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Morita–Baylis–Hillman Reaction: ESI-MS(/MS) Investigation with Charge Tags and Ionic Liquid Effect Origin Revealed by DFT Calculations

Thyago S. Rodrigues,[†] Valter H. C. Silva,[†,‡] Priscila M. Lalli,[§] Heibbe C. B. de Oliveira,[†] Wender A. da Silva,[†] Fernando Coelho,[§] Marcos N. Eberlin,[§] and Brenno A. D. Neto*[,†]

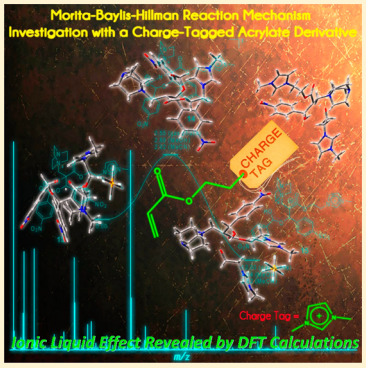
[†]Laboratory of Medicinal and Technological Chemistry, University of Brasília, Chemistry Institute (IQ-UnB), Campus Universitário Darcy Ribeiro, P.O. Box 4478, 70904-970 Brasília, DF, Brazil

[‡]Unidade Universitária de Ciências Exatas e Tecnológicas, Universidade Estadual de Goiás, P.O. Box 459, 75001-970 Anápolis, GO, Brazil

[§]ThoMSon Mass Spectrometry Laboratory, University of Campinas-UNICAMP, 13083-970 Campinas, SP, Brazil

Supporting Information

ABSTRACT: The use of a charge-tagged acrylate derivative bearing an imidazolium tag to study the Morita–Baylis–Hillman reaction via ESI-MS(/MS) monitoring and the effect of such tag (imidazolium cations and ion pairs) over TSs is described. The ionic nature of the substrate was meant to facilitate ESI transfer to the gas phase for direct mass spectrometric analysis. The detection and characterization of charged intermediates has suggested major reaction pathways. DFT calculations considering the effect of a polar and protic solvent (methanol), of a polar and aprotic solvent (acetonitrile), and of no solvent (gas phase) were used to predict possible TSs through a common accepted intermediate. The controversial proton transfer step, which may proceed via Aggarwal's or McQuade's proposals, was evaluated. Calculations predicted the formation of electrostatic intermediate complexes with both the cation and anion when charge-tagged reagents are used. These complexes contribute to the positive ionic liquid effect, and based on the formation of these unique complexes, a rationale for the ionic liquid effect is proposed. These complexes also pointed to a plausible explanation for the positive ionic liquid effect observed in several reactions that are difficult to be carried out in organic solvents but have shown a beneficial effect when performed in ionic liquids.



INTRODUCTION

Proper knowledge of reaction mechanisms guides the development of rationally designed catalysts, appropriate stereochemical control, and the elaboration of efficient synthesis of new molecules, especially those with biological and/or technological interest. The Morita–Baylis–Hillman (MBH) reaction provides an elegant and efficient route to generate new σ C–C bonds yielding α-methylene-β-hydroxy derivatives.[1−3] The MBH reaction has been known for a long time,[4] but it is currently experiencing a return to prominence due to recent improvements in the experimental conditions and catalysts leading to higher yields and selectivities.[5−7]

Despite its broad use, the MBH reaction mechanism (Scheme 1) and the actual transition states to some key intermediates are still a matter of debate and intense investigation.

The commonly accepted mechanism for the MBH transformation (Scheme 1) involves reversible conjugated addition of the nucleophilic catalyst (usually an amine or phosphine) to the activated alkene to generate an enolate (step I), which is followed by nucleophilic attack of this in situ formed enolate on the aldehyde, affording therefore a second zwitterionic intermediate (steps II and III). An elimination reaction (step IV) that releases the amine catalyst forms the final MBH product. The MBH mechanism was initially proposed by Hill and Isaacs[8] and later revisited by others.[9,10] The ongoing debate on the MBH mechanism has been fuelled by recent experimental and theoretical contributions.[11−14] The general catalytic cycle depicted in Scheme 1 seems to be now well accepted,[15] and debates are now centered on the rate-determining step, that is, the dynamics of the hydrogen shift (as well as the source of this hydrogen) from **5** (Scheme 1). Two major propositions for the H-shift have been offered by Aggarwal[16] and McQuade[17,18] (Scheme 2) based on kinetics and isotopic effects.

The two alternative propositions refute the direct intramolecular H-transfer previously suggested (Scheme 2). Aggarwal's proposition seems to be preferred in protic and polar solvents (e.g., methanol, ethanol), and that of McQuade is more likely in aprotic solvents, whereas the simultaneous occurrence of both seems likely in some cases,[15] especially depending on the amount of protic species on the reaction

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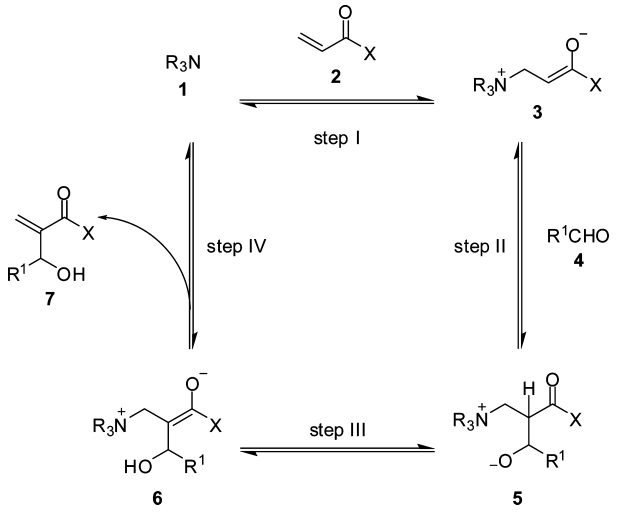
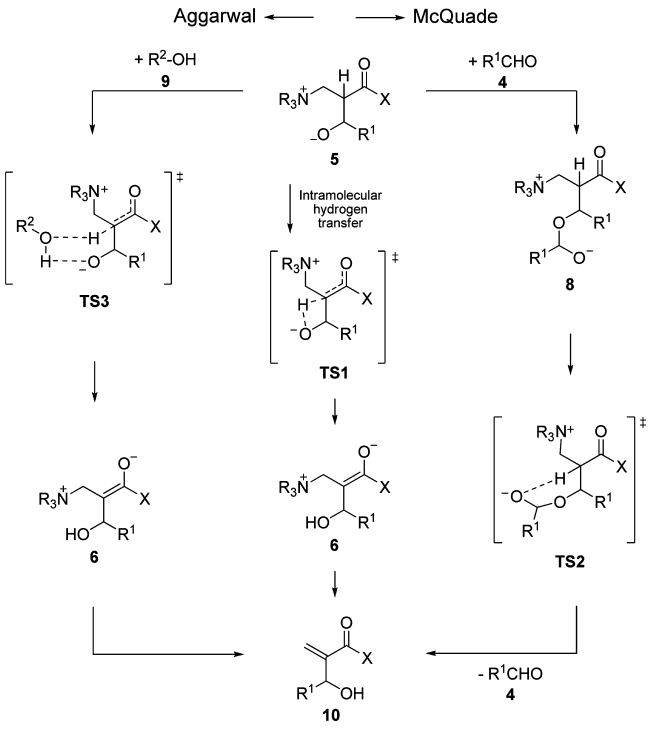
Scheme 1. Basic Catalytic Cycle for the Morita–Baylis–Hillman (MBH) Reaction and MBH Adduct (7) Formation



Scheme 2. Alternative Routes for the Hydrogen Transfer Rate-Limiting MBH Step from Intermediate 5 As Proposed by Aggarwal and McQuade



medium. An interesting unified mechanistic view has been also proposed by Kappe.[15]

Electrospray ionization (tandem) mass spectrometry (ESI-MS and ESI-MS/MS) has been demonstrated to provide a suitable tool to monitor reaction solutions and has been extensively explored to study the MBH reaction,[19−21] as reviewed elsewhere.[22] ESI-MS is visualized as functioning as a bridge connecting solution and gas phase chemistries,[23] gently transferring ions from reaction solutions to the gas phase. This direct "fishing" of charged species[24] occurs for anions and cations or even charged radicals.[25] This possibility of direct transfer to the gas phase of major, intact, and undisturbed chemical species present in reaction solutions has therefore established ESI-MS as an efficient technique applicable to the online evaluation of reaction solutions and mechanisms.[26] Due to its high sensitivity and fast analyses, ESI-MS has also been shown to be able to characterize even transient species that are formed and consumed rapidly, therefore not accumulating in the reaction solution.[27] ESI-MS has been therefore capable of providing continuous snapshots of the ionic composition of many different reaction solutions. A major limitation of ESI-MS is, however, its blindness to neutrals, and therefore in most cases acidification or basification of the reaction solution is required so as to promote either protonation or deprotonation of neutrals. This pH change may influence reactivity, whereas some key neutrals may escape detection due to inefficient ionization. To overcome this drawback, an elegant strategy based on the use of charge tags has been developed.[28] Such a charge tag favors ESI transfer, thus warranting fishing of most species including some that could have eventually remained undetected. The charge tag strategy has been successfully used, for instance, to monitor transient species of Pd-promoted cross-coupling reaction.[29,30] Recently, we have shown the in situ formation of reactive organometallics for Heck and Suzuki reactions by using an imidazolium moiety as the charge tag.[31] We have also studied the oxidation[32] and reduction[33] of olefins by using a charge-tagged iron complex with successful detection of transient high-valent iron species. This elegant strategy of charge tags also allowed us to investigate the Ugi multi-component (four-component) reaction.[34]

Additionally, the use of imidazolium-ion charge tags would make the intercepted species attractive probes to study the effect of an ionic medium, especially the ionic liquid (IL) effect,[35−37] on the stability and reactivity of MBH intermediates. The beneficial use of ILs for the MBH reaction has been described. For instance, imidazolium-based ILs have been used as solvents for the MBH reaction, and improved yields were noted.[38] Latter, it was demonstrated that imidazolium ions from ILs used as reaction media may induce side reactions such as carbene (generated in situ) addition to the aldehyde.[39] Some task-specific ILs were further tested as the promoters of the MBH reaction with excellent yields,[40−43] including some chiral versions.[44−46] In general, ILs have been observed to have a positive effect over the MBH reaction, but the origin of the IL effect itself has been highly controversial. Hydrogen bonds have been considered to play a crucial role[35] for cation–anion interactions, whereas others have attributed high importance to pure electrostatic interactions.[47]

In this context, this paper describes the monitoring via ESI-MS[48−51] of a MBH reaction using an imidazolium ion as the charge tag. We have previously used ESI-MS to investigate different aspects of the mechanism of the MBH reaction,[19−21,52−55] but charge tags have not been previously applied in such investigations. The use of charge tag in this study was meant to both facilitate uniform (quantitative) ESI fishing of major reaction intermediates,[52,54,55] therefore allowing the most comprehensive as possible detection of major MBH intermediates, as well as to allow investigation of the IL effect. To help us to propose a solid rationale for the origin of the positive IL effect on the MBH reactions, theoretical evaluation (DFT calculations) of major TSs were performed, bearing in mind the ion-pairing effects, and a comparison for structures calculated in the presence and absence of the IL anion, and the likely formation of the so-called electrostatic intermediate complexes in the intrinsic reaction coordinate.

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RESULTS AND DISCUSSION

An acrylate derivative with an imidazolium-ion charge tag (**11**) was used (Figure 1).

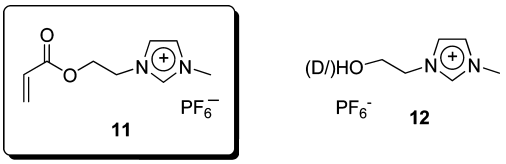

Figure 1. Charge-tagged derivatives.

To form **11**, the known alcohol **12**[56] was treated with acryloyl chloride in acetonitrile or methyl imidazol added to the chlorine-containing ester (Supporting Information, Scheme S1). Acrylate **11** was characterized by high-resolution and accuracy ESI(+)-MS/MS (Supporting Information, Figure S1). Reaction solutions (100 μM) of **11**, DABCO (amine catalyst), and 4-nitrobenzaldehyde with and without the addition of thiourea were prepared and analyzed by ESI(+)-MS, and the spectra were compared after 5 and 60 min of reaction (Figure 2).

We have investigated the role of thioureas as catalysts in MBH reactions via ESI-MS monitoring, showing that thioureas activate the acrylate C═O for electrophilic attack.[53] Indeed, thiourea-containing derivatives with acidic hydrogens have been used as organocatalysts capable of activating C═O bonds toward addition reactions,[57−59] including the MBH reaction, as reviewed elsewhere.[60] Confirming this role, if thiourea is added, indeed a key species of m/z 257 corresponding to **11** (m/z 181) plus thiourea, that is, [**11** + thiourea]$^+$ of m/z 257, is promptly detected after 5 or 60 min (Figure 2B and D). Figure 3 shows the ESI(+)-MS/MS of [**11** + thiourea]$^+$ of m/z 257.

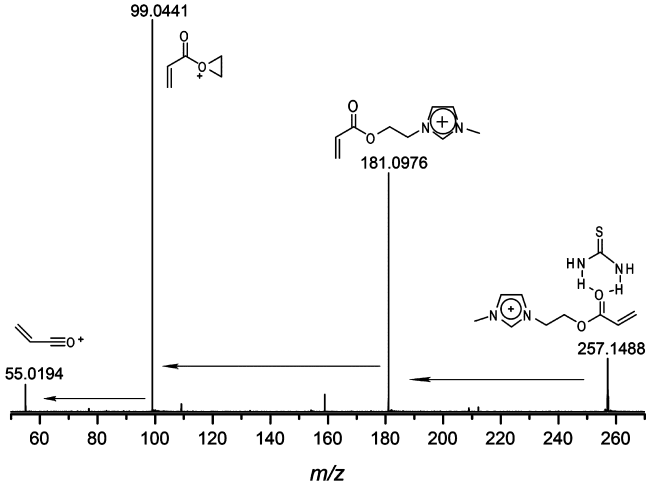

Figure 3. ESI(+)-MS/MS of the supramolecular species of m/z 257 (i.e., [**11** + thiourea]$^+$).

Dissociation by loss of thiourea followed by dissociation of the charge-tagged **11** confirms the structural assignment. The ion of m/z 453 was attributed to [**11** + **12** + PF_6^-]$^+$ (Supporting

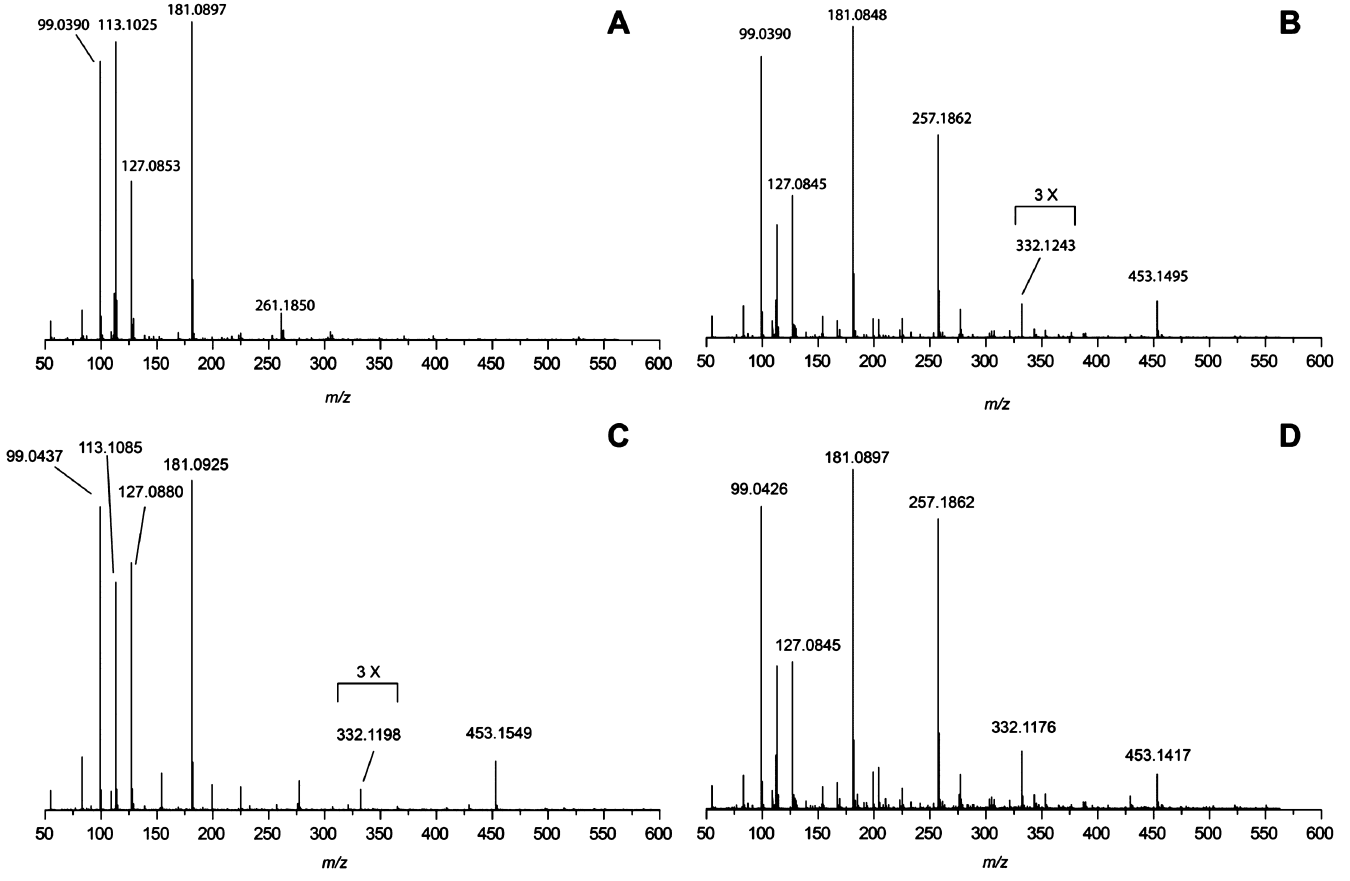

Figure 2. ESI(+)-MS of the reaction solution of **11**, DABCO, and 4-nitrobenzaldehyde after 5 min (A, B) or 60 min (C, D) of reaction in the absence (A, C) or presence (B, D) of thiourea.

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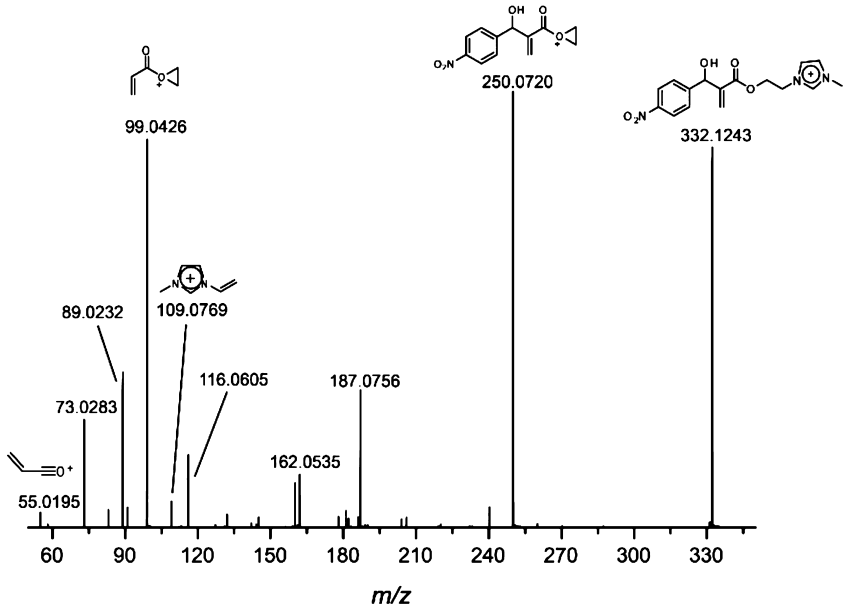

Figure 4. ESI(+)-MS/MS of the final MBH adduct of m/z 332. Note the low basicity expected for the untagged adduct and the essential role of the charge tag for its efficient ESI(+) fishing.

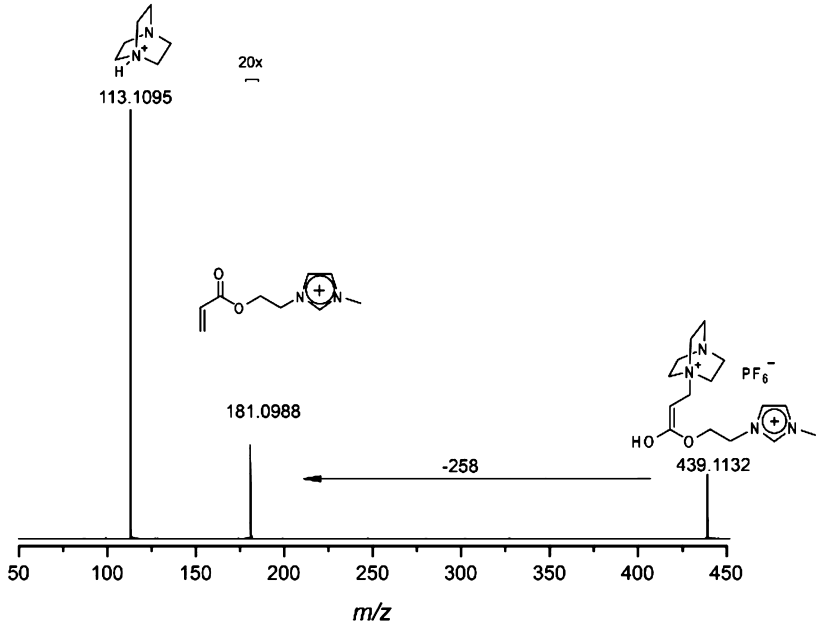

Figure 5. ESI(+)-MS/MS of the ion of m/z 439.

Information, Figure S2). It seems therefore that partial hydrolysis of **11** to **12** occurs and its detection is facilitated by the charge tag, that is, via **12** (m/z 127) and $[\mathbf{11} + \mathbf{12} + PF_6^-]^+$ (m/z 453). The ESI(+)-MS/MS of the ion of m/z 127 confirmed its identification as **12** (Supporting Information, Figure S3). The ion of m/z 113 is attributed to protonated DABCO.

Due to the charge tag, the final MBH adduct of m/z 322 could also be directly and efficiently intercepted and characterized (Figure 4). Note that the fishing of the final product warrants that reaction is taking place to its full extend, that is, from reactants to products, and that ESI(+) is efficient in intercepting accumulating species. Without the charge tag, the MBH adduct would be neutral and of relatively low basicity, and therefore disfavored protonation equilibrium could hamper its ESI(+) detection.

Two minor but key MBH intermediates could also be intercepted and characterized. Figure S4 in Supporting Information shows a second Michael addition reaction forming a dicharged ion of m/z 237 in accordance with the Rauhut–Currier reaction pathway.[5] The very low abundance of such product indicates the preferential pathway for the MBH adduct formation. The minor doubly charged ion of m/z 147 was attributed to the Michael addition of DABCO to the charge-tagged acrylate derivative **11** (Supporting Information, Figure S5, that is, analogous to **3** in Scheme 1). This intermediate was also intercepted as the ion of m/z 439 (single charged) in association with PF_6^- anion and characterized via ESI-MS/MS

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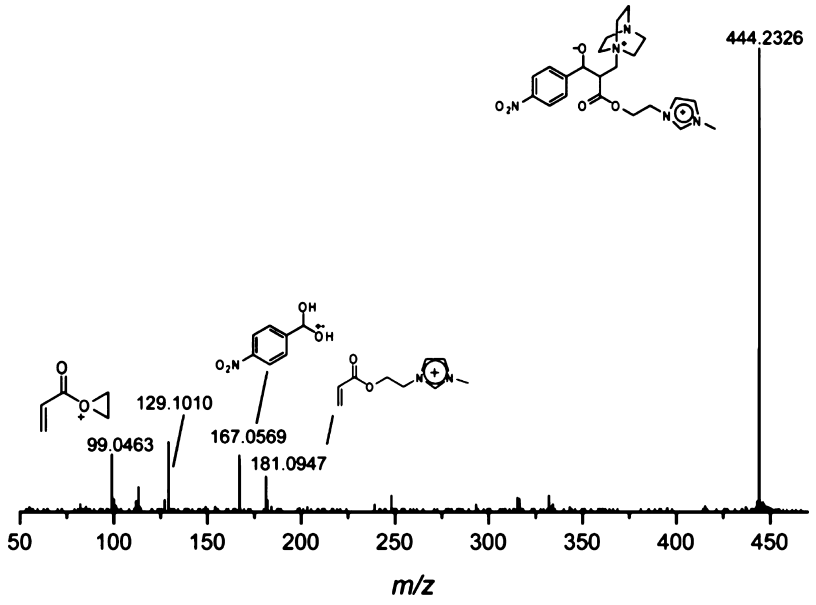

Figure 6. ESI(+)-MS/MS of the ion of m/z 444, a key MBH intermediate for aldol condensation.

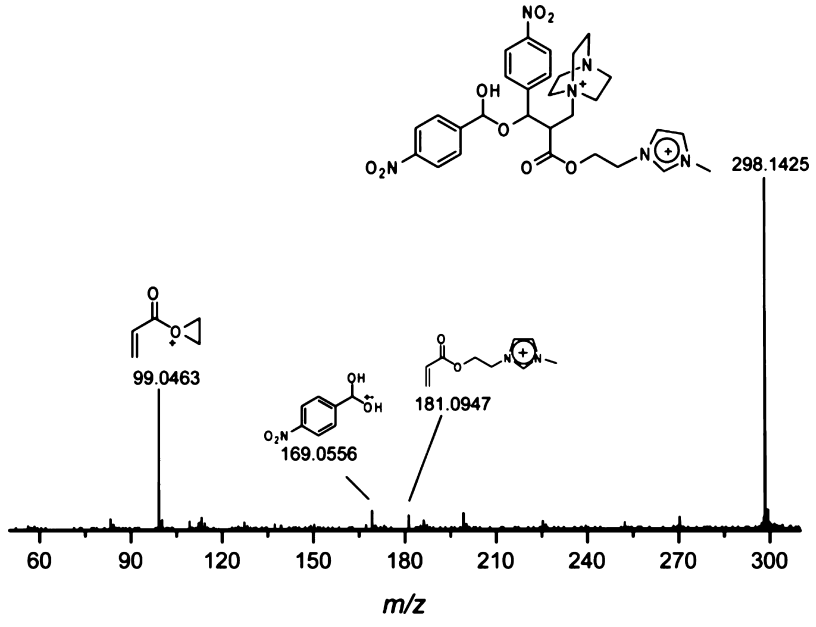

Figure 7. ESI(+)-MS/MS of the doubly charged ion of m/z 298 attributed to a McQuade intermediate.

(Figure 5). This ion provides strong evidence for the IL effect on accelerating MBH reactions and that this positive effect occurs through ion-pairing formation and structural organization (in accordance with Dupont's organizational theory[35−37]), but we will discuss this effect later.

An ion of m/z 444 (Figure 6) was also detected and characterized. This is likely the key intermediate from the aldol reaction (steps II and III in Scheme 1). Note that this intermediate could have escaped ESI(+) fishing for the untagged reaction in which it should be zwitterionic (neutral), and thus proper transfer to the gas phase would have to rely on favored protonation equilibrium and pH adjustment. The charge tag has therefore allowed the direct ESI(+) fishing of this key intermediate in the undisturbed MBH reaction solution.

Finally, we looked for ions that could be attributed to routes involved in the Aggarwal and McQuade propositions. We have used ESI-MS monitoring of the untagged reaction and detected an intermediate related to Aggarwal's preposition,[19] but for the tagged MBH reaction in acetonitrile, a doubly charged ion of m/z 298 corresponding to intermediate **8** in Scheme 2 related to McQuade's proposition could now be also detected and characterized (Figure 7).

Knowing that the amount of the protic species in the reaction solution controls which one of two competing mechanisms depicted in Scheme 1 takes place,[15] the charge-tagged alcohol **12** (Supporting Information, Figure S3) was added to the MBH reaction solution, but no intermediate of interest could be intercepted. Methanol was also used as the solvent so as to favor the detection of an intermediate related to the Aggarwal preposition, but no MBH intermediates

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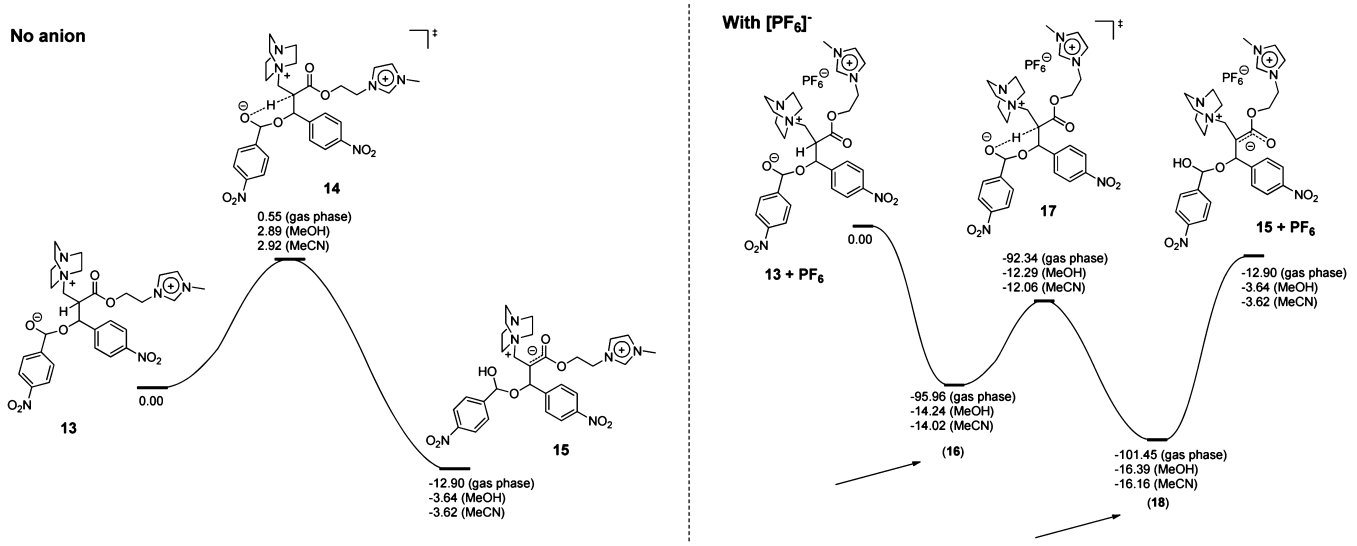
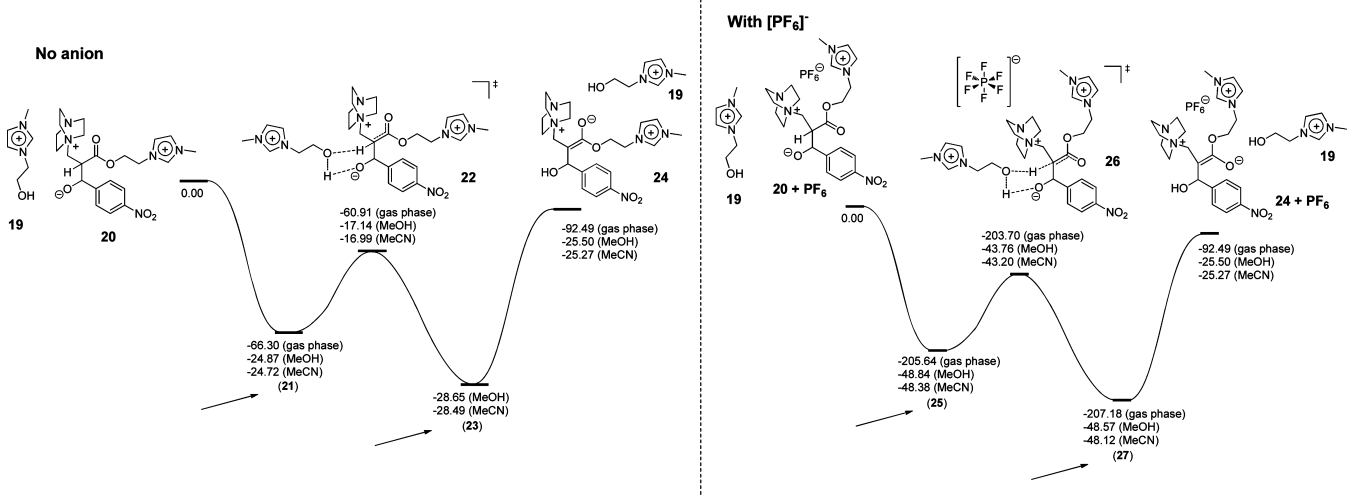
Scheme 3. Relative Energy Profiles (kcal mol^{-1}) Calculated at the M06-2X/6-311G(d,p) Level for the Proposed McQuade's Mechanistic Pathway Calculated in the Gas Phase or Considering Solvent Effect (Methanol and Acetonitrile)[a]



[a]The arrows indicate the electrostatic intermediate complex formation observed as the 'apparent negative activation energy' in the intrinsic reaction coordinate. Initial condition for the supramolecular structure in the right panel (**13** + PF_6^-) is the sum of the isolated species.

Scheme 4. Relative Energy Profiles for the Proposed Aggarwal's Mechanistic Pathway; Structures Were Also Calculated Considering the Solvent Effect (Methanol and Acetonitrile)[a]



[a]Structures and solvents effects calculated at the M06-2X/6-311G(d,p) level (kcal mol^{-1}). The arrows indicate the electrostatic intermediate complex formation observed as the apparent negative activation energy in the intrinsic reaction coordinate. Initial condition for the supramolecular structure in the right panel (**19** + **20** + PF_6^-) is the sum of the isolated species.

associated with **12** could be intercepted as well. The reaction was finally monitored with deuterated **12** (Supporting Information, Figure S6), but again no Aggarwal intermediate could be fished. A possible reason for the failure to intercept such intermediate may be due to the very transient nature of the Aggarwal intermediate (TS3 in Scheme 2).

To help us rationalize the IL effect (imidazolium cation) on MBH reactions, DFT calculations at the M06-2X/6-311G(d,p) level of theory were performed. The direct intramolecular proton transfer was also investigated (structures **24**, **28**−**32** in the Supporting Information). Quite high energy was found to be associated with intramolecular proton transfer, as expected due to a four-membered ring TS, revealing this mechanistic view as indeed improbable (Supporting Information, Scheme S2). Supporting Information shows fully optimized structures and TSs (**13**−**24**) for this pathway.

Both mechanistic views (McQuade and Aggarwal) were also theoretically investigated, with and without solvent effects (Schemes 3 and 4). We have also considered the formation of ionic pairs[37,61] between the charged intermediates with PF_6^- to evaluate the IL effect involved in the transformation.[35,36,62] Figure 8 shows the calculated TS for both transformations in the gas phase and in the presence or absence of PF_6^-. In the absence of PF_6^- (Scheme 3), the McQuade pathway displays a normal energetic profile, and no significant solvent effect (MeOH or MeCN) could be noted. In the presence of PF_6^-, however, a very strong effect was noted. Both solvents (methanol and acetonitrile) were also found to significantly

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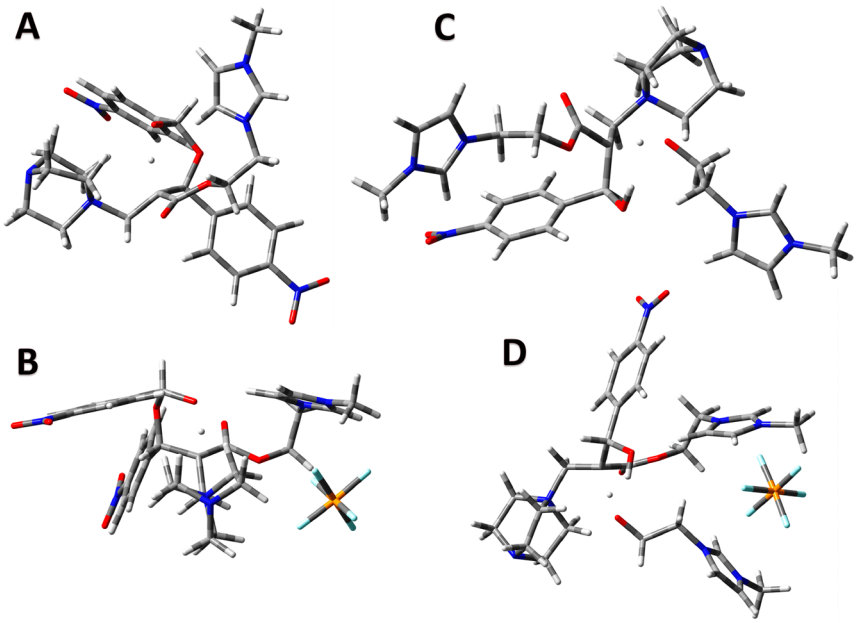

Figure 8. DFT optimized structures at the M06-2X/6-311G(d,p) level of theory. TS from McQuade's (left) and Aggarwal's (right) propositions in the absence (A and C) and presence (B and D) of the anion PF_6^-. Note the entropic organization in the presence of the anion.

stabilize TS **17** (Scheme 3) by ca. −80 kcal mol^{-1}. Solvents are known to have profound effects on MBH reactions.[15]

In the presence of PF_6^- anion (Scheme 3), besides the entropic organization in the presence of the anion (entropic driver effect[36]), note also the so-called 'apparent negative activation energy' in the intrinsic reaction coordinate (IRC) that occurs due to the formation, prior to and after TS **17**, of an electrostatic intermediate complex **16** (and **18**). The formation of these very unique transient complexes, which may take place prior to and/or after TS, have been recently reviewed.[63]

The so-called intermediate complex, which is noted when a calculated apparent negative activation energy is present,[64] has been proposed as a plausible explanation for the apparent discrepancy from the usual direct mechanism. This hotly debated behavior may be attributed therefore when there is observed (by theoretical calculation) the formation of electrostatic intermediate complexes in the IRC through an apparent negative activation energy, which means the contribution of additional borderline interaction(s) prior to and/or after the TS formation. This unique apparent negative potential may be attributed to quasibound states[65] in which the potential may undergo a kind of "prereaction" in the IRC, that is, the electrostatic intermediate complex formation. When these very transient intermediate complexes form in the IRC, their formation in the entrance and/or exit of a TS may strongly affect the outcome of the reaction. For instance, this kind of intermediate complex formation and its implications on an addition/substitution mechanism have been recently demonstrated.[66] These singular "prereactive" complexes have been proved to exert a significant role in the outcome of bimolecular reactions and allowed a plausible explanation for the apparent negative activation energy in ion-neutral reactions, radical-neutral reactions, and radical-radical reactions, as very recently reviewed.[67] Indeed, the original idea of an apparent negative activation energy has been proposed for a long time;[68−70] however, only recently have discussions of "intermediate complexes vs direct mechanisms" warmed up because of their importance in the comprehension of several elementary reactions, as reviewed.[67]

Typically, ion/molecule-ruled reactions with the possibility of long-range electrostatic interactions are highly sensitive to electrostatic intermediate complex formation effect,[71] which is specifically the case of ion-pairing (and larger supramolecular aggregates) formation of imidazolium derivatives. Therefore, the outcome of the chemical transformation is directly influenced by that region of the potential energy surface that is not in the vicinity of the TS.[65] These singular complexes are known to be formed when two or more molecules (or other chemical species) are brought together by means of significant intermolecular interactions (such as H-bonds[72]), especially when pronounced Columbic forces play a role, that is, the case of imidazolium-based IL. Despite its importance for many bimolecular reactions,[73] to the best of our knowledge, this is the first time this theory has been applied to explain the IL effect and to propose a plausible explanation for its origin.

When **13** (Scheme 3), which is analogous to **8** in Scheme 2, is associated with PF_6^-, a new and completely different molecular arrangement is noted (also see Figure 8) and the two cations (DABCO and imidazolium) are brought together by the anion trough in electrostatic interaction and most probably also by H-bonds. Therefore, the anion is acting as an "entropic driver" forming a well-organized structure, as expected for the reactions with an positive IL effect.[36] Considering an additional contribution beyond electrostatic interaction such as the "forced" hydrogen bonding, formation of an organized electrostatic intermediate complex, displaying directionality and in accordance with Dupont's theory[35−37] of organized supramolecular imidazolium structures, can be rationalized. Considering that the interactions discussed above also control larger aggregate formation of associated cations and anions,[74] a rationale for the origin of the IL effect can be proposed, but now including the electrostatic intermediate complex formation. It is seen in Scheme 3 that the entropic control and the formation of more stable TSs are related with the apparent

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Table 1. Energetic Barriers for Selected Steps Shown in Schemes 3 and 4

proposition	anion	step	solvent	energetic barrier (kcal mol^{-1})
McQuade		**13** → **14** (Scheme 3)		0.55
			methanol	2.89
			acetonitrile	2.92
Aggarwal		**21** → **22** (Scheme 4)		5.39
			methanol	7.73
			acetonitrile	7.73
McQuade	PF_6^-	**16** → **17** (Scheme 3)		3.62
			methanol	1.95
			acetonitrile	1.96
Aggarwal	PF_6^-	**25** → **26** (Scheme 4)		1.94
			methanol	5.08
			acetonitrile	5.18

Table 2. Calculated Thermodynamics Values for Selected Steps from Schemes 3 and 4

proposition	anion	step	solvent	ΔH (kcal mol^{-1})	ΔG (kcal mol^{-1})
McQuade		**13** → **14** (Scheme 3)		−13.15	−11.16
Aggarwal		**21** → **22** (Scheme 4)		−2.25	−3.15
McQuade		**13** → **14** (Scheme 3)	CH_3OH	−3.75	−1.61
Aggarwal		**21** → **22** (Scheme 4)	CH_3OH	−3.79	−2.59
McQuade		**13** → **14** (Scheme 3)	MeCN	−3.71	−1.51
Aggarwal		**21** → **22** (Scheme 4)	MeCN	−3.79	−2.49
McQuade	PF_6^-	**13** → **14** (Scheme 3)			−5.56
Aggarwal	PF_6^-	**21** → **22** (Scheme 4)		−1.06	−2.46
McQuade	PF_6^-	**13** → **14** (Scheme 3)	CH_3OH	−2.06	−1.64
Aggarwal	PF_6^-	**21** → **22** (Scheme 4)	CH_3OH	0.81	0.17
McQuade	PF_6^-	**13** → **14** (Scheme 3)	MeCN	−2.05	−1.63
Aggarwal	PF_6^-	**21** → **22** (Scheme 4)	MeCN	0.81	0.09

negative activation energy,[75] that is, the formation of the electrostatic intermediate complex.

A similar effect, with electrostatic intermediate complex formation, may also be invoked therefore for many reactions that are difficult to occur in organic solvents but have also been observed to experience a beneficial effect on their rates and/or selectivities when carried out in IL.[76−79] Indeed, as demonstrated herein, the formation of such complexes during the reaction (observe in IRC) seems to provide a proper rationale for the origin of the IL effect.

The calculations for the Aggarwal mechanistic path (Scheme 4) provided interesting predictions as well. The presence of a cationic charge-tagged alcohol (**19**) in a supramolecular association with **20** also allowed the electrostatic intermediate complex (**21**) formation that is observed in the apparent negative activation energy region on the IRC. Again, association with PF_6^-, and also considering the solvent effects, substantially lowers the energetic barriers (see Tables 1 and 2).

Table 1 compares the energetic barriers for both the McQuade and Aggarwal pathways. Note that the actual barriers are predicted to be very low in energy (lower than 8.0 kcal mol^{-1}) and that there is therefore no clear preference for a specific mechanism independent of the presence or absence of the IL. Note also that IL effect is able to organize (entropic drive effect[36]) and lower the energetic barrier through electrostatic complex formation during the reaction course considering the solvent effects. The formation of such complexes suggests the origin of the positive IL effect in which these ionic fluids (also for task-specific ILs) facilitate the formation and stabilization of charged (and/or polar) intermediates and TSs when acting as entropic drivers. It means this effect may be observed when ILs are acting as structure-directing agents, as also suggested elsewhere.[80−82]

The thermodynamics for those selected steps have also been calculated (Table 2). Table 2 shows that the anion does play a role in how crucial the solvent effect is for the transformation. Importantly, only considering the anion effect, which is a reality in IL as the media, Aggarwal's proposition showed positive values for the Gibbs free energy. Since the calculated values are not very high, Aggarwal's pathway cannot be discarded at all. Importantly, the results also provide insights on the proposition that the IL effect is due to the stabilization of charged (and polar) intermediates and transition states through ion-pairing and the formation of larger supramolecular aggregates, therefore in accordance with Dupont's theory.[35−37] Our results corroborate this hypothesis but also indicate how the stabilization may take place, that is, through the likely electrostatic intermediate complex formation, thus leading to TSs of lower barrier energies and therefore facilitating the chemical transformation in the presence of both the imidazolium cation and the PF_6^- anion. Finally, it is noted that in the presence of PF_6^-, McQuade's propositions always have lower energetic values than those for Aggarwal's propositions but not with a considerable difference, thus indicating the feasibility of both paths.

In summary, the ESI-MS monitoring of the MBH reaction employing a charge-tagged reagent, that is, an imidazolium cation as the tag, and for a reaction performed in an undisturbed media (no pH adjustments), the detailed calculations considering both solvent and IL effects, as well as the presence of a proton donor, have reinforced that H-shift is indeed the rate-limiting step (step III in Scheme 1) for MBH

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reactions. Intramolecular H-transfer has been calculated as a highly energetic and hence unfeasible process. The H-transfer may take place therefore by either one of the much more favorable, low energy demanding pathways as proposed by Aggarwal and McQuade (Scheme 2) or even through the concomitant occurrence of both. Indeed, when conditions allow, most likely both processes take place, in accordance with the unified view already proposed by Kappe.[15] The IL effect via loosely bonded ion-pair complexes (and larger aggregates) that we proposed before when investigating the IL effect[55] over the MBH were again corroborated herein but with a plausible explanation for its origin. DFT calculations revealed the formation of electrostatic intermediate complexes in the presence of the anion (PF_6^-) and of the charged alcohol. The origin of the IL effect over a chemical transformation may be therefore related to organization effects (when ILs are acting as entropic drivers) via the formation of these unique complexes (i.e., electrostatic intermediate complexes), which are expressed in the IRC as the apparent negative activation energy. This effect takes place via spontaneous ion pairs and larger supramolecular aggregate formation, which indeed opens access to energetically more accessible TSs in the IRC. In this sense, the IL effect and its origin have been explained on the basis of the formation of those unique electrostatic intermediate complexes, which take place during a specific chemical transformation in which ion-pairing effects are noted for imidazolium derivatives. Finally, the current results open up a large avenue of possibilities for better comprehension and proper interpretation of MBH reactions performed in ILs and task-specific ILs, as well for other reactions with positive IL effect.

EXPERIMENTAL SECTION

ESI-MS and ESI-MS/MS measurements were performed in the positive ion mode (m/z 50−2000 range) on a HDMS Synapt G2 instrument. This instrument has a hybrid quadrupole/ion mobility/orthogonal acceleration time-of-flight (oa-TOF) geometry and was used in the TOF V+ mode. All samples were dissolved in acetonitrile to form 100 μM solutions and were directly infused into the ESI source at a flow rate of 10 μL/min. ESI source conditions were as follows: capillary voltage 3.0 kV, sample cone 20 V, extraction cone 3 V. Collision energies were optimized to obtain the most comprehensive set of fragmentation for all MS/MS analyses. All electronic structure calculations performed in this work were carried out within Kohn−Sham Density Functional Theory (DFT) formalism using the M06-2X exchange-correlation functional combined with the large 6-311g(d,p) Pople split-valence basis set. The transition states were located using the synchronous transit-guided quasi-Newton QST2 method. All structures were optimized, and frequency calculations were performed to ensure the absence of any imaginary frequencies on local minima and the presence of only one imaginary frequency on transition states and were also used to compute zero-point vibrational energy (ZPVE) and to derive the thermochemical corrections for enthalpy and for Gibbs free energy. Zero-point energies and thermodynamic functions were calculated at 298.15 K and 1 atm. To include the solvent effects (acetonitrile and methanol) in our theoretical calculations, we have employed the self-consistent reaction field (SCRF) approach with the polarizable continuum model (PCM) where the solute molecule is enclosed in a cavity embedded in a dielectric medium. Both geometrical and electronic theoretical calculations were carried out using Gaussian 09 program suite.

ASSOCIATED CONTENT

Supporting Information

ESI-MS/MS spectra, Cartesian coordinates and energies for all the calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: brenno.ipi@gmail.com

Notes

The authors declare no competing financial interest.

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