Advanced Synthesis & Catalysis

Title: Assessing the pKa-Dependent Activity of Hydroxyl Hydrogen Bond Donors in the Organocatalyzed Cycloaddition of Carbon Dioxide to Epoxides: Experimental and Theoretical Study

Authors: Prapussorn Yingcharoen, Chutima Kongtes, Sunatda Arayachukiat, Kittipong Suvarnapunya, Sai V.C. Vummaleti, Sippakorn Wannakao, Luigi Cavallo, albert poater, and Valerio D'Elia

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201801093

Link to VoR: http://dx.doi.org/10.1002/adsc.201801093

10.1002/adsc.201801093

UPDATE

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Assessing the pK_a-Dependent Activity of Hydroxyl Hydrogen Bond Donors in the Organocatalyzed Cycloaddition of Carbon Dioxide to Epoxides: Experimental and Theoretical Study

Prapussorn Yingcharoen,[a, †] Chutima Kongtes,[a,†] Sunatda Arayachukiat,[a] Kittipong Suvarnapunya,[a,b] Sai V. C. Vummaleti,[c] Sippakorn Wannakao,[a] Luigi Cavallo,[c] Albert Poater,[d]* and Valerio D' Elia[a]*

[a] Department of Materials Science and Engineering, School of Molecular Science and Engineering, Vidyasirimedhi Institute of Science and Technology, (VISTEC) Wang Chan, Thailand; email: valerio.delia@vistec.ac.th
[b] Department of Immunology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.
[c] King Abdullah University of Science & Technology, KAUST Catalysis Center (KCC), 23955-6900 Thuwal, Saudi Arabia.
[d] Institut de Química Computacional i Catàlisi and Departament de Química, Universitat de Girona, c/Maria Aurèlia Capmany 69, 17003 Girona, Catalonia, Spain; email: albert.poater@udg.edu
† P.Y. and C.K. contributed equally.

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract: The development of hydrogen bond donors (HBDs) as catalytic moieties in the cycloaddition of carbon dioxide to epoxides is an active field of research to access efficient, inexpensive and sustainable metal-free systems for the conversion of carbon dioxide to useful chemicals. Thus far, no systematic attempt to correlate the activity of a diverse selection of HBDs to their physico-chemical properties has been undertaken. In this work, we investigate factors influencing the catalytic activity of hydroxyl HBDs from different chemical families under ambient conditions by considering the HBDs Brønsted acidity (expressed as pK_a), the number of hydroxyls and structural aspects. As an effect, this study highlights the crucial role of the hydroxyl protons' Brønsted acidity in determining the catalytic activity of the HBDs, identifies an ideal range for the hydroxyl HBDs proton acidity ($9 < pK_a < 11$) and leads to a revaluation of phenol and to the discovery of a simple ascorbic acid derivative as efficient HBDs for the title cycloaddition reaction. Density functional theory (DFT) calculations show mild reactions barriers for the reaction catalysed by phenol and suggest the occurrence of aggregation between molecules of ascorbic acid as a further factor affecting catalytic activity.

Keywords: Cycloaddition of CO_2; Cyclic carbonates; Organocatalysis, Brønsted acidity, hydrogen bond

Introduction

The last few decades have seen the impressive rise of organocatalysis as a way to establish metal-free processes that might result advantageous in terms of catalyst costs, toxicity, stability and availability when compared to the classical metal-based systems.[1] Organocatalysts are often readily accessible renewable compounds such as aminoacids,[2] peptides,[3] sugars[4] and vitamins[5] or their derivatives. Among several families of organocatalysts, HBDs occupy a prominent position for their ability to activate the reaction substrates by a well-defined array of H-bonds.[6]

The cycloaddition of CO_2 to epoxides[7] is counted among viable strategies for the chemical fixation of CO_2 into commodity chemicals.[8] It leads to industrially relevant cyclic organic carbonates[9] that find increasing application as chemical intermediates[10] and green solvents.[11] The cycloaddition reaction can take place under atmospheric conditions, or even from flue gas,[12] when applying several types of catalytic systems including organocatalysts,[5,13] metal-organic complexes[14] coordination compounds[15] and porous organic polymers[16] thus resulting in a potentially sustainable, low-energy intensive process for CO_2 fixation.[7c,17]

In this context, the activity of organocatalysts in the cycloaddition of CO_2 to epoxides is generally lower than that of metal-based systems.[7c] Nevertheless, given several advantageous aspects of organocatalysis in terms of costs and sustainability,[1] the development of more active organocatalytic systems for the conversion of CO_2 to cyclic carbonates is highly sought after and constitutes an active field of research.[7e-g,18] HBDs are known to activate the epoxide substrate by the formation of H-bonds facilitating its ring-opening by the attack of the nucleophilic catalytic component.[5,19] Active HBDs for the cycloaddition of CO_2 to epoxides include several

classes of compounds that have been careful reviewed.[7e-g] Among them, hydroxyl HBDs are likely to represent the broadest family of catalytically active species and include functionalized monoalcohols,[20] glycols,[21] polyalcohols,[22] fluorinated alcohols,[23] hydroxy-functionalized N-heterocycles,[24] silanediols,[25] boronic acids,[26] carboxylic acids,[27] ascorbic acid[5] and several compounds containing phenolic[28] or polyhydroxyphenolic moieties.[19a,29] Despite the extensive use of hydroxyl HBDs in literature as catalytic components for the title cycloaddition, there have been very few systematic attempts to correlate their catalytic performance to their physico-chemical properties; most reports investigating the performance of a single species or of a restricted selection of analogous HBDs.

Tassaing *et al.* have analysed the catalytic activity of a broad selection of commercially available HBDs at 60 °C, 20 bar CO_2 pressure finding higher catalytic activity for polyhydroxyphenols (catechol, pyrogallol, gallic acid) and for fluorinated benzylic alcohols.[23] However, the authors did not attempt to correlate the physico-chemical properties of the HBDs to the observed trend of catalytic activity. In an earlier study, Kleij *et al.* investigated the catalytic activity of phenol and polyhydroxy phenols.[19a] Pyrogallol was found as the most efficient HBD. With the support of DFT calculations, the latter observation was attributed to the stabilization of the reaction intermediate by a network of H-bonds. In a study on Fiddler crab-type imidazolium salts for the cycloaddition of CO_2 to epoxides, Dai *et al.* observed dependency of the catalytic activity on the pH generated by the HBDs in CH_2Cl_2/MeOH solutions.[30]

In this work, we initially studied the catalytic activity of several, structurally diverse, readily available HBDs for the cycloaddition of CO_2 to epichlorohydrin under ambient conditions (r.t., 1 bar CO_2) and we analysed the dependency of the observed performance on the Brønsted acidity of the HBDs and on the number of hydroxyls in the scaffold. We show that the catalytic activity of the HBDs is strongly dependent on the pK_a of the most acidic proton in the HBD molecule and that the presence of multiple hydroxyls in the HBD is generally not crucial to achieve high catalytic activity, but it might play a role in tuning the HBD performance. Compounds with pK_a in the 9-11 range are the most efficient hydroxyl HBDs for the cycloaddition of CO_2 to epoxides under ambient conditions. Moreover, the catalytic mechanism of the most relevant catalysts is analysed by a comparative DFT investigation.

Results and Discussion

Catalytic studies

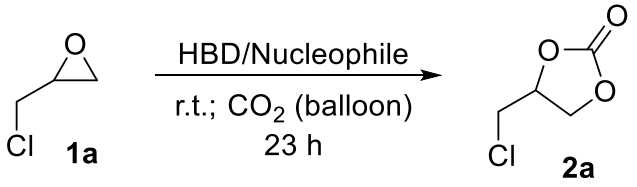
We evaluated a selection of readily available hydroxyl HBDs in the cycloaddition of CO_2 of epichlorohydrin (**1a**) under ambient conditions (r.t., CO_2 balloon). to afford the corresponding carbonate (**2a**, Table 1). Two parameters were evaluated, i.e. the initial reaction rate, determined by *in situ* IR, in the first 20 min of reaction,[14e,31] and the reaction turnover frequency (TOF) calculated based on conversion after 23 h. The HBDs include phenols, ascorbic acid and its derivatives **3**-**5**, carboxylic acids, mono- and polyalcohols (Scheme S1 in the SI). The current choice of HBDs enables comparison between different kinds of hydroxyls, covers a broad range of pK_a values, from about 3 of salicylic acid to about 15.5 of cyclohexanol, and includes HBDs with 1 to 5 H-bond donor moieties. Importantly, it allows the study of series and combinations of HBDs for which a) the number of hydroxyls in structurally similar compounds varies without leading to strong changes of pKa (for instance, phenol-catechol-pyrogallol; ascorbic acid-**3, 4-5** b) the pK_a is varied by modification (protection, substitution, addition) of a single functional group of the scaffold (for instance *p*-methoxyphenol-phenol-*p*-nitrophenol-salicylic acid, **3**-**4**, pyrogallol-gallic acid etc.). These concepts are shown graphically in Scheme S2 in the SI. All HBDs were soluble in **1a** except for ascorbic acid, fructose and erythritol. However, the latter compounds became completely (ascorbic acid, fructose) or partially (erythritol) soluble in the presence of TBAI and gave clear solutions with the progress of the reaction.

Besides the HBD, the coupling of CO_2 and epoxides requires a nucleophile for the step of epoxide ring-opening.[31] To avoid possible bias due to the use of a single nucleophile, a representative selection of the HBDs was tested in combination with a full set of nucleophiles including quaternary ammonium salts (TBAI and TBAB = tetrabutylammonium iodide and bromide, respectively), a pyridine nucleophile (DMAP; *N,N*-dimethylamino pyridine), polycyclic tertiary amine DABCO (1,4-Diazabicyclo[2.2.2]octane) and amidine base DBU (1,8-Diazabicyclo [5.4.0]undec-7-ene).

By analysing the results in Table 1 some trends of activity can be observed: (i) phenol, *p*-methoxyphenol and its polyhydroxyphenol analogues (Table 1 entries 2-5) are the most active HBDs for all nucleophiles. (ii) the best catalytic performances were observed in all cases when TBAI was used as the nucleophile.

10.1002/adsc.201801093

Table 1. Screening of various HBDs and nucleophiles for the cycloaddition of CO_2 to epichlorohydrin.[a]



Entry	HBD	Conversion of **1a** (%)[b]					pK_a[c]	TON/ TOF (h^{-1})[d]	k_{rel}[e]
		TBAI	TBAB	DMAP	DBU	DABCO			
1		31	35	13	33	6		15.5/0.67	
2	Phenol	87	78	39	31	28	9.90	43.5/1.89	1.00
3	*p*-methoxyphenol	84					10.21	41/1.83	1.00
4	Catechol	82	67	33	36	19	9.34	41/1.78	0.97
5	Pyrogallol	82	68	32	31	7	9.05	41/1.78	0.95
6	*p*-nitrophenol	65					7.15	32.5/1.41	0.84
7	Gallic acid	70					4.40	35/1.52	0.62
8	Salicylic acid	57					2.98	28.5/1.24	0.35
9	(L)-Ascorbic acid	70[f]	55[f]	15	17	8	4.04	35/1.52	0.61
10	Benzoic acid	63					4.20	31.5/1.37	0.58
11	Lactic acid	59	52	25	36	11	3.86	29.5/1.28	0.59
12	(D)-Fructose	78					12.03	39/1.70	0.82
13	Glycerol carbonate	63					13.71	31.5/1.37	0.63
14	*meso*-Erythritol[g]	54	45	13	21	4	13.90	27/1.17	0.26
15	*trans*-Cyclohexanediol	61					14.5	30.5/1.33	0.61
16	Cyclohexanol	57					15.5	28.5/1.24	0.35
17	**3**	58[f]					4.06	29/1.26	0.53
18	**4**	74					≈11.3[h]	37/1.61	0.84
19	**5**	80					≈11.3[h]	40/1.74	1.01

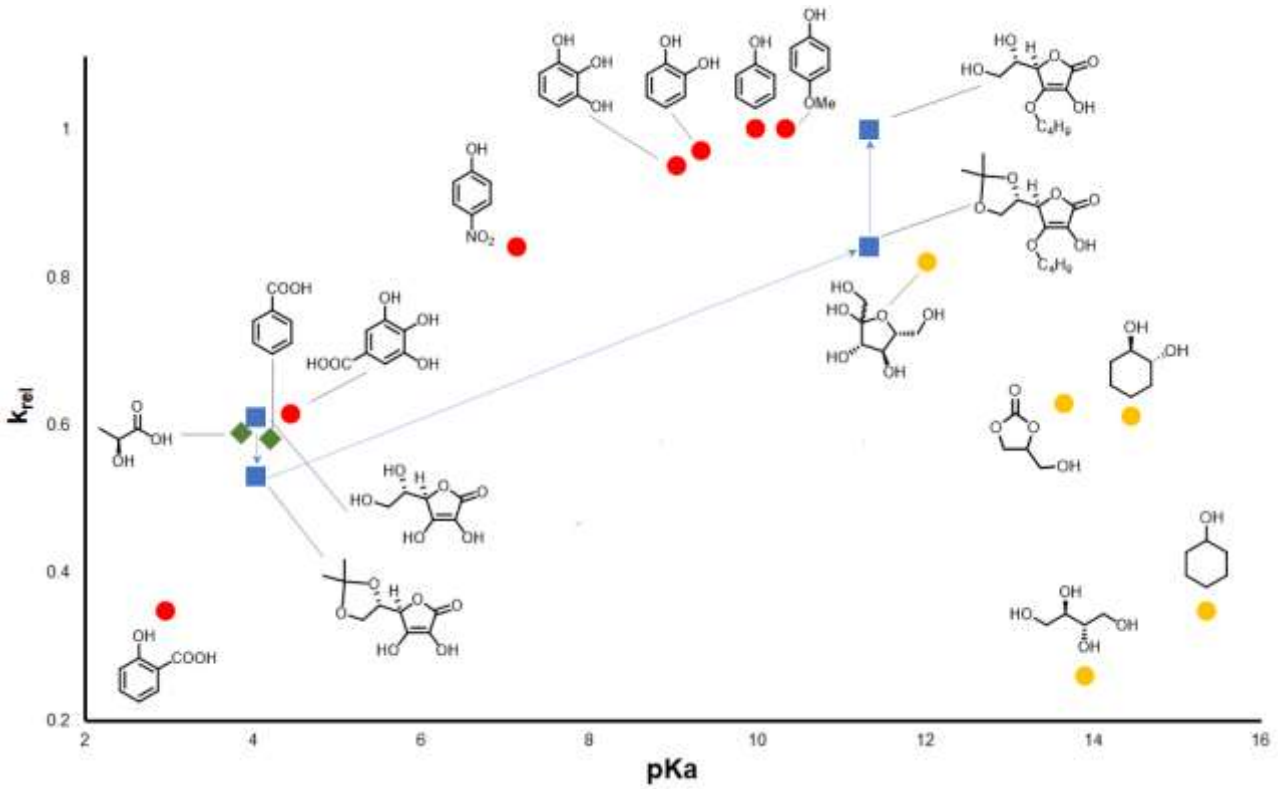
[a] **1a** (25 mmol), HBD 0.5 mmol (2 mol %) and nucleophile 1 mmol (4 mol %), r.t., 1 bar CO_2 (balloon), 23 h. [b] Conversion determined by ^{1}H NMR (See the SI file). [c] Relative to the most acidic proton of the HBD. [d] TON and TOF values are for the reaction catalysed by HBD/TBAI. [e] k_{rel}: ratio between the initial rate of formation of **2a** for the HBD/TBAI pair and for phenol/TBAI; the initial rates of **2a** formation were determined by *in situ* IR by monitoring the time evolution of the band relative to the C=O stretching of **2a** (See section S7 in the SI). [f] Taken from reference [5]. [g] HBD initially insoluble. [h] Estimated values based on pK_a(2) of ascorbic acid (See Section S6 of the SI).

(iii) The order of activity of the nucleophiles follows, as well, a general trend (TBAI>TBAB>DBU≈DMAP>DABCO). Therefore, as TBAI is generally the most active nucleophile, and as the order of activity of the HBDs is broadly preserved for all nucleophiles, we will focus our attention exclusively on the HBD/TBAI systems. (iv) All HBD/TBAI catalytic systems showed a better conversion than TBAI alone (Table 1, Entry 1) suggesting, in all cases, a contribution of the HBD to the observed catalytic activity. The initial rate of erythritol was, however, low compared to the final conversion and TOF values observed after 23 h that are more in line with those of the other alcoholic compounds (Table 1, Entries 13-16). This is attributable to its initial partial insolubility in the reaction mixture that affected the measurement of the initial rate. By plotting the initial rates in Table 1 versus the number of hydroxyls in the HBDs (Figure S21 in the SI), the absence of a clear correlation between catalytic activity and the number of hydroxyls in the HBDs is evident: catalysts with similar activity are found for different number of hydroxyls and HBDs with very different activity are found for the same number of hydroxyls. Additionally, a single hydroxyl group is sufficient to achieve relatively high catalytic activity. Indeed, the catalytic activity does not increase in the phenol-catechol-pyrogallol series. The addition of a carboxylic acid to the scaffolds of phenol (salicylic acid) and pyrogallol (gallic acid) led to a decrease of activity. Conversely, ascorbic acid (4 hydroxyls) is more active than **3** with 2 hydroxyls. The same is true for **5** and **4** (See also discussion in the computations section). At variance with our observations, Kleij *et al.* found pyrogallol as a most active compound than phenol and catechol for the cycloaddition of CO_2 to epoxides.[19a] This conclusion was supported by a comparative study by Tassaing *et al.*[23] However, in both cases, the initial assessment of catalytic activity was carried out under different conditions than ours (T = 45 °C, P_{CO2} = 10 bar using methyl ethyl ketone (MEK) as the solvent

for Kleij *et al.* T = 60°C, P_{CO2} = 20 bar for Alves *et al.*)

By plotting the relative initial rates in Table 1 versus the HBDs pK_a values (See also Section S6) a clear pK_a-dependent trend is revealed (Figure 1). The catalytic activity progressively increases by increasing the pK_a in the 3-11 range. Phenolic compounds such as phenol, *p*-methoxyphenol, catechol and pyrogallol lay within an optimal range of Brønsted acidity (pK_a = 9-10.5). An increase of pK_a over 12 leads to decrease of the catalytic performance. Compounds bearing acidic carboxylic groups have generally lower activity than their counterparts. Interestingly, protection of the most acidic conjugated enediolic hydroxyl proton (pK_a =4.04-4.06) of ascorbic acid or **3**, to afford, respectively, **5** and **4**, led to less acidic and more active HBDs ($pK_a \approx 11.34$). Whereas initial reaction rates are reliable kinetic parameters for benchmarking catalysts,[32] TOF values are average rates through the whole course of the reaction and are often used for catalytic activity comparison.[33] By analysis of the dependency of the TOF values in Table 1 versus the pK_a (See Figure S22 of the SI), the trend of Figure 1 was generally reproduced. Ascorbic acid and *meso*-erythritol show slightly higher activity compared to what expected based on the initial reaction rates. To note, with the progress of the reaction, the **1a** substrate is progressively replaced as the reaction medium by its much more polar carbonate analogue. This change in the polarity can lead to the slight differences observed when comparing the initial rates (Figure 1) and TOF plots (Figure S22). To demonstrate that the obtained trend does not depend on the use of **1a** as substrate, we studied a representative selection of the HBDs presented in Table 1 for propylene oxide (PO) using TBAI as the nucleophile (Table S1 in the SI). As for the case of **1a**, phenol was the most active HBD with an activity very similar to that of **5**. Moreover, **5** was more active than **4** and both were more active than ascorbic acid. Compound **3** was the least active HBD. Additionally, the catalytic activity of phenol was higher than that of ascorbic acid (Table S1, Entries 6-11) and comparable to that of **5** (Table S1, Entries 12-14) for several other epoxides. Interestingly, **5**, a readily available derivative of non-toxic and renewable ascorbic acid, is as a highly active HBD for the cycloaddition of CO_2 to terminal epoxides generally leading to high yields of carbonate under ambient conditions that become quantitative under very mild conditions (40 °C, 1 bar CO_2; see Table S1, Entries 12-15).

Figure 1. Relationship between pK_a of the HBDs and the relative initial rates (k_{rel}, Table 1) for the cycloaddition of CO_2 to **1a** under ambient conditions. Red dots: phenols; green diamonds: carboxylic acids; yellow dots: mono- and polyalcohols, blue squares: ascorbic acid and its derivatives. The blue dashed line is a guide to highlight the pKa-dependent change of catalytic activity among ascorbic acid and its analogues.

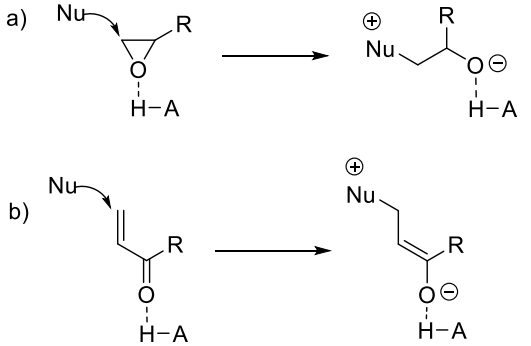


Mechanistic considerations and computational investigation

Brønsted acidity and H-bond strength are closely related; the strength of the H-bond between the HBD and the acceptor molecule can be evaluated by the pK_a-slide rule.[34] Epoxides (*i.e.* cyclic ethers) are expected to form H-bonds of medium strength with alcohols and medium-strong H-bonds with phenols and compounds of similar acidity (pK_a 9-11). Even stronger H-bonds should be established between epoxides and HBDs with pK_a close to 4 and lower.

To note, a comparable bell-shaped dependency of catalytic efficiency on HBDs Brønsted acidity (pK_a) was previously identified for other catalytic reactions such as the aza- and the Morita-Baylis-Hillman (MBH) reactions. In these cases, the optimal HBD pK_a was found to be around 8 (3,5-bis(trifluoromethyl)phenol) and 7.2 (*p*-nitrophenol), respectively.[35] Interestingly, the cycloaddition of CO_2 to epoxides and the MBH reaction are both catalysed by binary systems composed of a nucleophile and a HBD and involve zwitterionic intermediates (Scheme 1). Zipse *et al*. showed that the addition of excessive amounts of *p*-nitrophenol as HBD to the aza-Morita-Baylis-Hillman would led to a slow-down of the reaction rate due to the protonation of the key zwitterionic intermediate.[36] Similarly, the use of excessively acidic HBDs, could lead to the protonation of the reaction intermediates formed in the mechanistic steps of the cycloaddition of CO_2 to epoxides. Additionally, as recently reported by Hong *et al*.,[28f] the use of very strong HBDs could be detrimental if the cleavage of the H-bond in the final cyclization process (*vide infra for reaction mechanism*) is the rate-determining step of the reaction. Finally, Chen *et al*. proposed that highly acidic C2 protons of imidazole HBDs could inhibit CO_2 insertion because of strong interactions between the HBD and the ring-opened alkoxide intermediate.[30]

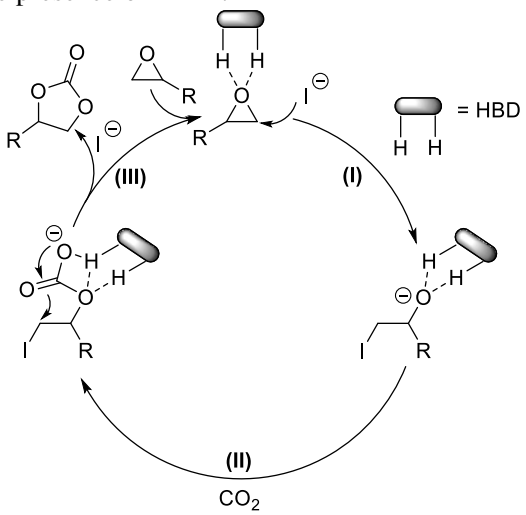
Scheme 1. Zwitterionic reaction intermediates within the catalytic cycles of a) the cycloaddition of CO_2 to epoxides, b) the Morita-Baylis-Hillman reaction.



Based on these factors, the bell-shaped curve in Figure 1 could be tentatively explained as a trade-off between "strong enough" H-bonds (required for the activation of the epoxide), and the undesired protonation, or too strong coordination, of key zwitterionic reaction intermediates occurring for the most acidic HBDs.

To gain further mechanistic insight, we performed density functional theory (DFT) calculations at the GGA B3LYP/6-31G+(d,p) level, including the D3 dispersion correction scheme (See section S8 of the SI for details), using the cycloaddition of CO_2 to PO as a model reaction. The reaction barriers for the three elementary steps (epoxide ring opening (**I**), CO_2 insertion (**II**) and carbonate ring closure (**III**))[5,19a,31] of the reactions catalysed by **4**, **5** (See also Figures S23 and S24 of the SI) and phenol in the presence of TBAI were calculated (Table 2). For the sake of comparison, previously reported[5] barriers for ascorbic acid/TBAI and **3**/TBAI are also displayed in Table 2 along with the barriers calculated by Whiteoak *et al.* for phenol using a DFT (B3LYP) functional in MEK.[19a] The cycloaddition reaction elementary steps have comparable energy barriers and, therefore, they might all play a relevant role in the catalytic process.[37]

Table 2. Calculated barriers for mechanistic steps **I**-**III** for the cycloaddition of CO_2 to PO catalysed by ascorbic acid, ascorbic acid derivatives **3**-**5** and phenol in the presence of TBAI.



Entry	HBD	Energy Barriers (kcal/mol)[a]		
		I	**II**	**III**
1[b]	Ascorbic acid	13.0	12.2	**15.4**
2[b]	**3**	16.2	17.9	**19.0**
3	**4**	28.0	30.4	**31.5**
4	**5**	23.9	24.1	**25.1**
5	phenol	18.0	**20.2**	8.6
6[c]	phenol	31.7	**37.7**	8.7

[a] The values in bold are for the rate determining step. [b] Taken from reference [5]. [c] Taken from reference [19a].

The rate determining step for ascorbic acid and its derivatives (Table 2, Entries 1-4) is the carbonate ring closure, whereas, for the case of phenol, CO_2 insertion displays the highest barrier (20.2 kcal/mol, Table 2, Entry 5). Both upper reaction barriers for **4** and **5** are higher than for phenol (31.5, 25.1 versus 20.2 kcal/mol respectively) that is qualitatively in agreement with the better catalytic performance of phenol compared to **4**, and similar to **5**, for the cycloaddition of CO_2 to PO (Table S2 in the SI). To note, the predicted upper barrier of 20.2 kcal/mol for phenol is much lower than that of 37.7 kcal/mol earlier reported by Whiteoak *et al.* (Table 2, Entry 6) and in line with the reported catalytic activity at r.t. The latter calculations, published in 2012, were in MEK and did not include the dispersion Grimme corrections that is crucial to describe adequately H-bond networks.[38] The recalculation at the B3LYP/6-31G(d,p)-SMD level starting with the current optimized B3LYP/6-31+G** geometries confirmed again the importance of the missing dispersion corrections for the energy data reported in the past (See Table S2). The upper reaction barrier for phenol (20.2 kcal/mol) is comparable to that calculated by Maeda *et al.* for a calix[4]pyrrole/TBAI organocatalytic system (21.1 kcal/mol)[39] and about 6-10 kcal/mol lower than for other recently studied organocatalysts.[40] The upper barrier for compound **4** (31.4 kcal/mol, Table 2, Entry 3) is higher than for **5** (25.1 kcal/mol, Table 2, Entry 4). This difference can be explained by the availability of the additional hydrogen-bonding ethyldiol protons in the side chain of **5** that contribute to the stabilization of the reaction intermediates (Figures S23 and S24 in the SI). A similar result was previously observed when exploring the difference of activity between **3** and ascorbic acid.[5] These observations suggest that, in case of analogous compounds with the same Brønsted acidity (**3** and ascorbic acid, **4** and **5**), also structural features, such as the availability of additional H-bonding moieties, might have an impact on catalytic activity. Remarkably, the lowest upper reaction barriers overall were calculated for ascorbic acid and its derivative **3** (Table 2, Entries 1, 2). As expected,[28f] these more acidic compounds show the lowest energy barriers for ring opening and CO_2 insertion (**I**, **II**) among all HBDs in Table 2. At variance with what suggested by Dai *et al.*, the acidity of ascorbic acid and **3** does not lead to high energy barriers for the insertion of CO_2.[30]

As discussed above, a possible explanation for their lower observed catalytic activity compared to **4**, **5** and phenol, despite the lower calculated energy barriers, could be the protonation of the alkoxide intermediate produced in step **I** by the acidic conjugated enediolic proton. Additionally, the tendency of the more acidic HBDs to aggregate in the aprotic epoxide medium should be considered. Whereas the energy barriers relative to the dissociation of the H-bond between molecules of alcohol[41] or phenol[42] are generally relatively low (5-10 kcal/mol), it has been shown that carboxylic acids form trimers in aprotic solvents with stabilization energies in the range of 25 kcal/mol and $\Delta G<0$.[43] Such tendency to aggregation might have the effect of lowering the HBDs actual concentration with detrimental effects on activity. Indeed, for the case of ascorbic acid our calculations (See Figure S25 of the SI) show that the formation of a dimer is favoured in PO by 3.7 kcal/mol (ΔH =-20.5 kcal/mol). This hypothesis could be tentatively confirmed by ^1H NMR analysis of solutions of ascorbic acid/TBAI in **1a** (See Section S9, SI). In case of **5**, protection of the most acidic proton with the *n*-butyl chain disfavours the formation of dimers (ΔH: -9.5 kcal/mol; ΔG = +2.3 kcal/mol; see Figure S25). Therefore, the higher activity of phenol, **4** and **5** compared to ascorbic acid can be justified by their lower Brønsted acidity. Additionally, the lack of intermolecular association between the molecules of HBD could also play a role.

Conclusion

We investigated the correlation between the catalytic activity of hydroxyl HBDs in the cycloaddition of CO_2 to epoxides and physico-chemical properties such as the number of hydroxyls and the HBDs' Brønsted acidity. By catalytic screening of several families of HBDs in the coupling of CO_2 to **1a** under ambient conditions, we found out a clear correlation between pK_a and catalytic activity (Figure 1). The optimal pK_a region (9-11) corresponds to that of phenol and justifies the widespread use of this moiety as organocatalytic components for the title cycloaddition reaction. No correlation was found between the number of hydroxyls in the HBDs and catalytic activity. However, the catalytic behaviour of ascorbic acid and its derivatives **3**-**5**, suggests that the presence of additional hydroxyl moieties might play a role in tuning the catalytic activity as long as their presence does not modify the HBD's pK_a. The observed trend is likely to arise from the balance of several factors that might affect the elementary steps of the reaction. High Brønsted acidity is likely to have a positive impact on H-bonding ability[34] and, therefore, on the initial step of ring opening of the epoxide substrate.[28f,30] However, it might slow down the release of the product in the cyclization step. Moreover, by analogy with previously studied MBH reactions, strong Brønsted acidity might lead to the protonation of crucial reaction intermediates.[36] Finally, ascorbic acid and

carboxylic acids might form dimers and trimers in solution thus limiting their capability to access the catalytic cycle. DFT calculations show that phenol displays mild reaction barriers for the cycloaddition reaction that are compatible with the good catalytic performance at r.t. Interestingly, the lowest upper reaction barrier was determined for experimentally-less active ascorbic acid. However, we calculated that ascorbic acid tends to form dimers in solution.
We believe that the trend in Figure 1 could be used for the estimation of the catalytic activity of HBDs in the solvent-less cycloaddition of CO_2 to epoxides under ambient or mild conditions and for their structural design and tuning. This predictive concept is confirmed by the fact that, by modifying the ascorbic acid scaffold to achieve compounds with pK_a closer to the optimal value, a more efficient HBD is obtained with a performance comparable to that of phenol. In the perspective of higher sustainability, the development of highly active organocatalysts derived from renewable scaffolds remains more attractive than the use of oil-based and toxic phenolic compounds.[5,44]

Experimental Section

The procedure for a typical reaction setup is reported below; detailed experimental procedures are reported in the SI. The epoxide (25 mmol) was charged in a 50 mL round bottom Schlenk flask equipped with a magnetic stirrer. The HBD (0.5 mmol, 2 mol%) and the nucleophilic cocatalyst (1 mmol, 4 mol%) were added. A rubber balloon containing about 2 L CO_2 was connected to the Schlenk flask and part of the CO_2 was used to flush the flask to replace air. The reaction vessel was well sealed to prevent losses of CO_2 and stirred at r.t. for 23 h. After this period, an aliquot of the reaction mixture was added to a NMR tube to determine substrate conversion by ^{1}HNMR spectroscopy in $CDCl_3$.

Acknowledgements

V.D.E. thanks the Thailand Research Fund (Grant No. RSA6080059) for funding this research. A.P. thanks the Spanish MINECO for a project CTQ2014-59832-JIN, the Generalitat de Catalunya for the project 2017SGR39 and EU for a FEDER fund (UNGI08-4E-003).

References

[1] a) D. W. C. MacMillan, *Nature* **2008**, *455*, 304-308; b) S. E. Denmark, G. L. Beutner, *Angew. Chem. Int. Ed.* **2008**, *47*, 1560-1638.

[2]a) B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396; b) L.-W. Xu, *ChemCatChem* **2013**, *5*, 2775-2784.

[3] M. B. Schmid, M. Fleischmann, V. D'Elia, O. Reiser, W. Gronwald, R. M. Gschwind, *ChemBioChem* **2009**, *10*, 440-444.

[4]J. Agarwal, *Org. Biomol. Chem.* **2016**, *14*, 10747-10762.

[5] S. Arayachukiat, C. Kongtes, A. Barthel, S. V. C. Vummaleti, A. Poater, S. Wannakao, L. Cavallo, V. D'Elia, *ACS Sustainable Chem. Eng.* **2017**, *5*, 6392-6397.

[6] a) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520-1543; b) S. Sopeña, E. Martin, E. C. Escudero-Adán, A. W. Kleij, *ACS Catal.* **2017**, *7*, 3532-3539.

[7] a) C. Martín, G. Fiorani, A. W. Kleij, *ACS Catal.* **2015**, *5*, 1353-1370; b) J. W. Comerford, I. D. V. Ingram, M. North, X. Wu, *Green Chem.* **2015**, *17*, 1966-1987; c) R. R. Shaikh, S. Pornpraprom, V. D'Elia, *ACS Catal.* 2018, *8*, 419-450; d) H. Büttner, L. Longwitz, J. Steinbauer, C. Wulf, T. Werner, *Top. Curr. Chem.* **2017**, 375; e) G. Fiorani, W. Guo, A. W. Kleij, *Green Chem.* **2015**, *17*, 1375-1389; f) M. Cokoja, M. E. Wilhelm, M. H. Anthofer, W. A. Herrmann, F. E. Kühn, *ChemSusChem* **2015**, *8*, 2436-2454; g) M. Alves, B. Grignard, R. Mereau, C. Jerome, T. Tassaing, C. Detrembleur, *Catal. Sci. Technol.* **2017**, *7*, 2651-2684.

[8] a) J. Artz, T. E. Müller, K. Thenert, J. Kleinekorte, R. Meys, A. Sternberg, A. Bardow, W. Leitner, *Chem. Rev.* **2017**, *118*, 434-504; b) Q.-W. Song, Z.-H. Zhou, L.-N. He, *Green Chem.* **2017**, *19*, 3707-3728; c) Z. Zhang, L.-L. Liao, S.-S. Yan, L. Wang, Y.-Q. He, J.-H. Ye, J. Li, Y.-G. Zhi, D.-G. Yu, *Angew. Chem. Int. Ed.* **2016**, *55*, 7068-7072; d) M. K. Samantaray, E. Pump, A. Bendjeriou-Sedjerari, V. D'Elia, J. D. A. Pelletier, M. Guidotti, R. Psaro, J.-M. Basset, *Chem. Soc. Rev.* **2018**, DOI: 10.1039/C8CS00356D e) N. A. Tappe, R. M. Reich, V. D'Elia, F. E. Kühn, *Dalton Trans.* **2018**, *47*, 13281-13313.

[9] a) S. Fukuoka, M. Kawamura, K. Komiya, M. Tojo, H. Hachiya, K. Hasegawa, M. Aminaka, H. Okamoto, I. Fukawa, S. Konno, *Green Chem.* **2003**, *5*, 497-507; b) Z. Han, L. Rong, J. Wu, L. Zhang, Z. Wang, K. Ding, *Angew. Chem. Int. Ed.* **2012**, *51*, 13041-13045.

[10] a) W. Guo, L. Martínez-Rodríguez, R. Kuniyil, E. Martin, E. C. Escudero-Adán, F. Maseras, A. W. Kleij, *J. Am. Chem. Soc.* **2016**, *138*, 11970-11978; b) W. Guo, R. Kuniyil, J. E. Gómez, F. Maseras, A. W. Kleij, *J. Am. Chem. Soc.* **2018**, *140*, 3981-3987; c) H. Liu, Z. Huang, Z. Han, K. Ding, H. Liu, C. Xia, J. Chen, *Green Chem.* **2015**, *17*, 4281-4290; d) M. Blain, H. Yau, L. Jean-Gérard, R. Auvergne, D. Benazet, P. R. Schreiner, S. Caillol, B. Andrioletti, *ChemSusChem* **2016**, *9*, 2269-2272; e) W. Guo, J. E. Gomez, A. Cristofol, J. Xie, A. W. Kleij, *Angew. Chemie Int. Ed.* **2018**, *57*, 13735-13747; f) L. Maisonneuve, O. Lamarzelle, E. Rix, E. Grau, H. Cramail, *Chem. Rev*. **2015**, *115*, 12407-12439.

[11] a) B. Schäffner, F. Schäffner, S. P. Verevkin, A. Börner, *Chem. Rev.* **2010**, *110*, 4554-4581; b) S. B. Lawrenson, R. Arav, M. North, *Green Chem.* **2017**, *19*, 1685-1691.

[12] a) A. Barthel, Y. Saih, M. Gimenez, J. D. A. Pelletier, F. E. Kühn, V. D'Elia, J.-M. Basset, *Green Chem.* **2016**, *18*, 3116-3123; b) M. J. Kelly, A. Barthel, C. Maheu, O. Sodpiban, F.-B. Dega, S. V. C. Vummaleti, E. Abou-Hamad, J. D. A. Pelletier, L. Cavallo, V. D'Elia, J.-M. Basset, *J. CO2 Util.* **2017**, *20*, 243-252; c) I. S. Metcalfe, M. North, R. Pasquale, A. Thursfield, *Energy Environ. Sci.* **2010**, *3*, 212-215.

[13] a) H. Zhou, G.-X. Wang, W.-Z. Zhang, X.-B. Lu, *ACS Catal.* **2015**, *5*, 6773-6779; b) L. Wang, K. Kodama, T. Hirose, *Catal. Sci. Technol.* **2016**, *6*, 3872-3877.

[14] a) C. J. Whiteoak, N. Kielland, V. Laserna, F. Castro-Gómez, E. Martin, E. C. Escudero-Adán, C. Bo, A. W. Kleij, *Chem. Eur. J.* **2014**, *20*, 2264-2275; b) J. A. Castro-Osma, K. J. Lamb, M. North, *ACS Catal.* **2016**, *6*, 5012-5025; c) J. Steinbauer, A. Spannenberg, T. Werner, *Green Chem.* **2017**, *19*, 3769-3779; d) C. Maeda, J. Shimonishi, R. Miyazaki, J.-y. Hasegawa, T. Ema, *Chem. Eur. J.* **2016**, *22*, 6556-6563; e) W. Clegg, R. W. Harrington, M. North, R. Pasquale, *Chem. Eur. J.* **2010**, *16*, 6828-6843.

[15] B. Dutta, J. Sofack-Kreutzer, A. A. Ghani, V. D'Elia, J. D. A. Pelletier, M. Cokoja, F. E. Kühn, J.-M. Basset, *Catal. Sci. Technol.* **2014**, *4*, 1534-1538.

[16] J. Liang, Y.-B. Huang, R. Cao, *Coord. Chem. Rev. 2017*, DOI: 10.1016/j.ccr.2017.11.013

[17] M. North, P. Styring, *Faraday Discuss.* **2015**, *183*, 489-502.

[18] a) S. Sopeña, M. Cozzolino, C. Maquilón, E. C. Escudero-Adán, M. Martínez-Belmonte, A. W. Kleij, *Angew. Chem. Int. Ed.* **2018**, *57*, 11203-11207 b) O. Martínez-Ferraté, G. Chacón, F. Bernardi, T. Grehl, P. Brüner, J. Dupont, *Catal. Sci. Technol.* **2018**, *8*, 3081-3089; c) T. Ema, M. Yokoyama, S. Watanabe, S. Sasaki, H. Ota, K. Takaishi, *Org. Lett.* **2017**, *19*, 4070-4073.

[19] a) C. J. Whiteoak, A. Nova, F. Maseras, A. W. Kleij, *ChemSusChem* **2012**, *5*, 2032-2038; b) F. D. Bobbink, D. Vasilyev, M. Hulla, S. Chamam, F. Menoud, G. Laurenczy, S. Katsyuba, P. J. Dyson, *ACS Catal.* **2018**, *8*, 2589-2594.

[20] a) F. Della Monica, A. Buonerba, A. Grassi, C. Capacchione, S. Milione, *ChemSusChem* **2016**, *9*, 3457-3464; b) V. B. Saptal, B. M. Bhanage, *ChemSusChem* **2017**, *10*, 1145-1151; c) H. Büttner, J. Steinbauer, T. Werner, *ChemSusChem* **2015**, *8*, 2655-2669.

[21] Z. Guo, Q. Jiang, Y. Shi, J. Li, X. Yang, W. Hou, Y. Zhou, J. Wang, *ACS Catal.* **2017**, *7*, 6770-6780.

[22] M. E. Wilhelm, M. H. Anthofer, M. Cokoja, I. I. E. Markovits, W. A. Herrmann, F. E. Kühn, *ChemSusChem* **2014**, *7*, 1357-1360.

[23] M. Alves, B. Grignard, S. Gennen, R. Mereau, C. Detrembleur, C. Jerome, T. Tassaing, *Catal. Sci. Technol.* **2015**, *5*, 4636-4643.

[24] a) L. Wang, G. Zhang, K. Kodama, T. Hirose, *Green Chem.* **2016**, *18*, 1229-1233; b) T. Werner, N. Tenhumberg, H. Büttner, *ChemCatChem* **2014**, *6*, 3493-3500.

[25] A. M. Hardman-Baldwin, A. E. Mattson, *ChemSusChem* **2014**, *7*, 3275-3278.

[26] J. Wang, Y. Zhang, *ACS Catal.* **2016**, *6*, 4871-4876.

[27] X.-F. Liu, Q.-W. Song, S. Zhang, L.-N. He, *Catal. Today* **2016**, *263*, 69-74.

[28] a) Y.-M. Shen, W.-L. Duan, M. Shi, *Adv. Synth. Catal.* **2003**, *345*, 337-340; b) H. Büttner, J. Steinbauer, C. Wulf, M. Dindaroglu, H.-G. Schmalz, T. Werner, *ChemSusChem* **2017**, *10*, 1076-1079; c) Y. Toda, Y. Komiyama, A. Kikuchi, H. Suga, *ACS Catal.* **2016**, *6*, 6906-6910; d) S. Liu, N. Suematsu, K. Maruoka, S. Shirakawa, *Green Chem.* **2016**, *18*, 4611-4615; e) J. A. Castro-Osma, J. Martínez, F. de la Cruz-Martínez, M. P. Caballero, J. Fernández-Baeza, J. Rodríguez-López, A. Otero, A. Lara-Sánchez, J. Tejeda, *Catal. Sci. Technol.* **2018**, *8*, 1981-1987; f) M. Hong, Y. Kim, H. Kim, H. J. Cho, M.-H. Baik, Y. Kim, *J. Org. Chem.* **2018**, *83*, 9370-9380.

[29] a) L. Martínez-Rodríguez, J. Otalora Garmilla, A. W. Kleij, *ChemSusChem* **2016**, *9*, 749-755; b) S. Sopeña, G. Fiorani, C. Martín, A. W. Kleij, *ChemSusChem* **2015**, *8*, 3248-3254.

[30] F. Chen, D. Chen, L. Shi, N. Liu, B. Dai, *J. CO2 Util.* **2016**, *16*, 391-398.

[31] V. D'Elia, A. A. Ghani, A. Monassier, J. Sofack-Kreutzer, J. D. A. Pelletier, M. Drees, S. V. C. Vummaleti, A. Poater, L. Cavallo, M. Cokoja, J.-M. Basset, F. E. Kühn, *Chem. Eur. J.* **2014**, *20*, 11870-11882.

[32] T. Bligaard, R. M. Bullock, C. T. Campbell, J. G. Chen, B. C. Gates, R. J. Gorte, C. W. Jones, W. D. Jones, J. R. Kitchin, S. L. Scott, *ACS Catal.* **2016**, *6*, 2590-2602.

[33] J. Rintjema, A. W. Kleij, *ChemSusChem* **2017**, *10*, 1274-1282.

[34] P. Gilli, L. Pretto, V. Bertolasi, G. Gilli, *Acc. Chem. Res.* **2009**, *42*, 33-44.

[35] a) P. Buskens, J. Klankermayer, W. Leitner, *J. Am. Chem. Soc.* **2005**, *127*, 16762-16763; b) M. Shi, Y.-H. Liu, *Org. Biomol. Chem.* **2006**, *4*, 1468-1470.

[36] C. Lindner, Y. Liu, K. Karaghiosoff, B. Maryasin, H. Zipse, *Chem. Eur. J.* **2013**, *19*, 6429-6434.

[37] S. Kozuch, S. Shaik, *Acc. Chem. Res.* **2011**, *44*, 101-110.

[38] a) S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104; b) J. Antony, S. Grimme, D. G. Liakos, F. Neese, *J. Phys. Chem. A* **2011**, *115*, 11210-11220.

[39] C. Maeda, S. Sasaki, K. Takaishi, T. Ema, *Catal. Sci. Technol.* **2018**, *8*, 4193-4198.

[40] a) J.-Q. Wang, K. Dong, W.-G. Cheng, J. Sun, S.-J. Zhang, *Catal. Sci. Technol.* **2012**, *2*, 1480-1484; b) T. Ema, K. Fukuhara, T. Sakai, M. Ohbo, F.-Q. Bai, J.-y. Hasegawa, *Catal. Sci. Technol.* **2015**, *5*, 2314-2321; c) A.-L. Girard, N. Simon, M. Zanatta, S. Marmitt, P. Gonçalves, J. Dupont, *Green Chem.* **2014**, *16*, 2815-2825; d) S. Foltran, R. Mereau, T. Tassaing, *Catal. Sci. Technol.* **2014**, *4*, 1585-1597.

[41] G. R. Desiraju, *Acc. Chem. Res.* **2002**, *35*, 565-573.

[42] M. Kołaski, A. Kumar, N. J. Singh, K. S. Kim, *Phys. Chem. Chem. Phys.* **2011**, *13*, 991-1001.

[43] D. Di Tommaso, K. L. Watson, *J. Phys. Chem. A* **2014**, *118*, 11098-11113.

[44] H. Shadnia, J. S. Wright, *Chem. Res. Toxicol.* **2008**, *21*, 1197-1204.

10.1002/adsc.201801093

UPDATE

Assessing the pKa-Dependent Activity of Hydroxyl Hydrogen Bond Donors in the Organocatalyzed Cycloaddition of Carbon Dioxide to Epoxides: Experimental and Theoretical Study

Adv. Synth. Catal. **2018**, *Volume*, Page – Page

Prapussorn Yingcharoen,[a, †] Chutima Kongtes,[a,†] Sunatda Arayachukiat,[a] Kittipong Suvarnapunya,[a,b] Sai V. C. Vummaleti,[c] Sippakorn Wannakao,[a] Luigi Cavallo,[c] Albert Poater,[d]* and Valerio D' Elia[a]*