11,12} These values were obtained using Arrhenius phenomenological law and were found to be in agreement with barriers obtained from static calculations. RRK theory can also directly measure the threshold energies: a recent study on a model system has shown that the classical energy threshold differs from the quantum just by the (known) zero-point energy (ZPE) difference between the reactants and the products.¹³



Scheme 1. Fragmentation reactions for benzylpyridinium (BnPy^+ , upper panel) and benzhydrylpyridinium (BhPy^+ , lower panel) ions. In the present work, we have explicitly studied the methyl substituted ions ($R=\text{Me}$).

The results of chemical dynamics rely on the method used to describe, on-the-fly, the potential energy surface (PES) of the system. Accurate theoretical methods like coupled cluster or even extended basis sets with density functional theory (DFT) or MP2 are not feasible for relatively large systems. To obtain enough statistics, DFT (with small basis sets) or semi-empirical Hamiltonians are often used in chemical dynamics simulations of unimolecular fragmentation.^{14,15} Semi-empirical Hamiltonians are particularly used to study large systems, since one needs an ensemble of trajectories and different energy points to obtain the desired quantities. These simulations are mainly aimed to model ion trap-like experiments by activating the system via an excess internal energy. Results are collected as a function of this energy, but it is hard to make a direct comparison with experimental energies. The use of thermometer ions can be a possible way to calibrate simulations as done in experiments.

At this end, we have first investigated the ability of chemical dynamics in reproducing the known fragmentation properties of two thermometer ions (*p*-Me-BnPy⁺ and Me₂Me-BhPy⁺), belonging to the aforementioned BnPy and BhPy classes of compounds (they correspond to R=Me in structures reported in **Scheme 1**). In particular, we have tested the semi-empirical Hamiltonians, tight-binding DFT (DFTB), and DFT with relatively small basis set.

Secondly, we studied how simple kinetic theories, like RRK and Arrhenius-like, are able in obtaining threshold/activation energies and how they compare with static BDE. The use of more sophisticated kinetic approaches (like, e.g. those developed by Troe¹⁶⁻¹⁹ and usually applied to small systems) will need the knowledge of molecular parameters which will be almost impossible for large systems, like peptides or sugars. This will be crucial to correctly calibrate simulations of new systems with respect to the thermometer ion. Finally, we can have direct access to the molecular fragmentation mechanisms and products and verify what is proposed experimentally.

Our work aims to study how the chemical dynamics approach simulates the fragmentation of two prototypical thermometer ions. In particular we focus on how simple kinetic theories can be applied in order to further use them to calibrate fragmentation simulations in energy. This will finally allow to be more quantitative when using simulations in modeling multiple-collision fragmentations of complex systems.

2. Methods

2.1 Quantum Chemistry Calculations

Geometries for *p*-Me-BnPy⁺ and Me₂Me-BhPy⁺ were first optimized using Universal Forcefield²⁰ followed by four semi-empirical methods, density functional based tight binding (DFTB),²¹ and density functional theory (DFT). Static calculations were performed for the two systems to compute the numerical frequencies and bond dissociation energies (BDE) with or without zero-point energies (ZPE). Semi-empirical methods include PM7,²² PM6-D3,^{23,24} AM1,²⁵ and RM1.²⁶ DFTB with non-SCC^{27,28} (non-self-consistent charge) approximation was used. In particular we used the DFTB+ implementation of DFTB²⁹ containing many extensions to the original method. Slater-Koster parametrization set for C-H-N-O was used as reported by Gaus et al.³⁰ For DFT, different GGA, meta-GGA, and LDA functionals were tested in preliminary calculations. B3LYP^{31,32} and M06-2X³³ functionals were selected since they provided the best results. Thus, we considered for these two functionals different basis sets: 6-31G(d), 6-311+G(d,p) and cc-pVDZ. Chemical dynamics simulations were performed with 6-31G(d) (bigger basis sets are computationally too expensive to be practical). Note also that B3LYP and M06-2X are very popular functionals available in most quantum chemistry packages.

Semi-empirical calculations were performed with MOPAC2016,³⁴ DFT calculations with NWChem 6.8,³⁵ and DFTB with DFTB+ software.³⁶

2.2 Chemical Dynamics Simulations

The unimolecular dissociation dynamics of *p*-Me-BnPy⁺ and Me₂Me-BhPy⁺ were studied by direct dynamics simulations, which were performed using PM6-D3, non-SCC DFTB and M06-2X/6-31G(d). These methods were chosen as the best representatives for semi-empirical, DFTB

and DFT classes, based on the agreement with the experimental BDEs and the practicality of the computational expense.

Initial conditions were chosen as follows. First, the minimum energy geometries of the two systems were located for each different method. Then, the vibrational modes of these ions were randomly excited using classical microcanonical normal mode sampling,³⁷ resulting in initial positions and velocities in internal coordinates which reflected the excess vibrational energy considered. In particular we used initial excitation energies between 10.84 and 23.85 eV. The rotational energy of the ions was sampled using a Boltzmann distribution at 300 K. Then, initial positions and momenta were converted into Cartesian coordinates and trajectories were run with these initial conditions. Note that, for each method and system, this corresponded to an ensemble of initial conditions and thus an ensemble of resulting trajectories.

Trajectories were then produced by numerical integration of Newton equations of motion. In particular, we used the fourth-order symplectic algorithm^{38,39} with PM6-D3 Hamiltonian and velocity-Verlet⁴⁰ algorithm with DFTB and M06-2X simulations. The time steps (listed in the **Tables S1** and **S2** in the Supporting Information), as well as the integration method, were chosen to achieve energy conservation within 2%. Simulation times were set between 3 and 30 ps, as a function of the method and the energy. Details on simulation time length as well as the number of trajectories for each method, system and energy are listed in **Tables S1** and **S2**. Note that these chemical dynamics simulations provide the time evolution of atomic positions (and momenta). The analysis of key atomic distances is used to identify dissociation of a bond which represents a reactive trajectory. More details on simulations procedure are reported in a recent review article.⁹

PM6-D3 simulations were performed using the VENUS/MOPAC software package, in which MOPAC electronic structure computer program³⁴ is interfaced with VENUS chemical dynamics computer program.^{41,42} Simulations with DFTB+ were done using in-house VENUS/DFTB+ interface and M06-2X direct dynamics trajectories were performed with VENUS/NWChem interface.

2.3 Kinetic Analysis

From unimolecular fragmentation, it is possible to follow the abundance of precursor ion as a function of time, by counting at each time step the number of non-reactive ions, $N(t)$. Since there was no re-crossing of products to reactants in either system, a trajectory was considered reactive once C-N bond distance reached 3.0 Å. Monitoring this distance in time is crucial to follow the occurrence of the principal dissociation pathways of p -Me-BnPy⁺ and Me₂Me-BhPy⁺.

The decay of the initial population can be fitted with an exponential function,

$$\frac{N(t)}{N(0)} = e^{-kt} \quad (1)$$

obtaining the unimolecular rate constant, k (where $N(0)$ is the number of trajectories and t is the time). The fitted values of rate constants are reported with uncertainty providing 95% confidence interval.

The energy dependence can be reformulated in terms of temperature dependence, since for a classical system of s harmonic oscillators the well-known relation holds:⁴³

$$E_v = sk_B T \quad (2)$$

where E_v is the vibrational energy, k_B the Boltzmann constant and T the temperature. Both systems, p -Me-BnPy⁺ and Me₂Me-BhPy⁺, have a large number of normal modes: 78 and 117, respectively. It has been established previously⁴⁴ that for a molecule with a large number of normal modes s such that $s \approx s-1$, the classical Rice-Ramsperger-Kassel-Marcus (RRKM) rate constant $k(E)$ becomes equivalent to the classical transition state theory (TST) rate constant $k(T)$ if $E_o/E \ll 1$, where E_o is the unimolecular dissociation energy (in the Supporting Information we report the simple demonstration).⁴⁵ Both of these criteria are met for the simulations reported here. Since there is only one dissociation pathway for either system, its rate constant may be represented by the Arrhenius equation,

$$k(T) = Ae^{-\frac{E_a}{k_B T}} \quad (3)$$

where A is the pre-exponential factor (here temperature independent) and E_a , the activation energy, should correspond to the classical dissociation energy E_o ⁴⁶ and may be compared to the values given by the electronic structure theory methods used for the simulations. In previous studies, Arrhenius parameters have been derived from rate constants determined from direct and chemical dynamics simulations.^{11,12,44,47,48}

This simple approach, the Arrhenius theory, disregards any temperature dependence of the pre-exponential factor and activation energy. Often, an improved version of the Arrhenius expression is used:⁴⁹

$$k(T) = AT^m e^{-E/k_B T} \quad (4)$$

where $m < 0$ when E_a is lower than the barrier height of the underlying potential energy surface. It is in fact well documented that activation energies obtained from Arrhenius plots can underestimate the true underlying barrier.⁴⁹ This improved expression is able sometimes to provide a better description of the reactivity, with an activation energy closer to the barrier height, since it introduces the temperature dependence of the pre-exponential factor.^{13,49,50} We have thus also used Eq. 4 to analyze simulation results.

Simulations are microcanonical, so they can be analyzed using the RRKM theory, and they are also Newtonians, so the classical RRK theory holds:

$$k(E) = \nu \left(\frac{E - E_o}{E} \right)^{s-1} \quad (5)$$

where ν is a frequency factor (here an effective frequency) and E_o the energy threshold. From equation 5 it is possible to obtain equation 3 as reported in the Supporting Information.

The three models (corresponding to equations 3-5) were considered and equations were fitted using rate constants and their standard deviations as obtained from simulations using gnuplot software for fitting.

3.Results

3.1 Bond Dissociation Energy

Fragmentation of thermometer ions is usually characterized by a specific bond dissociation energy (BDE) which depends on the substituent group and its location on the benzyl ring.^{6,51} For BnPy ions, this BDE is for the C-N bond between the substituted benzylium cation and the neutral pyridine whereas for BhPy ions it is the dissociation energy between substituted benzyldrilium ion and the neutral pyridine (see **Scheme 1**, in the present case R=Me).⁵² It has been observed previously,^{6,7,51} that this reaction proceeds through a loose transition state (TS) i.e. reverse activation barrier can be neglected and the BDE can be calculated as the zero-point energy difference between the reactants and the products.

We report in **Table 1** the BDEs for both *p*-Me-BnPy⁺ and Me₂Me-BhPy⁺ as obtained from different theoretical methods and basis sets. Data are reported with and without ZPE to compare with the experimental as well as Newtonian simulation results. Note that experimental values were obtained presuming that the reaction occurred via a loose TS.^{7,53}

Table 1. Bond dissociation energies (in eV) for fragmentation of *p*-Me-BnPy⁺ and Me₂Me-BhPy⁺ (values at 0 K). In parenthesis, we report values without ZPE correction.

Method	<i>p</i> -Me-BnPy ⁺	Me ₂ Me-BhPy ⁺
B3LYP/6-31G(d)	1.92 (2.08)	0.88 (1.00)
B3LYP/6-311+G(d,p)	1.80 (1.96)	0.78 (0.92)
B3LYP/cc-pVDZ	1.89 (2.06)	0.42 (0.61)
M06-2X/6-31G(d)	2.42 (2.56)	1.61 (1.74)
M06-2X/6-311+G(d,p)	2.37 (2.55)	1.31 (1.44)
M06-2X/cc-pVDZ	2.44 (2.58)	1.40 (1.54)
AM1	1.61 (1.77)	0.78 (0.91)
RM1	1.94 (2.07)	1.39 (1.52)
PM6-D3	2.09 (2.21)	1.41 (1.53)
PM7	1.93 (2.08)	1.26 (1.38)
DFTB	2.11 (2.31)	1.45 (1.60)
DLPNO-CCSD(T) ^a	2.23 (2.36)	1.52 (1.63)
DLPNO-CCSD/CBS ^b	2.26	1.52
Experiments	2.26±0.13 ^c	1.55±0.13 ^d

^a DLPNO-CCSD(T)/pVTZ energies from M06-2X/6-311+G(d,p) geometries; ^bTheoretical values from PBE0/D3BJ geometries as reported by Rahrt et al.⁷; ^cExperimental values from Ref.53; ^dExperimental values from Ref.7.

CCSD(T) calculations provide BDEs in very good agreement with TCID experiments, that are reported to be 2.26±0.13 eV and 1.55±0.13 eV for *p*-Me-BnPy⁺ and Me₂Me-BH⁺, respectively.^{7,53} Note that our CCSD(T) results are also almost identical to recent calculations reported by Rahrt et al. at a very similar level of theory,⁷ DLPNO-CCSD/CBS//PBE0/D3BJ, reporting 2.26 and 1.52 eV for *p*-Me-BnPy⁺ and Me₂Me-BH⁺, respectively.

Unfortunately, CCSD(T) method is computationally too expensive to be used in direct dynamics simulations. We have thus tested the capability of computationally cheaper method in reproducing BDEs. We compare here values with and without ZPE. In fact, the former can be directly compared with experiments while the latter can be used to investigate how activation

or threshold energies extracted from chemical dynamics results compare with BDEs (trajectories are Newtonian and thus they do not have ZPE).

Concerning DFT results, the values obtained from M06-2X functional are globally more in agreement with experiments and CCSD(T) results than those from B3LYP. In the case of *p*-Me-BnPy⁺, M06-2X BDEs are overestimated by about 0.1-0.2 eV, while B3LYP underestimate them by about 0.3-0.4 eV, and for Me₂Me-BhPy⁺ M06-2X values are about 0.1-0.2 eV off from experiments, while B3LYP provides much bigger difference (underestimation between 0.67 to 1.13 eV). Interestingly, M06-2X with a relatively small basis set like 6-31G(d) provides BDEs not far from the experiments. M06-2X/6-31G(d) method was thus used in DFT simulations. DFTB BDEs are underestimated by only 0.13 eV and 0.10 eV for *p*-Me-BnPy⁺ and Me₂Me-BhPy⁺, respectively.

Between the different semi-empirical Hamiltonians used, PM6-D3 provides results that are more in agreement with experiments. In fact, BDE of *p*-Me-BnPy⁺ is underestimated by 0.17 eV and for Me₂Me-BhPy⁺ by 0.14 eV, which are close to the experimental uncertainty of 0.13 eV. We have thus used PM6-D3 in chemical dynamics simulations as well.

Globally, few methods which can be used in chemical dynamics simulations provide BDE values which are inside the experimental uncertainty: M06-2X/6-311+G(d,p) for *p*-Me-BnPy⁺ and M06-2X/6-31G(d), PM6-D3 and DFTB for Me₂Me-BhPy⁺. We have thus used M06-2X/6-31G(d), PM6-D3 and DFTB. Furthermore, for another ion of the BnPy family (the *para*-methoxy), we found relatively good agreement between values reported previously at CCSD(T) level of theory and calculated here, in particular when using M06-2X, DFTB and PM6-D3 (values are reported in **Table S3**).

Without consideration of ZPE the barrier increases by about 0.13 and 0.11 eV for *p*-Me-BnPy⁺ and Me₂Me-BhPy⁺, respectively. This should be considered in simulations, which are Newtonian and thus unimolecular dissociation will be slower than what is expected on the same potential energy surface including ZPE.

3.2 Unimolecular Fragmentation Rate Constants

Fragmentation dynamics were done at three levels of theory: M06-2X/6-31G(d), DFTB and PM6-D3. Both *p*-Me-BnPy⁺ and Me₂Me-BhPy⁺ provided only the expected fragmentation, i.e. the breaking of the C-N bond, as a result of the simple unimolecular dissociation. It is thus possible to follow the decay of the precursor ion as a function of time for each value of energy (and corresponding temperature). As shown in **Figure 1**, we obtain exponential decays, such that it was possible to fit these curves to obtain unimolecular rate constants. Results of the fits are reported in **Table 2**.

Trajectories were obtained by solving numerically the Newton's equations of motion and by on-the-fly calculations of energy and gradients using the three methods mentioned above. Resulting fragmentations thus reflect the motion on the classical potential energy surface (PES) and the associated BDEs are those reported without ZPE. The rate constants strongly depend on the method chosen because, as reported and discussed above, different methods provide different BDE values. This is particularly evident for lower energies (temperatures) which are closer to the barrier. For example, *p*-Me-BnPy⁺ at 13.0 eV internal energy shows a rate constant of 3•10⁹ s⁻¹ at DFTB level of theory, while the fragmentation is one order of magnitude faster

at PM6-D3 ($1.68 \cdot 10^{10} \text{ s}^{-1}$). This reflects the difference in BDE, which is lower at PM6-D3 level of theory than DFTB.

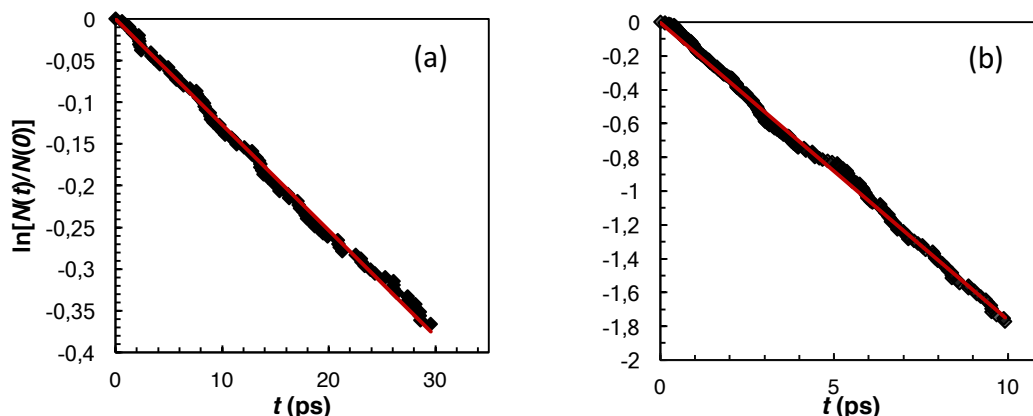


Figure 1. Plot of $\ln[N(t)/N(0)]$ vs t . for the simulations using DFTB for (a) Me-BnPy⁺ at 2266 K (15.18 eV) and (b) Me,Me-BhPy⁺ at 2374 K (23.85 eV). $N(t)$ is the number of surviving precursor ions at time t . The R^2 values for the fits are -0.9960 (panel a) and -0.9964 (panel b).

Table 2. Unimolecular rate constants (in s^{-1}) obtained from unimolecular fragmentation during chemical dynamics simulations. Results are reported as a function of energy and temperature which are coupled by Eq. 2.

	Energy (eV)	Temperature (K)	M06-2X	DFTB	PM6-D3
<i>p</i> -Me-BnPy ⁺					
	10.84	1618.8	-	-	$2.20 \pm 0.23 \cdot 10^9$
	11.92	1780.6	-	$9.00 \pm 0.29 \cdot 10^8$	$6.30 \pm 0.14 \cdot 10^9$
	13.00	1942.5	-	$3.00 \pm 0.41 \cdot 10^9$	$1.68 \pm 0.10 \cdot 10^{10}$
	14.09	2104.4	-	$5.90 \pm 0.30 \cdot 10^9$	$3.18 \pm 0.08 \cdot 10^{10}$
	15.18	2266.2	$1.74 \pm 0.53 \cdot 10^{10}$	$1.27 \pm 0.21 \cdot 10^{10}$	$6.03 \pm 0.07 \cdot 10^{10}$
	16.26	2428.1	$3.16 \pm 0.47 \cdot 10^{10}$	$2.68 \pm 0.16 \cdot 10^{10}$	-
	17.34	2590.0	$7.75 \pm 0.27 \cdot 10^{10}$	$4.94 \pm 0.13 \cdot 10^{10}$	$1.36 \pm 0.07 \cdot 10^{11}$
	19.51	2913.8	$2.00 \pm 0.21 \cdot 10^{10}$	$1.25 \pm 0.12 \cdot 10^{11}$	$2.50 \pm 0.09 \cdot 10^{11}$
	21.68	3237.5	$4.98 \pm 0.21 \cdot 10^{10}$	$2.87 \pm 0.12 \cdot 10^{11}$	-
Me,Me-BhPy ⁺					
	10.84	1079.2	-	-	$1.90 \pm 0.23 \cdot 10^9$
	13.00	1295.0	-	$3.00 \pm 0.77 \cdot 10^8$	$1.20 \pm 0.10 \cdot 10^{10}$
	15.18	1510.8	-	$4.20 \pm 0.61 \cdot 10^9$	$4.92 \pm 0.07 \cdot 10^{10}$
	16.26	1618.8	$6.17 \pm 0.31 \cdot 10^{10}$	-	-
	17.34	1726.7	$1.20 \pm 0.32 \cdot 10^{11}$	$9.90 \pm 0.40 \cdot 10^9$	$7.52 \pm 0.11 \cdot 10^{10}$
	19.51	1942.5	$3.29 \pm 0.22 \cdot 10^{11}$	$3.27 \pm 0.20 \cdot 10^{10}$	$1.79 \pm 0.15 \cdot 10^{11}$
	21.68	2158.3	$4.21 \pm 0.25 \cdot 10^{11}$	$9.44 \pm 0.15 \cdot 10^{10}$	$3.13 \pm 0.09 \cdot 10^{11}$
	23.85	2374.2	$5.86 \pm 0.22 \cdot 10^{11}$	$1.76 \pm 0.12 \cdot 10^{11}$	-

Due to the differences in BDEs calculated with each method, we sampled different energy values, that correspond to their fragmentation lifetimes, ($\tau = 1/k$). In fact, it is computationally expensive to simulate very slow processes with accurate statistics. Since PM6-D3 shows faster reactivity with respect to DFTB we were able to simulate lower activation energies with this

semi-empirical Hamiltonian, given that the two methods are computationally similar in terms of simulation time. M06-2X simulations are intrinsically computationally much slower and thus we could not simulate reactions with rate constants smaller than 10^{10} s^{-1} . Note also that M06-2X BDEs are higher than those obtained by PM6-D3 and DFTB. Details on reactivity percentage as a function of method and system are reported in the supporting information in **Tables S1 and S2**.

3.3 Activation, Threshold and Dissociation Energies

Rate constants reported in section 3.2 are then used to estimate activation and threshold energies, using Arrhenius and RRK dependence of the rate constant. The equivalence with temperature is possible, as detailed in section 2.3, for classical systems with a large number of degrees of freedom and energies much higher than the threshold. Phenomenologically, it was also seen that peptide fragmentation follows an Arrhenius like behavior.^{11,12,47} Results for both $p\text{-Me-BnPy}^+$ and $\text{Me}_2\text{Me-BhPy}^+$ reported in **Figure 2** show that also in this case an Arrhenius like behavior was observed. Thus, using Eq. 3 we obtain activation energies, which are reported in **Table 3**. The pre-exponential parameters are reported in the supporting information, **Table S4**.

Table 3. Activation, threshold and dissociation energies (in eV) as obtained from Arrhenius and RRK fits. In brackets we report the difference with respect to BDE value as calculated for each system and method.

	Method	$E_a^{(1)}$	$E^{(2)}$	$E_0^{(3)}$
$p\text{-Me-BnPy}^+$				
	M06-2X	2.20 ± 0.02 [-0.36]	2.78 ± 0.09 [+0.22]	1.98 ± 0.01 [-0.58]
	DFTB	1.95 ± 0.03 [-0.36]	2.40 ± 0.01 [+0.09]	1.74 ± 0.03 [-0.57]
	PM6-D3	1.51 ± 0.05 [-0.70]	1.96 ± 0.03 [-0.25]	1.37 ± 0.03 [-0.84]
$\text{Me}_2\text{Me-BhPy}^+$				
	M06-2X	0.97 ± 0.04 [-0.77]	1.40 ± 0.11 [-0.34]	0.94 ± 0.11 [-0.80]
	DFTB	1.52 ± 0.03 [-0.08]	1.91 ± 0.07 [+0.31]	1.41 ± 0.06 [-0.19]
	PM6-D3	0.94 ± 0.04 [-0.59]	1.25 ± 0.04 [-0.28]	0.88 ± 0.03 [-0.65]
MUA ⁽⁴⁾		0.48	0.25	0.60

⁽¹⁾ Arrhenius fit as from Eq.3; ⁽²⁾ modified Arrhenius fit with $m=-2.5$ as from Eq.4; ⁽³⁾ RRK fit as from Eq.5; ⁽⁴⁾ Mean Unsigned error (in eV) with respect to BDE values.

Here we can evaluate the ability of a simple Arrhenius fit in estimating the BDE, by comparing E_a with BDEs at the same level of theory and without ZPE, since the trajectories are Newtonian. For all methods and systems studied here, E_a values are systematically lower than corresponding BDEs. For $p\text{-Me-BnPy}^+$, M06-2X and DFTB show the same deviation (-0.36 eV) from the corresponding BDE (despite statistical sampling for M06-2X was much smaller than for DFTB), while PM6-D3 underestimates the value by 0.70 eV. On the other hand, for the larger system, $\text{Me}_2\text{Me-BhPy}^+$, M06-2X simulations report the largest difference from the corresponding BDE (-0.77 eV) whereas DFTB provides the fitted activation energy which is closer to its corresponding BDE (-0.08 eV).

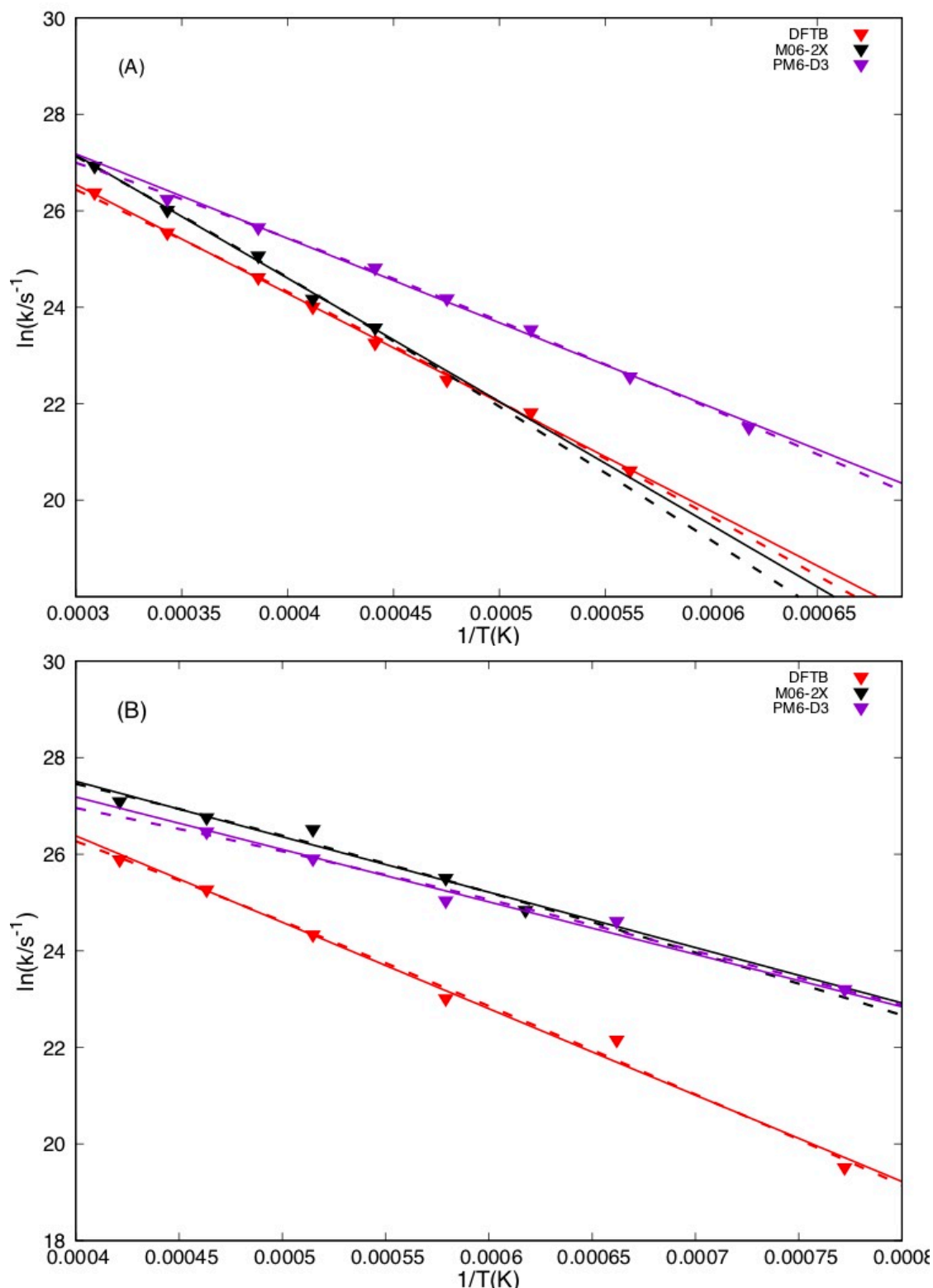


Figure 2. Rate constants (in s^{-1}) plotted against the inverse of temperature (T in K) for p -Me-BnPy⁺ and Me,Me-BhPy⁺ simulations (panels A and B, respectively). We report also the results of Arrhenius (continuous lines) and modified Arrhenius (dashed lines) fits (Eq. 3 and 4, respectively).

As discussed in section 2.3, often the Arrhenius activation energy is lower than the known energy threshold. A generalized Arrhenius law (Eq. 4), which introduces a temperature

dependence on the pre-exponential factor is often useful and is used here. In the present case, this introduces an additional parameter m , but as recently done for CH₄ model fragmentation,¹³ the data can be more efficiently fitted by fixing m . After some tests, we found that $m=-2.5$ provides small uncertainties in the fitting parameters and thus we used this value. Results are reported in the **Tables 3** and **S4**. Note that the m value is very close to what obtained for CH₄ with the same approach and it is negative, reflecting the fact that $E_a < \text{BDE}$. The modified-Arrhenius fit always results in an improvement of the energy threshold estimation, except for the case of Me₂Me-BhPy⁺ with DFTB in which the simple Arrhenius expression provides E_a very close to the corresponding BDE.

Microcanonical Newtonian simulations should follow an RRK behavior. In **Figure 3** we show energy dependence of rate constants together with RRK fits. The threshold energies obtained by the RRK fit, reported in **Table 3**, are systematically underestimated with respect to corresponding BDEs, following a behavior that is similar to what observed for E_a values obtained from simple Arrhenius fits.

Experimentally, rate constants were reported for the two systems, but only up to 6 and 4 eV for *p*-Me-BnPy⁺ and Me₂Me-BhPy⁺, respectively,^{7,53} and thus a direct comparison cannot be done. However, since the values at the highest energies reported (about $4 \cdot 10^9 \text{ s}^{-1}$ and 10^{10} s^{-1} for *p*-Me-BnPy⁺ and Me₂Me-BhPy⁺, respectively) are on the order of magnitude of what is found in simulations at higher energies, we can expect that simulations at low energies will largely underestimate the reaction rates. We should note that our extrapolations of rate constants at low energies can be poorly estimated for different reasons, like for example: (i) nuclear quantum effects are not taken into account; (ii) we cannot use Arrhenius-like expressions since $E \sim E_a$ (see section 2.3); (iii) we can use only the RRK expression which provides the worst description; (iv) simulations at low energies should be done, since finally the estimated E_o depends on the energy range, but this is not possible even by using cheaper methods like PM6-D3 or DFTB. Surely this should be kept in consideration when using thermometer ions simulations to calibrate other simulations and their comparison with experiments.

One important point concerns the ability (or not) of Arrhenius and RRK plots to provide energy thresholds closer to BDEs. In general, modified-Arrhenius equation provides E_a values which are closer to the corresponding BDEs as compared to Arrhenius and RRK fitted values. This finding is quantified by the mean unsigned error (MUA) calculated from the absolute difference between the activation or threshold energy, calculated from the fitting, and the BDE determined for each system and method (see **Table 3**). Clearly RRK fit provides the worst agreement, whereas the modified-Arrhenius provides values with the smallest MUA. Of course, the modified-Arrhenius expression has an extra parameter, improving the fit, but it also introduces a physical effect, namely the temperature dependence of the pre-exponential factor. In principle, it is possible to include energy dependence of pre-exponential factor and threshold energy in RRK theory, but the models available (also the simple one proposed by Song and Hase some years ago⁵⁴) introduce too many parameters with multiple exponentials, making the fit totally unstable. We should note, in fact, that when the fragmentation passes through a loose-TS, the energy threshold in RRK(M) theory has a temperature dependence, since the TS is defined from variational transition state theory (VTST).⁵⁵ Here the simple fits used clearly provide an average value for the energy region considered. This can be at the basis of the discrepancy between E_a and E_o and BDE. Note that in VTST the energy of the TS is always lower than the BDE, which is reflected in simple Arrhenius and RRK fit. Thus, to obtain E_o values closer to BDE, without introducing any temperature or energy dependence in the rate constant expression, one should

decrease the excess energy as much as possible in chemical dynamics simulations, which is computationally too slow to produce any meaningful results.

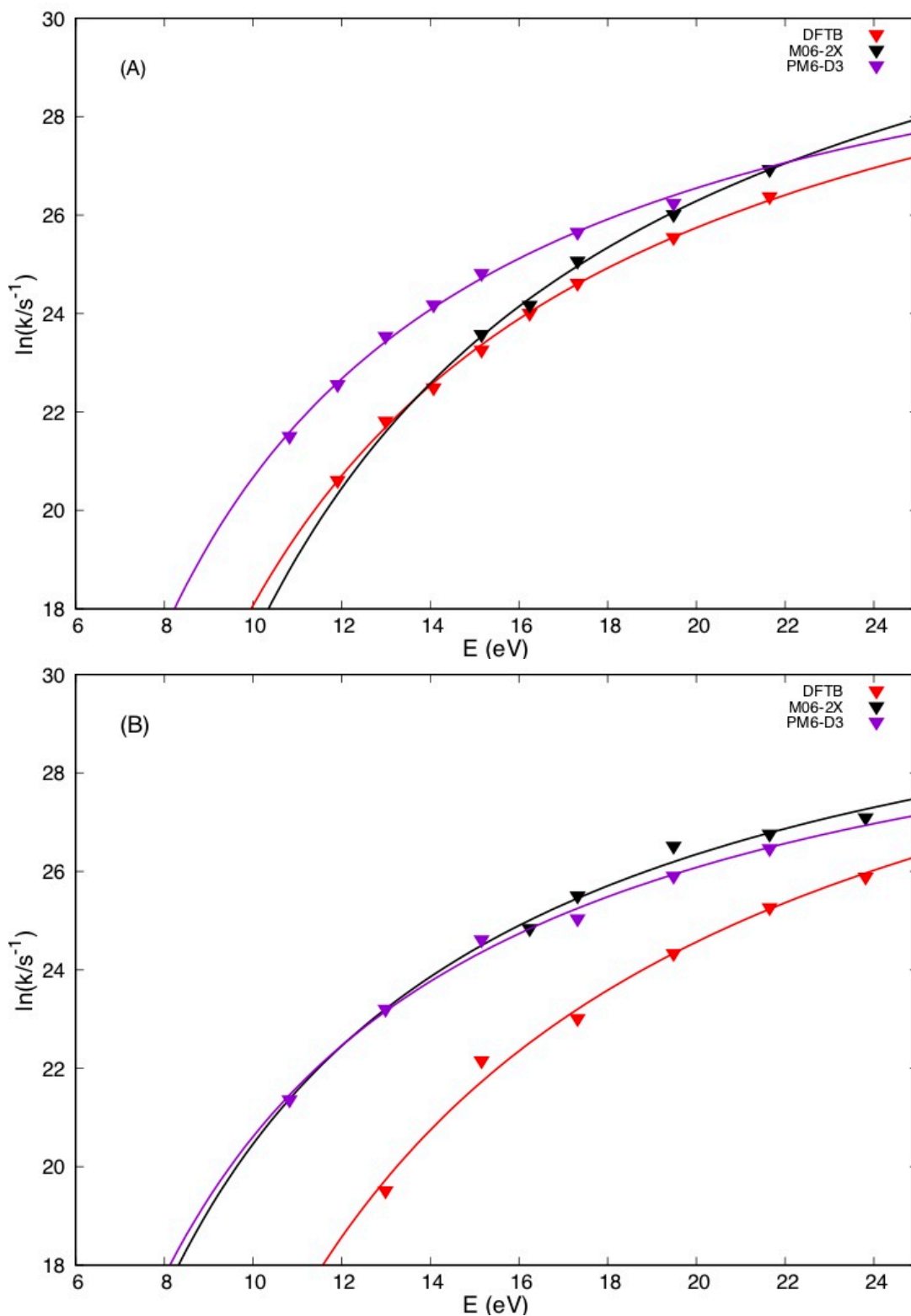


Figure 3. Rate constants as a function of internal energy and associated RRK fit as obtained from simulations of p -Me-BnPy⁺ (panel A) and Me,Me-BhPy⁺ (panel B).

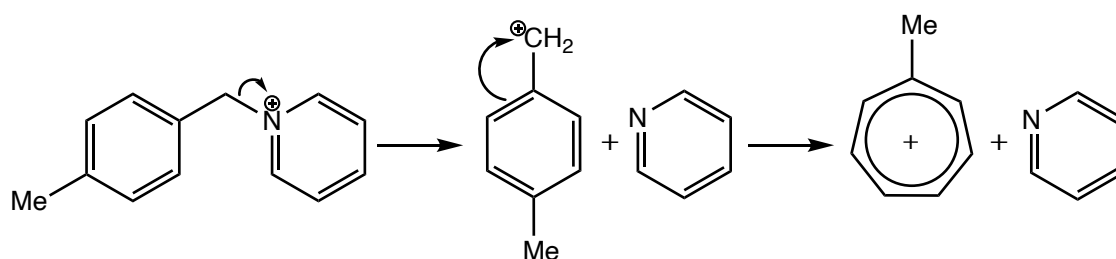
3.4 Reaction products

This section reports the fragmentation mechanisms of thermally excited p -Me-BnPy⁺ and Me₂Me-BhPy⁺ during direct dynamics simulations using M06-2X/6-31G(d), DFTB, and PM6-D3. Interestingly, for both ions the only bond dissociation observed is the one of C-N bond, as shown in **Scheme 1**.

For both systems, M06-2X required substantially higher energies to achieve fragmentation. The lowest energies considered for p -Me-BnPy⁺ and Me₂Me-BhPy⁺ using M06-2X were 15.18 and 16.26 eV, respectively. In comparison, for DFTB the lowest energies were 11.92 and 13.0 eV and 10.84 eV for PM6-D3. DFT simulations are computationally much slower, thus shorter simulation times and less trajectories are simulated. Globally, the aim was to have enough reactive trajectories for each method to calculate kinetic parameters in sections 3.2 and 3.3. Here we now provide some important mechanistic aspects of fragmentation.

Two competing fragmentation mechanisms have been suggested for benzylium ions.^{52,56} The first mechanism involves a loose transition state with direct bond cleavage (DC) to give a benzylium cation and neutral pyridine molecule.⁵² Following the second mechanism, the system is supposed to undergo a rearrangement process (RP) to generate a tropylium ion via a tight transition state.^{52,56-58} De Pauw et al. found, during the experimental studies, that it is unlikely that the mechanism proceeds through RP instead it is solely due to DC.⁵² During the simulations, only the DC mechanism was observed for p -Me-BnPy⁺ at all three levels of theory. As also reported by De Pauw, tropylium ion formation was not observed until C-N bond dissociated. De Pauw noted that harsher conditions and longer times in ion trap MS would lead to formation of tropylium whereas shorter times gave predominantly benzylium cation. Note that also Armentrout and co-workers provided experimental evidence that the tropylium cation is not formed.⁵³ Our simulation study confirms all these findings.

During thousands of simulations reported here for p -Me-BnPy⁺, the exclusive mechanism observed for product formation involved formation of a benzylium cation. In small percentage of trajectories at 10.84 and 13.0 eV, using PM6-D3 method, formation of tropylium ion was observed (3.9 % and 4.3 % of reactive trajectories) but only after substantial time had passed following C-N bond dissociation. In other terms, the mechanism involves breaking the C-N bond to form the benzylium ion which later may rearrange to yield a tropylium ion (see **Scheme 2** and a movie reported as supporting material, *trop_full.mov*, where unnecessary frames have been removed since benzylium to tropylium ion conversion takes a long time). For DFTB simulations tropylium ion formation was observed, in a similar fashion as PM6-D3, at 21.68 eV (1.7 % of reactive trajectories). This observation supports the previous findings that, if allowed, benzylium cation will form an equilibrium mixture favoring the thermodynamically more stable tropylium ion.^{52,59} In fact, the tropylium ion was found to be more stable than benzylium ion by 0.20 eV with PM6-D3, 0.33 eV with DFTB, and 0.32 eV with M06-2X/6-31G(d). As reference, we should notice that both M06-2X/6-311+G(d,p) and DLPNO-CCSD(T)/pVTZ reports an energy difference of 0.25 eV, in agreement with experimental values for different BnPy⁺ ions which are in 0.2-0.4 eV range.⁵³ Tropylium ion formation was not observed in direct dynamics simulations with M06-2X, likely because they were run for shorter time periods due to computationally expensive calculations.



Scheme 2. Fragmentation mechanism for the formation of tropylium ion through benzylium isomer intermediate following C-N bond dissociation in *p*-Me-BnPy⁺.

In simulations of benzhydrylpyridinium ion we do not observe the formation of any other product ion, neither before nor after C-N bond dissociation. This provides another advantage, in addition to the lower BDE, for using benzhydrylpyridinium ions as thermometer ions as compared to benzyldpyridinium ions since a competing dissociation pathway could compromise the reliability of calibration procedure.^{56,57} In our simulations of Me₂Me-BhPy⁺ using M06-2X/6-31G(d), DFTB, and PM6-D3 there was no competing pathway observed as compared to dissociation of C-N bond, forming a benzhydrylium ion and a neutral pyridine molecule, even though a wide range of energies (10.84 to 23.85 eV) were used to excite Me₂Me-BhPy⁺ in an attempt to model both softer and harsher experimental conditions.

4. Conclusions

In the work presented here chemical dynamics simulations were employed to investigate the unimolecular fragmentation energy thresholds and mechanisms of two thermometer ions, *p*-Me-BnPy⁺ and Me₂Me-BhPy⁺. The two systems have loose transition states and the threshold energies were used to determine the most efficient approach that can be used to estimate activation or threshold energies from chemical dynamics simulations.

Concerning the electronic structure theory, between the methods considered, M06-2X/6-31G(d), DFTB, and PM6-D3 provide the BDEs from static calculations that are most in agreement with experiments and highly-correlated calculations. They can be then used, with some care, in subsequent fragmentation simulations.

From simulations, rate constants were directly extracted and used from Arrhenius and RRK kinetic theories to estimate activation and threshold energies, respectively. A comparison of these values with BDEs, calculated with the same theory, showed that the modified-Arrhenius results are more in agreement with corresponding BDEs. Note that when a reaction has a loose TS, the variational transition state theory is the appropriate theory to define it, and as a consequence its position along the reaction coordinate (and associated energy) depends on the activation energy. Simple Arrhenius and RRK theories do not consider it explicitly and thus the resulting activation and threshold energies are underestimated with respect to the BDE. As briefly discussed in section 2.3 (and more developed in the Supporting Information) the two expressions are linked and the Arrhenius-like behavior can be applied only for activation energies that are much higher than the threshold energy. It is thus normal that both methods underestimate the barrier with respect to BDE. The modified-Arrhenius introduces empirically a temperature dependence on the pre-exponential factor, which in many cases improves the activation energy with respect to corresponding theoretical BDE. The activation or threshold energies obtained from different electronic structure theories have different trends with respect

to their corresponding BDEs (on average DFTB dynamical values are more similar to their corresponding static ones than M06-2X and PM6-D3): this is an interesting aspect which shows that other regions of the sampled potential energy surfaces also contribute to unimolecular fragmentation kinetics. In conclusion, it seems that the modified-Arrhenius expression should be considered most when using trajectories to evaluate activation energies.

Of course, the activation energies obtained from simulations should be, at a certain point, compared with experimental BDEs. The agreement depends on two aspects: (i) how does the electronic structure theory describe the potential energy surfaces and (ii) how do the trajectories and subsequent kinetic theories reproduce the BDE from activation or threshold energies. Considering the experimental uncertainty, one should look for values in the 2.13 – 2.39 and 1.4 – 1.68 eV range for *p*-Me-BnPy⁺ and Me₂Me-BhPy⁺, respectively. This is obtained in M06-2X simulation with Arrhenius fit, and in DFTB simulations with modified-Arrhenius fit for *p*-Me-BnPy⁺ and M06-2X with modified Arrhenius and DFTB with Arrhenius and RRK fits for Me₂Me-BhPy⁺. We should mention that simulations are Newtonian, so to be more quantitative with respect to experiments, nuclear quantum effects should be considered. Recently we have done a first test on a simple model unimolecular fragmentation reaction including nuclear quantum effects via the quantum thermal bath method.¹³ Now, we are planning to apply the same approach to more complex systems with semi-empirical and/or DFTB electronic structure theories and the thermometer ions should be surely considered when they will be computationally doable.

Thus, the present study opens the possibility of using chemical dynamics simulations to calibrate energy contents of ions when simulating fragmentation processes related to mass spectrometry by direct comparisons of reactivity between the thermometer and other ions of interests as a function of internal energy and simulation time-lengths. Of course, the known deviation of activation (or threshold) energy from experimental BDE should also be considered to finally link the energized ions in real mass spectrometers with the simulated ones.

Finally, simulations were able to show that the fragmentation of the thermometer ions occur only by direct cleavage of C-N bond. In the case of *p*-Me-BnPy⁺ some tropylium ions were found, but only after the rearrangement of the primary fragmentation product, benzylium ion. These observations suggest that there is no competition between direct cleavage and a rearrangement process and thus no tight transition state is involved in fragmentation. Notably, in addition to its lower bond dissociation energy, Me₂Me-BhPy⁺ fragmentation never showed the formation of other product ions, suggesting that this system can be a better candidate to act as a thermometer ion than *p*-Me-BnPy⁺.

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Supporting Information

In the supporting material, we report: Tables with details on simulation conditions, bond dissociation energies of *p*-OMe-BnPy⁺ at different levels of theory and pre-exponential parameters obtained from Arrhenius and RRK fits, derivation of equation 3 from equation 5. We also report the video file *trop_full.mov*.

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