5-Membered cyclic ethers via phenonium ion mediated cyclization through carbonate chemistry

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Abstract: Cyclization of 2-(2-hydroxyethyl)phenol via DMC chemistry in acidic conditions is herein discussed for the first time. Reaction conditions have been investigated and optimized. This substrate is quite appealing as it incorporates a 2-hydroxyethyl moiety in *ortho* to the aromatic hydroxyl group capable of stabilizing the related phenonium ion.
When the reaction mechanism was investigated via theoretical calculations, the results suggest that the most favorable pathway encompasses a DMC-mediated formation of the phenonium ion that is converted into the 2-(2-methoxyethyl)phenol. The related cyclic ether is then formed via intramolecular cyclization of this intermediate. This peculiar cyclization reaction is another example of the versatility of DMC herein used as solvent, methoxycarbonylation agent and leaving group in the intramolecular cyclization leading to the phenonium ion.

INTRODUCTION

The production of organic carbonates and in particular of dimethyl carbonate (DMC) on an industrial scale by greener synthetic approaches, i.e., catalytic oxycarbonylation of methanol[1-6] and more recently via CO_2 insertion into epoxides[7], propelled the scientists interest in the exploitation of these compounds as safe analogues for phosgene, dimethyl sulfate and methyl halides [8].

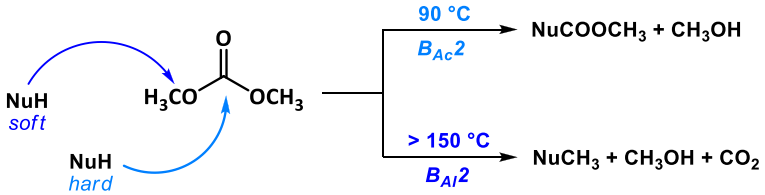
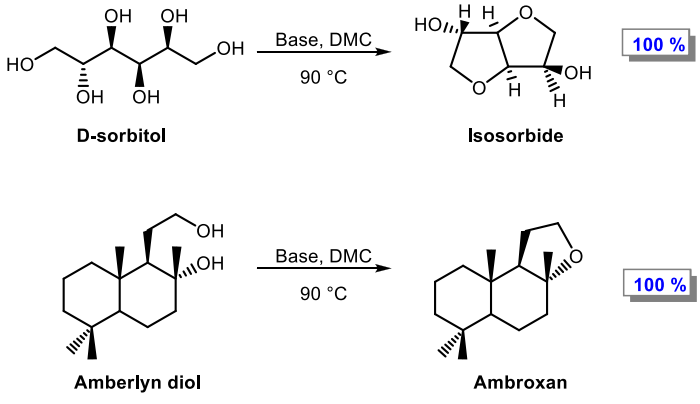


Figure 1. Reactivity of DMC according to the Pearson Hard-Soft Acid-Base theory.

Most of the early work published on dialkyl carbonates (DACs) focuses on the observation that their reactivity can be modulated according to the Hard-Soft Acid-Base (HSAB) theory of Pearson [9-13]. In fact, DMC acts as methoxycarbonylation agent with harder nucleophiles via a $B_{Ac}2$ mechanism at reflux temperature (T = 90 °C) and as methylating agent with softer nucleophiles via a $B_{Al}2$ mechanism, at higher temperature (T>150 °C) [14-22] (Figure 1).



Scheme 1. Synthesis of isosorbide and Ambroxan by cyclization via DMC chemistry.

However, recent works have demonstrated that DACs chemistry cannot be confined to the HSAB theory as it is more complex and intriguing. As an example, organic carbonates have been successfully employed in the chlorine-free, high yielding synthesis of numerous heterocycles [23-27]. In fact, when the cyclization takes place via intramolecular $B_{Al}2$ mechanism, DMC acts as sacrificial molecule and the heterocycle forms quantitatively already at the reflux temperature of DMC (90 °C) as a result of a high entropic contribution [28] (Scheme 1).

Recently, it has also been reported the easy preparation of a new class of organic carbonate, i.e., sulfur and nitrogen mustard carbonate analogues [29-33]. Investigation on their reactivity has been conducted with several nucleophiles both in autoclave conditions at high temperature (180 °C), as well as, in neat at lower temperature (150 °C). Reaction mechanism and kinetics have been studied confirming that these compounds retain the anchimeric effect of their mustard gas analogues, without being toxic. It is noteworthy that in these reactions, alkylation of the substrate takes place quantitatively without the use of any base or catalyst.

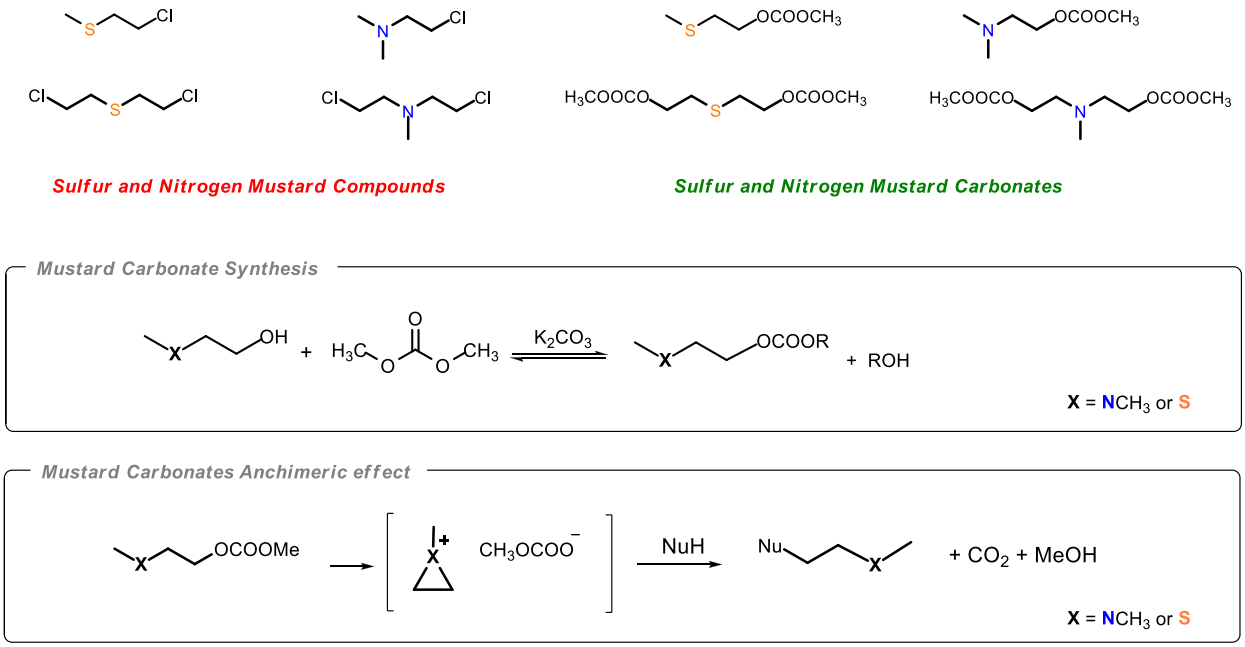
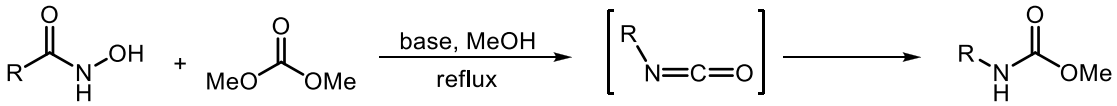


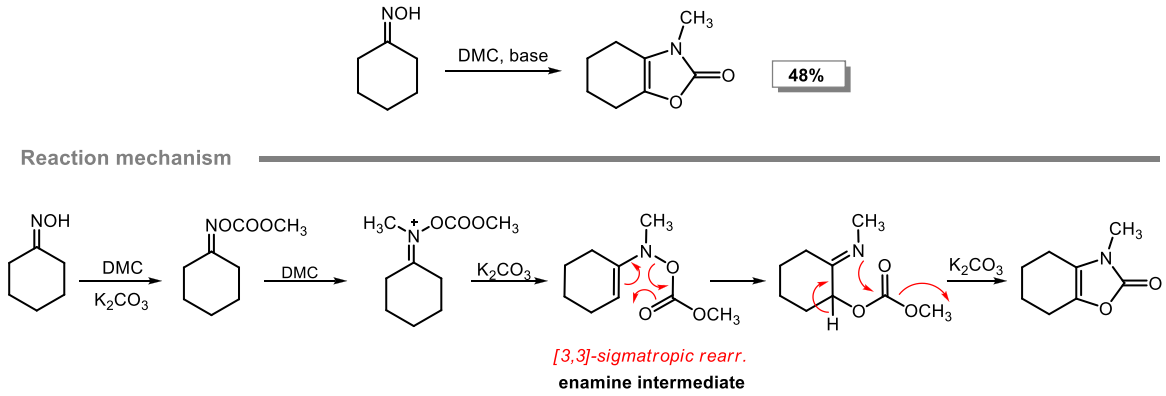
Figure 2. Molecular structure, synthesis and reactivity of mustard carbonates.

A further example of the DACs versatility is their ability to prompt transposition reactions. In this view, a variant of the Lossen rearrangement [33-36] via DACs chemistry was recently described. Herein DMC acts as activation reagent of hydroxamic acids in the presence of tertiary amine bases such as 1,5,7-[4.4.0]dec-5-ene (TBD), 1,8-biazabicyclo 5.4.0 undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane] (DABCO) or triethylamine and a small amount of methanol to initiate the rearrangement [37].



Scheme 2. A variant of the Lossen rearrangement via DACs chemistry.

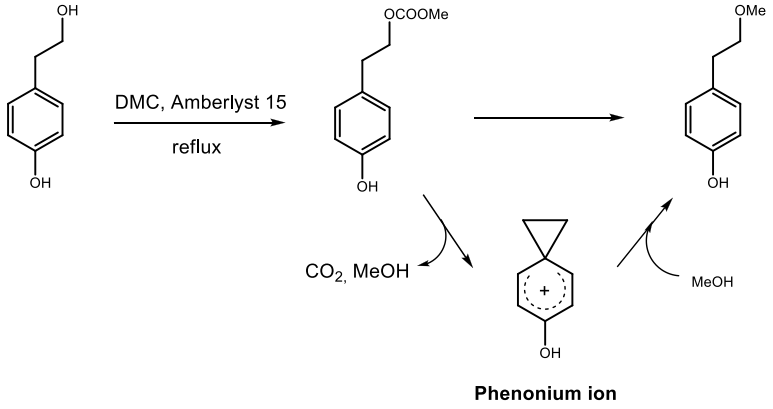
In another example, the reaction of oximes with DMC in the presence of a base resulted in the formation of substituted-4-oxazolin-2-ones via [3,3] simatropic rearrangement [38]. The key step of the reaction is the *N*-methylation of the O-carbonate derivative of the oxime, which produces the enamine intermediate. The latter undergoes a sigmatropic rearrangement followed by the cyclic carbamate formation via an intramolecular methoxycarbonylation reaction (Scheme 3). This reaction was proven to be generally applied to both aliphatic (alicyclic and linear) and aromatic ketone oximes with a limitation: the presence of a α-methylene group to the oxime.



Scheme 3. Substituted-4-oxazolin-2-ones via [3,3] simatropic rearrangement by reacting of oximes with DMC.

DACs promoted rearrangements include also enantioselective Steglich rearrangement of oxazolyl carbonates to synthesize C-carboxyazlactones [39-42] and the enantioselective rearrangement of indolyl carbonates to oxindoles [43].

Recently a simple one-pot procedure for selective etherification of 2-aryl-ethylalcohols has been achieved through Amberlyst 15-catalyzed reaction in DMC medium (Scheme 4) [44]. The proposed reaction mechanism involves the formation of phenonium ion by the loss of CO_2 and methanol, the latter acting as a nucleophile for the completion of the process.



Scheme 4. A variant of the Lossen rearrangement via DACs chemistry.

The phenonium ion was shown to be stabilized by electrondonating groups in *ortho* and *para* positions and destabilized by electron withdrawing groups. This reaction takes advantages of the activating effect of the phenonium ion and might as well leads to a transposition in case the three membered cyclic moiety is differently substituted [45]. The final result is an alkylation reaction of the substrate that, in these conditions, takes place at the reflux temperature of DMC (90 °C).

Prompted by these results, in this paper we have investigated the cyclization reaction in acidic conditions of a peculiar substrate i.e., 2-(2-hydroxyethyl)phenol that incorporates a 2-hydroxyethyl moiety in *ortho* to the aromatic hydroxyl group and thus might be capable of forming a phenonium ion as key reaction intermediate.

Previous investigation on this substrate have demonstrated that by its reaction with DMC in the presence of a stechiometric amount of a strong base [28] or a catalytic amount of a nitrogen bicyclic base [26], the related cyclic compound 2,3-dihydrobenzofuran **3** was the only product formed in quantitative yield (Scheme 3).

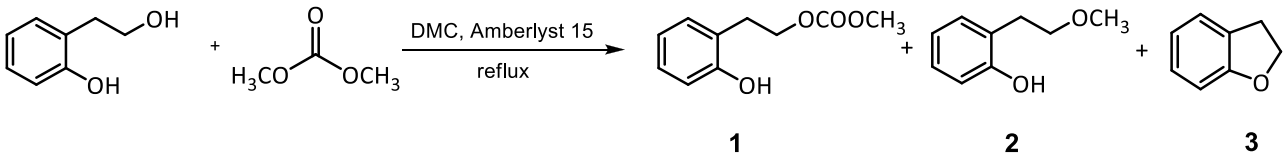
In this work it is shown that also in acidic condition the cyclic ether **3** is the main product observed although the cyclization required a longer time to reach completion (48 hours). Reaction conditions of this novel approach have been investigated and optimized by taking into consideration the substrate, the amount and the type of catalyst employed. Furthermore, the cyclization mechanism has been investigated via theoretical calculations. Data collected, consistently

with the outcome of the experiments, suggest that the formation of the cyclic takes place via a phenonium intermediate, thus through a completely different pathway compared to the base-catalyzed synthetic approach to heterocycles.

RESULTS AND DISCUSSION

Cyclic ethers via phenonium ion mediated cyclization through carbonate chemistry

2-(2-Hydroxyethyl)phenol, selected as substrate for this investigation, was reacted with an excess of DMC in the presence of different catalysts including weak base potassium carbonate, nitrogen superbase DBU, amphoteric catalyst hydrotalcite KW2000 and the acidic catalyst Amberlyst 15 (Scheme 5). This substrate incorporates both an aliphatic and an aromatic alcohol moiety.



1 **2** **3**

Scheme 5. Reaction of 2-(2-hydroxyethyl)phenol with DMC with Ambelyst 15 and structures of the products observed.

Table 1. Reactivity of 2-hydroxyphenethyl alcohol in the presence of different catalysts.[a]

#	Cat	Time	Conv.[b]	Products Selectivity[b] %		
	(mol. eq.)	h	%	**1**	**2**	**3**
1	K_2CO_3 (1.0)	24	100	0	0	100
2	DBU (1.0)	24	100	0	0	100
3	KW2000 (1 w/w)	48	67	48	0	52
4	Amberlyst 15 (25% w/w)	48	84	26	34	40

[a] 2-Hydroxyphenethyl alcohol (1.0 equiv.), DMC (60.0 equiv.) and the catalyst were reacted at 90 °C.
[b] Conversion and selectivity were calculated via NMR spectroscopy.

Table 1 accounts for the results obtained. In the presence of an equimolar amount of potassium carbonate, the substrate was completely converted after 24 hours and the cyclic ether **3** was the only product observed in the reaction mixture. The reaction conducted in the presence the nitrogen superbase DBU confirmed our previously reported results [26], i.e., 2,3-dihydrobenzofuran **3** forms in quantitative yield.

On the other hand, when the reaction was repeated employing hydrotalcite as catalyst, the conversion was not quantitative (67%) besides the cyclic ether **3** and the carbonate intermediate **1** were both present in the reaction mixture in ca 1:1 molar ratio.

The cyclization was then attempted using the acidic catalyst Amberlyst 15. Compared to the previous experiments (#1-3, Table 1), in this case, it was observed the formation in relevant amount of a third product. Purification via column chromatography of the reaction mixture allowed the isolation of the 2-(2-methoxyethyl)phenol **2** as confirmed both by NMR spectroscopy and mass spectrometry.

The presence of the 2-(2-methoxyethyl)phenol **2** in the reaction mixture seems to suggest that in the case of the Amberlyst 15-catalyzed cyclization, the reaction mechanism differs from the one previously reported in basic condition, where only the carboxymethyl derivative **1** was observed as reaction intermediate (Scheme 7a).

In order to optimized the acidic catalyzed cyclization of 2-(2-hydroxyethyl)phenol, several experiments were then conducted employing increasing amount of Amberlyst 15 (Table 2). As shown in Figure 2, the distinctive proton signals of the three pure compounds **1-3** allows an easy determination of conversion and selectivity of the cyclization reaction.

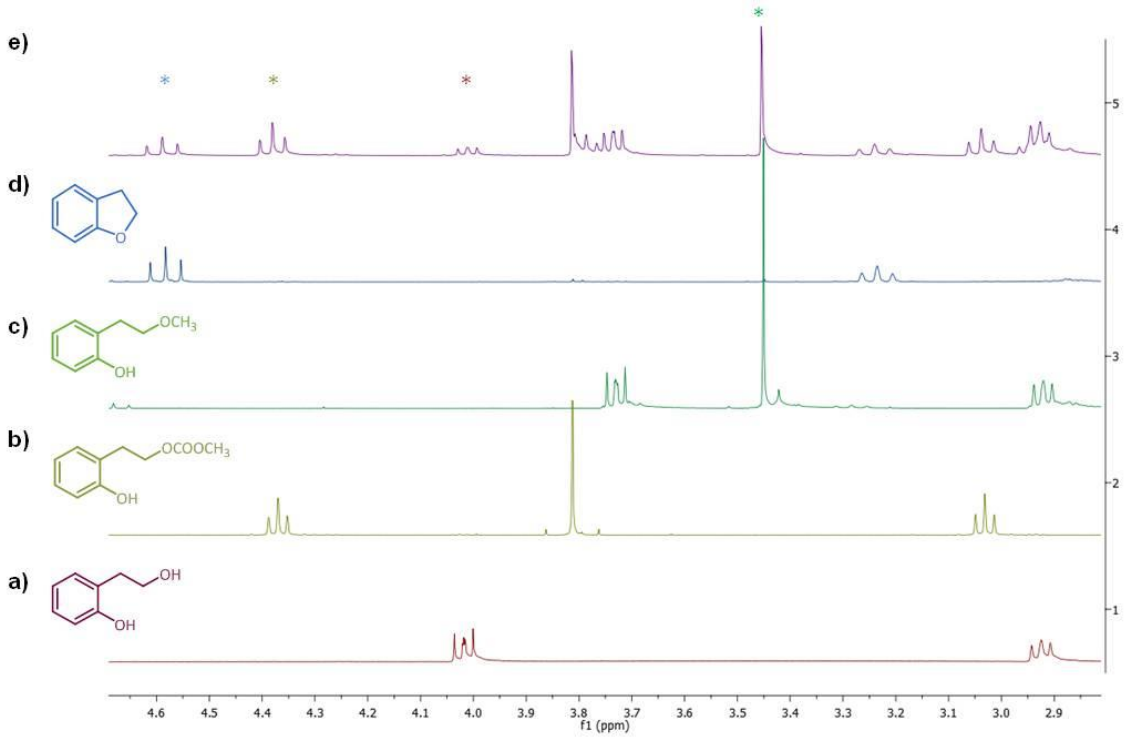


Figure 2. Section of ^{1}H NMR spectra of a) 2-(2-hydroxyethyl)phenol; b) carboxymethyl derivative **1**; c) 2-(2-methoxyethyl)phenol **2**; d) 2,3-dihydrobenzofuran **3** and e) reaction mixture from experiment 4 Table 1 (* indicate the signals used for the determination of conversion and selectivity)

Employing a catalyst:substrate weight ratio of 1:1 resulted in the quantitative formation of the cyclic ether **3** after 48 hours at the reflux temperature of DMC (#3, Table 2). An experiment was also carried out using an oven dry sample of Amberlyst 15 instead of the typical commercially available wet form. The weight lost in the dry sample was ca 16%, mostly due to moisture present in the wet form of the catalyst. The experiment showed that neither the reaction time nor the selectivity were affected using the dry Amberlyst 15 (#4, Table 2) as the 2,3-dihydrobenzofuran **3** formed also in this case in quantitative yield.

Table 2. Reactivity of 2-hydroxyphenethyl alcohol in the presence of different amount of Amberlyst 15.[a]

#	Amberlyst 15	Time	Conv.[b]	Products Selectivity[b] %		
	(w/w %)	h	%	**1**	**2**	**3**
1[c]	25	48	84	26	34	40
2	50	48	100	28	32	40
3	100	48	100	0	0	100
4[d]	100	48	100	0	0	100

[a] 2-Hydroxyphenethyl alcohol (1.0 equiv.), DMC (60.0 equiv.) and the catalyst were reacted at 90 °C.
[b] Conversion and selectivity were calculated via NMR spectroscopy.
[c] Results as in Table 1 entry 4.
[d] Amberlyst 15 has been dried overnight at 90 °C to remove the moisture (weight lost 16%).

The reactivity of DMC in acidic conditions is still nowadays quite unexplored. So far, only limited work has been reported on either amphoteric or acid catalysts [16, 46-47]. In this prospect, the acid-catalyzed cyclization of this substrate was also attempted in the presence of other acids such as an organic acid, i.e, trifluoroacetic acid and several Lewis acid, i.e, iron(III) chloride, aluminium chloride and boron trifluoride diethyl etherate (Table 3).

All the Lewis acids selected were tested in stoichiometric amount and led to the formation of the cyclic ether **3** although a small amount of 2-(2-methoxyethyl)phenol **2** was also detected. Boron trifluoride diethyl etherate resulted

quite efficient with an 2,3-dihydrobenzofuran **3** overall yield of 55% (calculated taking into account both conversion and selectivity of the product; #1, Table 3). A similar result was achieved with Lewis acid iron(III) chloride (41% yield) although the reaction mixture turned dark brown and had to be purified on a silica pad before conducting NMR spectroscopy analysis. When the reaction was conducted in the presence of aluminium chloride the conversion of the starting diol was only modest and the carbonate derivative **1** was the main product formed (#3, Table 3). Although the reaction was monitored for 48 hours, both conversion and selectivity remained unaltered after 24 hours.

Strong organofluorine acid TFA was the most efficient acid in promoting the cyclization reaction. After 48 hours the conversion of 2-(2-hydroxyethyl)phenol was 75% and the selectivity toward the cyclic ether 83% (overall yield 62%). However, comparing the results reported in Table 3 Amberlyst 15 still result the best catalyst for the cyclization reaction (#6; Table 3).

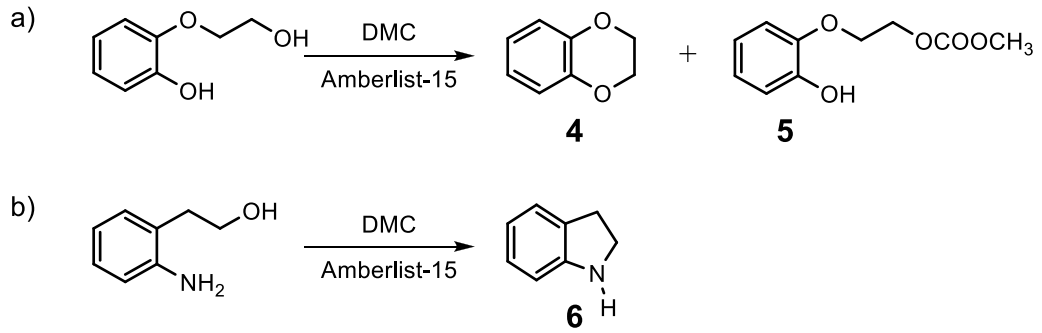
Table 3. Reactivity of 2-hydroxyphenethyl alcohol in the presence of different acidic catalysts.[a]

#	Catalyst (mol. eq.)		Time h	Conv.[b] %	Products Selectivity[b] % 1	2	3
1	$BF_3(OEt)_2$	(1.0)	48	82	30	2	68
2	$FeCl_3$	(1.0)	48	100	39	20	41
3	$AlCl_3$	(1.0)	48	40	60	7	33
4	TFA	(1.0)	48	75	17	0	83
5[c]	TFA	(1.0)	48	25	0	0	100
6[d]	Amberlyst 15 (1:1 w:w)		48	100	0	0	100

[a] 2-Hydroxyphenethyl alcohol (1.0 equiv.), DMC (60.0 equiv.) and the catalyst were reacted at 90 °C.
[b] Conversion and selectivity were calculated via NMR spectroscopy.
[c] 2-Hydroxyphenethyl alcohol (1.0 equiv.), acetonitrile (90.0 equiv.) and TFA at 90 °C.
[d] Results as in Table 1 entry 4.

It should be noted that cyclization reaction of diols in acidic conditions is a well know reaction [48-51], thus we cannot ruled out that part of the diol is directly converted into the cyclic ether without the support of DMC chemistry. In order to explore this possibility, an experiment has been carried mixing 2-(2-hydroxyethyl)phenol with TFA in acetonitrile as solvent. NMR spectroscopy of the reaction mixture showed a very modest conversion of the substrate (25%) and the presence of 2,3-dihydrobenzofuran **3** as the only product formed (#5, Table 3). In comparison, the reaction conducted with TFA in the presence of DMC led to the cyclic compound with more than a 2.5 fold yield (62%; #6, Table 3)

Cyclization reaction was also attempted on different substrates such as 2-(2-hydroxyethoxy)phenol and 2-(2-aminophenyl)-ethanol for the tentative synthesis of 2,3-dihydrobenzo[b][1,4]dioxine **4** and indoline **5** respectively (Scheme 6). However, in both the reactions the formation of the related cyclic compounds **4** and **6** were not observed.



Scheme 6. Attempted cyclization of 2-(2-hydroxyethoxy)phenol, 2-(2-aminophenyl)-ethanol and 1,2-phenylenedimethanol

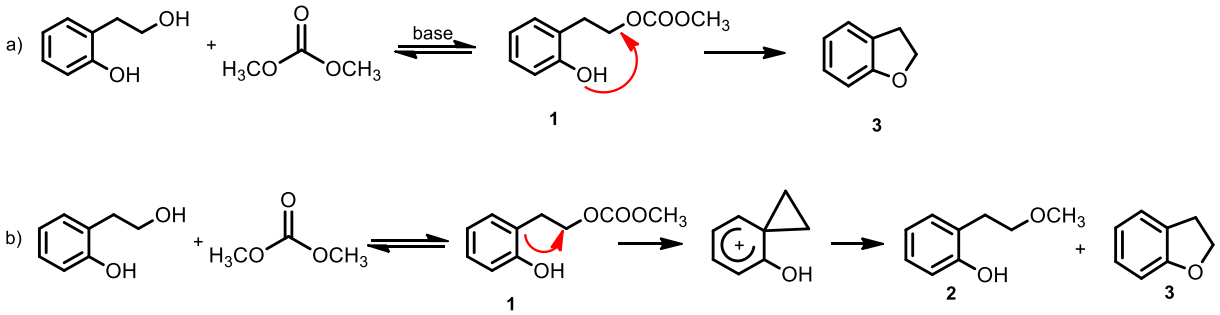
In the case of the 2-(2-hydroxyethoxy)phenol the only product formed was the methoxycarbonyl adduct **5**, most probably the cyclic ether does not form due to the the absence of the activation effect of the phenonium ion. Conversely

2-(2-aminophenyl)-ethanol could lead to the formation of the related phenonium ion, however the reaction does not take place as a result of the protonation of the amino moiety that prevent the formation of the cyclic key intermediate.

Considerations on the reaction mechanism based on the theoretical calculations

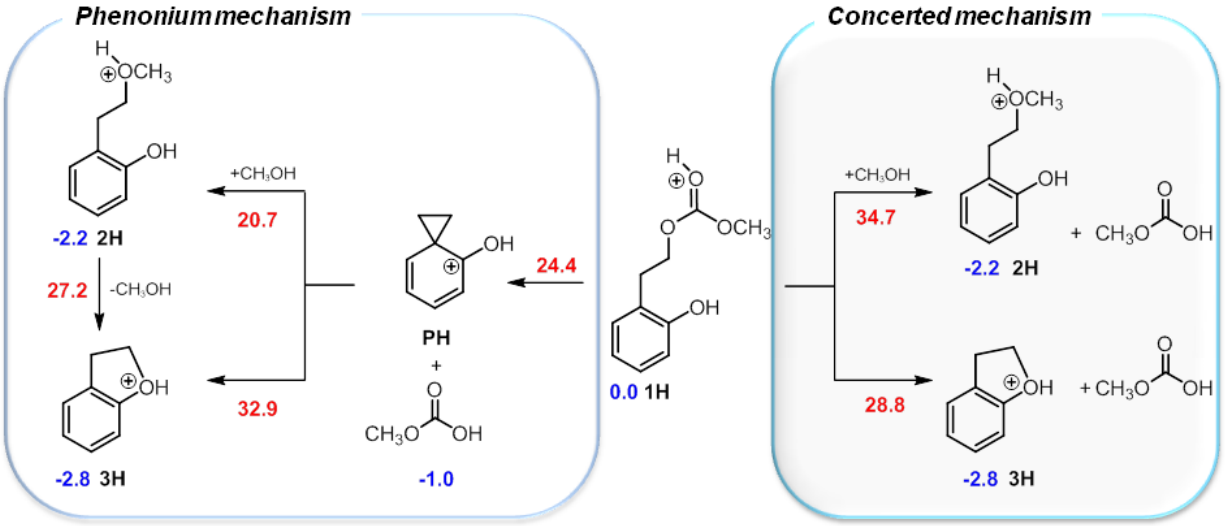
It should be pointed out that alkylation of an aliphatic alcohol at the reflux temperature of DMC (90 °C), as the one leading to the formation of 2-(2-methoxyethyl)phenol **2**, is quite unusual and was observed only when the product formation was energetically favored [16] or the substrate was activated by an anchimeric effect [44]. Furthermore, as previously mentioned, the presence of this methylated derivative **2** also seems to suggest that the acidic-catalyzed cyclization mechanism differs from the basic-catalyzed one (Scheme 7a) and might encompass the formation of a phenononium ion intermediate (Scheme 7b), similarly to what observed in the work published by Silvestri and co-workers [44].

In this view the 2-(2-hydroxyethyl)phenol cyclization was investigated via theoretical calculation in order to have a better insight on the related reaction mechanism.



Scheme 7. A comparison of the cyclization reaction conducted in basic condition (a) and in acidic condition (b).

In particular, this study was conducted assuming the relatively fast formation of the methoxycarbonate **1** from 2-(2-hydroxyethyl)phenol, which is then protonated by the Amberlyst 15 to form the intermediate **1H**. The protonated derivatives of the two major products **3H** and **2H** could then be formed according to either a concerted or a stepwise pathway (via the phenonium intermediate), as shown in Scheme 8.



Scheme 8. Concerted and stepwise (via phenonium) mechanisms starting from the protonated carbonate derivative **1H**. ΔG(363K) values at the DFT(M06-2X)+PCM/cc-pV*TZ* in kcal mol^{-1}.

Concerted mechanism. For this reaction mechanism, the pathways leading to the products **2H** and **3H** are both SN_2 reactions (Scheme 8). The intramolecular cyclization from **1H** to **3H** requires overcoming a free energy barrier of 28.8 kcal mol^{-1}. The compound **3H** is the precursor of the cyclic ether **3**, which can be formed by simple proton exchange with the catalyst or the solvent.

On the other hands, the bimolecular reaction with CH_3OH (from **1H** to **2H**) has a higher energetic barrier (ca 35 kcal mol^{-1}) and leads to **2H**.

In both reactions the leaving group i.e., methyl carbonic acid (CH_3OCOOH), is supposed to quickly dissociate into CO_2 and CH_3OH making all the steps irreversible. It should be pointed out that the latter step was not considered for this study as it does not seem to be relevant to the overall mechanism.

Mechanism via phenonium. According to this reaction pathway, the phenonium cation intermediate (**PH**) forms via intramolecular cyclization of **1H** with release of methyl carbonic acid (Scheme 8) with a relatively low barrier (24.4 kcal mol^{-1}). This barrier makes the reaction from **1H** to **PH** about two orders of magnitude faster than the one from **1H** to **2H** in the concerted mechanism.

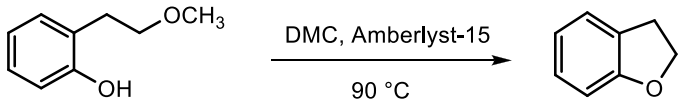
Once formed **PH** can undergo two pathways, i.e., an intermolecular or intramolecular alkylation.

The bimolecular reaction with CH_3OH that leads to **2H** has a free energy barrier of 22.7 kcal mol^{-1}. The methanol needed for this reaction is formed from the initial carboxymethylation reaction, as well as, from the decomposition of methyl carbonic acid released as leaving group in the phenonium formation. It is also noteworthy that the metoxy derivative **2** is only slightly more stable than **PH**.

Conversely, in the case of the intramolecular cyclization pathway, the hydroxyl group of the phenol acts as nucleophile (**PH** to **3H**) leading to the formation of the cyclic product **3H**. This step has a very high free energy barrier (ca 34 kcal mol^{-1}), and it is not competitive with the **PH** to **3H** step also at low concentration of CH_3OH.

Thus, the only feasible pathway leading to the cyclic ether **3H** is the conversion of **2H** into **3H**. A quite high free energy barrier (29.4 kcal mol^{-1}) characterizes this step and **3H** is only 0.6 kcal mol^{-1} more stable than **2H**, however this is sufficient to shift the equilibrium toward the ether, although it requires long times as seen experimentally.

In order to prove the feasibility of this hypothesized cyclization step, a sample of methoxy derivative **2** has been isolated as pure and its cyclization has been attempted using amberlyst 15 as catalyst and DMC as reaction media (Scheme 9). The collected results showed that after 72 hours 60% of the compound **2** has been converted into the cyclic ether **3**. The partial conversion of the substrate **2** into the cyclic ether **3** is an indication that this reaction is quite complex and the numerous concurrent equilibria might affect the experiment outcome.



2 **3**

Scheme 9. Attempted cyclization of methoxy derivative **2** into cyclic ether **3**.

As previously discussed, cyclization of 2-(2-hydroxyethyl)phenol in acid conditions could also produce the cyclic ether, without formation of the methoxycarbonate **1** (in this case DMC would act as simple unreactive solvent). However, the calculated barrier of this step is 27.5 kcal mol^{-1}, so the cyclization is expected to be quite slow. Assuming that the reaction with DMC is faster, the cyclization without DMC could, at most, represents only a minor pathway as demonstrated by the experimental results (see #5, Table 3).

Eventually, an experiment focusing on the reaction kinetic has also been conducted in order to confirm the theoretical calculation. Thus, a gram scale cyclization reaction of 2-(2-hydroxyethyl)phenol has been set up employing the condition reported in Table 2 entry 3. Several samples have been taken at time intervals; conversion of the reagent and selectivity of the products were measured via NMR spectroscopy. The results were coherent with the theoretical calculations showing a disappearance of the starting material over 22 hours with the formation of the carboxymethyl derivative **1**, the methylated adduct **2** and the cyclic compounds **3**. Thus, the amount of the reaction intermediates **1** and **2** diminished slowly over the time, whereas the yield of the cyclic compound reaches an almost quantitative amount.

CONCLUSIONS

In this paper it is reported for the first time an efficient cyclization reaction via DMC chemistry in acidic condition. The

reaction conditions have been optimized resulting in the case of 2-(2-hydroxyethyl)phenol in a quantitative conversion into the related cyclic derivative **3**. Several acids, both organic and inorganic, have been tested although Amberlyst 15 resulted the most efficient.

Most interestingly cyclization reaction of 2-(2-hydroxyethyl)phenol in acidic conditions led to the isolation of a methylated product, i.e., 2-(2-methoxyethyl)phenol **2** previously never observed. The presence of this compound was ascribed to the nucleophilic attack of methanol on a phenonium cation intermediate formed by aromatic intramolecular nucleophilic attack.

In order to validate this hypothesis the reaction mechanism has been investigated by theoretical calculations. Collected data confirmed the relatively fast formation of the phenonium **PH** intermediate from the carbonate derivative **1** of the starting diol, followed by reaction with CH_3OH to form the protonated 2-(2-methoxyethyl)phenol **2H**. Only at a later time, with a low kinetic, the cyclic ether **3H** could be formed. It is interesting to point out that in our case study the formation of the 2-(2-methoxyethyl)phenol **2** is not, as it might firstly appear, a limiting concurrent reaction of the cyclization as this compounds is indeed a key intermediate for the formation of 2,3-dihydrobenzofuran **3**.

The CH_3OH concentration plays an important role, because it can shift the equilibrium between **2H** and **3H**: at low concentration of CH_3OH more **3H** is expected. The cyclic ether is detected only after a long time and only after **2H** is produced.

This reaction is particularly interesting as it confirm the versatility of organic carbonates. Besides, in this case study the methoxycarbonate anion shows once again its ability as leaving group that leads to the formation of the phenonium ion intermediate. The latter, once formed it is first converted into the 2-(2-methoxyethyl)phenol **2** and thus via intramolecular cyclization into the 2,3-dihydrobenzofuran **3**. The complexity of this reaction mechanism also account for the longer reaction time required (48 h) in comparison with the base catalyzed cyclization of the same substrate (5 h). It is finally noteworthy that both the reaction media (DMC) and the catalysts (Amberlyst 15) could be easily recycled several times, preliminary investigations showed that the catalyst can be reused two times before needing reactivation.

EXPERIMENTAL SECTION

Experimental Details. General All reagents were purchased by Sigma Aldrich and used without any further purification. Mass spectra were run on GC-MS Agilent Technologies (GC System 6890N Network, Agilent Technologies Mass Selective Detector 5973, capillary column of silice HP-5). 1H NMR spectra were recorded on a Varian Unity (400 MHz) instrument and ^{13}C NMR spectra were recorded on a Bruker AC 200 (200 MHz) instrument at 25°C and in $CDCl_3$.

Amberlyst-catalysed synthesis of 2,3-dihydrobenzofuran in DMC: general procedure. To a solution of 2-hydroxyphenethyl alcohol (0.25 g, 1.81 mmol) in DMC (9.14 mL, 108.56 mmol) Amberlyst 15 hydrogen form (wet or dried from 25% to 100% w/w) was added and the mixture was heated to reflux under stirring for 48 h. Then, Amberlyst 15 hydrogen form was filtered off and the mixture was concentrated under vacuum. Conversion and selectivity were calculated by ^1H NMR analysis ($CDCl_3$, 400 MHz). Crudes obtained from the reactions performed by using 25% w/w of Amberlyst 15 hydrogen form wet and 25% w/w of Amberlyst 15 hydrogen form dried were collected and purified by gravimetric column chromatography on silica gel eluting with Hex/Et_2O from 98/2 to 90/10. 2-hydroxyphenethyl methyl carbonate and 2-(2-methoxyethyl)phenol were both isolated as yellow oils and characterised by NMR spectroscopy and HRMS spectrometry.

2-Hydroxyphenethyl methyl carbonate: ^1H NMR ($CDCl_3$, 400 MHz) δ(ppm) 7.19-7.12 (m, 2 H), 6.90 (t, 1 H), 6.84 (d, 1 H), 5.63 (br, 1 H), 4.37 (t, 2 H), 3.81 (s, 3 H), 3.03 (t, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 156.0, 154.3, 131.0, 128.4, 123.3, 120.8, 115.9, 67.7, 54.9, 30.2. HRMS: m/z $[M-H]^-$ calc. for $C_{10}H_{11}O_4$: 195.0663; found 195.0664.

2-(2-methoxyethyl)phenol: ^1H NMR ($CDCl_3$, 400 MHz) δ(ppm) 7.18 (t, 1 H), 7.07 (d, 1 H), 6.94 (d, 1 H), 6.86 (t, 1 H), 3.73 (t, 2 H), 3.45 (s, 3 H), 3.92 (t, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ(ppm) 155.8, 130.9, 128.4, 126.8, 120.2, 117.3, 74.7, 59.1, 33.3. HRMS: m/z $[M-H]^-$ calc. for $C_9H_{11}O_2$: 151.0765; found: 151.0765.

2,3-Dihydrobenzofuran: ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 7.11 (d, 1 H), 7.03 (t, 1 H), 6.76 (t, 1 H), 6.71 (d, 1 H), 4.47 (t, 2 H), 3.12 (d, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 160.0, 127.9, 126.9, 124.9, 120.3, 71.0, 29.8.

Reaction procedure for the $FeCl_3$-catalysed synthesis of 2,3-dihydrobenzofuran in DMC. To a solution of 2-hydroxyphenethyl alcohol (0.25 g, 1.81 mmol) in DMC (9.14 mL, 108.56 mmol) micronized $FeCl_3$*H_2O (0.49 g, 1.81 mmol) was added and the mixture was heated to reflux under stirring for 48 h. Then, the mixture was poured into $NaHCO_3$ sat. solution (10 mL) and extracted with EtOAc (3 x 10 mL). The collected organic phase was washed with $NaHCO_3$ sat. solution and brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Conversion and selectivity were calculated by ^{1}H NMR analysis ($CDCl_3$, 400 MHz).

Reaction procedure for the $AlCl_3$-catalysed synthesis of 2,3-dihydrobenzofuran in DMC. To a solution of 2-hydroxyphenethyl alcohol (0.25 g, 1.81 mmol) in DMC (9.14 mL, 108.56 mmol) micronized $AlCl_3$ (0.24 g, 1.81 mmol) was added and the mixture was heated to reflux under stirring for 48 h. Then, the mixture was poured into water (10 mL) and extracted with EtOAc (3 x 10 mL). The collected organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Conversion and selectivity were calculated by ^{1}H NMR analysis ($CDCl_3$, 400 MHz).

Reaction procedure for the BF_3*Et_2O-catalysed synthesis of 2,3-dihydrobenzofuran in DMC. To a solution of 2-hydroxyphenethyl alcohol (0.25 g, 1.81 mmol) in DMC (9.14 mL, 108.56 mmol) BF_3*Et_2O (0.22 mL, 1.81 mmol) was added and the mixture was heated to reflux under stirring for 48 h. Then, the mixture was poured into water (10 mL) and extracted with EtOAc (3 x 10 mL). The aqueous phase was neutralised with $NaHCO_3$ sat. solution and extracted with EtOAc (2 x 10 mL). The organic phases were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Conversion and selectivity were calculated by ^{1}H NMR analysis ($CDCl_3$, 400 MHz).

Reaction procedure for the TFA-catalysed synthesis of 2,3-dihydrobenzofuran in DMC. To a solution of 2-hydroxyphenethyl alcohol (0.25 g, 1.81 mmol) in DMC (9.14 mL, 108.56 mmol) TFA (0.14 mL, 1.81 mmol) was added and the mixture was heated to reflux under stirring for 48 h. Then, the mixture was neutralised with $NaHCO_3$ sat. solution and extracted with EtOAc (3 x 10 mL). The collected organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Conversion and selectivity were calculated by ^{1}H NMR analysis ($CDCl_3$, 400 MHz).

Reaction procedure for the Amberlyst-catalysed synthesis of 2,3-dihydrobenzofuran in DMC and MeOH. To a solution of 2-hydroxyphenethyl alcohol (0.25 g, 1.81 mmol) in DMC (9.14 mL, 108.56 mmol) and MeOH (2.93 mL, 72.40 mmol) Amberlyst 15 hydrogen form wet (0.25 g, 100% w/w) was added and the mixture was heated to reflux under stirring for 48 h. Then, Amberlyst 15 hydrogen form was filtered off and the mixture was concentrated under vacuum. Solely starting material was recovered.

Reaction procedure for the KW2000-catalysed synthesis of 2,3-dihydrobenzofuran in DMC. KW 2000 was calcined at 500 °C for 18 h and stored under vacuum prior to being used. To a solution of 2-hydroxyphenethyl alcohol (0.25 g, 1.81 mmol) in DMC (9.14 mL, 108.56 mmol) KW2000 (0.25 g, 100% w/w) was added and the mixture was heated to reflux under stirring for 48 h. Then the mixture was filtered through a pad of celite and concentrated under vacuum. Conversion and selectivity were calculated by ^{1}H NMR analysis ($CDCl_3$, 400 MHz).

Reaction procedure for the synthesis of 2,3-dihydrobenzofuran using ACN as solvent and Amberlyst as acid catalyst. To a solution of 2-hydroxyphenethyl alcohol (0.25 g, 1.81 mmol) in ACN (9.00 mL, 172.32 mmol) Amberlyst 15 hydrogen form wet (0.25 g, 100% w/w) was added and the mixture was heated to reflux under stirring for 48 h. Then, Amberlyst 15 hydrogen form was filtered off and the mixture was concentrated under vacuum. Solely starting material was recovered.

Reaction procedure for the synthesis of 2,3-dihydrobenzofuran using ACN as solvent and TFA as acid catalyst. To a solution of 2-hydroxyphenethyl alcohol (0.25 g, 1.81 mmol) in ACN (9.00 mL, 172.32 mmol) TFA (0.14 mL, 1.81 mmol) was added and the mixture was heated to reflux under stirring for 48 h. Then the mixture was neutralised with $NaHCO_3$ sat. solution and extracted with EtOAc (3 x 10 mL). The collected organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Conversion and selectivity were calculated by ^{1}H NMR analysis ($CDCl_3$, 400 MHz).

Reaction procedure for the DBU-catalysed synthesis of 2,3-dihydrobenzofuran in DMC. To a solution of 2-hydroxyphenethyl alcohol (0.25 g, 1.81 mmol) in DMC (9.14 mL, 108.56 mmol) DBU (0.27 mL, 1.81 mmol) was added and the mixture was heated to reflux under stirring for 48 h. Then the mixture was poured into water (10 mL) and extracted with EtOAc (3 x 15 mL). The collected organic phase was washed with a 0.1 M HCl aq. solution, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Conversion and selectivity were calculated by ^{1}H NMR analysis ($CDCl_3$, 400 MHz).

Reaction procedure for the K_2CO_3-catalysed synthesis of 2,3-dihydrobenzofuran in DMC. To a solution of 2-hydroxyphenethyl alcohol (0.25 g, 1.81 mmol) in DMC (9.14 mL, 108.56 mmol) K_2CO_3 (0.25 g, 1.81 mmoL) was added and the mixture was heated to reflux under stirring for 48 h. Then, K_2CO_3 was filtered off and the mixture was concentrated under vacuum. Conversion and selectivity were calculated by ^{1}H NMR analysis ($CDCl_3$, 400 MHz).

Amberlyst-catalysed synthesis of 2,3-dihydrobenzofuran in DMC starting from 2-(2-methoxyethyl)phenol. To a solution of 2-(2-methoxyethyl)phenol (0.03 g, 0.20 mmol) in DMC (0.99 mL, 11.83 mmol) Amberlyst 15 hydrogen form wet (0.03 g, 100% w/w) was added and the mixture was heated to reflux under stirring for 48 h. Then, Amberlyst 15 hydrogen form was filtered off and the mixture was concentrated under vacuum. Conversion and selectivity were calculated by ^{1}H NMR analysis ($CDCl_3$, 400 MHz).

Kinetic study: In order to evaluate the reaction kinetics, to a solution of 2-hydroxyphenethyl alcohol (1.00 g, 7.23 mmol) in DMC (434.24 mmol, 36.56 mL) Amberlyst 15 hydrogen form wet (1.00 g, 100% w/w) was added and the mixture was heated to reflux under stirring for 48 h. Conversion and selectivity were calculated by ^{1}H NMR analysis ($CDCl_3$, 400 MHz) from t_0 = 0 h to t_{18} = 48 h by taking a sample from the reaction mixture: every 0.5 h from t_0 = 0 h to t_7 = 3.0 h; every 1.0 h from t_8 = 4.0 h to t_{12} = 8.0 h; every 2 h from t_{13} = 24 h to t_{17} = 32 h.

Theoretical method

The stationary points of interest on the energy hypersurface are minima and first order saddle points, which correspond to stable species and transition structures (TS). Stable and TS, are determined by Density Functional Theory (DFT) [52] using the M06-2X functional [53] and gradient procedures [54-58]. Dunning's polarized valence-3ζ cc-pV*TZ* basis set [59] were used in the DFT-PCM optimizations (with PCM included), and the nature of the critical points was checked by vibrational analysis. The M06-2X functional was expected to perform acceptably on the basis of literature studies.[60]

Since the experimental part of the study was carried out in the liquid phase, solvent was simulated using the polarized continuum method, within the SMD [61] and IEF-PCM [62] schemes. The dielectric constant was set on the basis of literature values [63] as $\varepsilon = 3.087$, while $\varepsilon_{inf} = 1.87$. For a better energy assessment, and to take into account the strong hydrogen bond between solvent and intermediates, one molecule of explicit solvent (DMC) in interaction with the cationic center, was added in the computations. For the sake of clarity, this explicit DMC molecule was not shown in the Scheme 8, but it was reported in the Section A of the Supplementary Information.

According to the experimental section, the Gibbs free energies (ΔG) were estimated at T = 363 K, and were reported in the Schemes.

Quantum mechanical calculations were carried out by using the GAUSSIAN09 system of programs.[64]

Geometries and energetics of all the species were reported in the Supplementary Information (Section B).

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