(Thio)urea containing quaternary ammonium salts for the CO₂-fixation with epoxides

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Abstract
A detailed screening of differently substituted chiral and achiral (thio)urea-containing quaternary ammonium salts revealed their potential as catalysts for the CO₂-fixation with epoxides to obtain cyclic carbonates in high yields under operationally simple atmospheric pressure conditions. Additional DFT calculations substantiate a mechanism involving an initial addition of the nucleophilic iodide counter anion of the ammonium salt to the H-bonding activated epoxide, followed by stepwise CO₂-fixation and cyclization.

Graphical abstract

Keywords Organocatalysis · Bifunctional catalysis · Carbonates · DFT calculations

Introduction
Reactions of CO₂ with epoxides to form either cyclic carbonates, or polycarbonates are transformations that have attracted much interest over the last years [1–11]. A broad variety of different catalysts has been used to facilitate these reactions and especially metal complexes (usually in combination with nucleophilic additives) have been very carefully studied for the formation of cyclic carbonates 2 by CO₂ insertion into epoxides 1 [9, 10]. Besides that, also metal-free approaches, mostly using ionic liquids [11, 12] or small molecule organocatalysts [6], were systematically tested for this transformation. Among the used organocatalysts, especially dual catalyst systems or bifunctional organocatalysts consisting of a nucleophilic motive and an acidic functionality (that is supposed to activate the epoxide opening by the nucleophilic group leading to an alkoxide which then reacts with CO₂) have shown high potential for these reactions under mild atmospheric pressure conditions [13–25]. Our group has a fundamental interest in bifunctional ammonium salt catalysis (i.e., for asymmetric catalysis [26–28]), and we have recently also carried out CO₂-fixation reactions with epoxides in the presence of quaternary ammonium salt catalysts [22, 29, 30]. Based on a recent collaborative study with the Kass group wherein we demonstrated the potential of charge-containing thioureas for the CO₂-fixation with epoxides 1 under mild conditions [22], we have now carried out detailed experimental and theoretical investigations on the general use of urea- and thiourea containing chiral
and achiral quaternary ammonium salts as catalysts for this CO₂-fixation reaction (Scheme 1).

**Results and discussion**

**Catalyst identification, optimization of reaction conditions, and application scope**

It has been well documented in the past that simple achiral ammonium halides can be used to facilitate the CO₂-fixation with epoxides 1 [31–33], but it was also clearly shown that Lewis and/or Bronsted acids do significantly improve the reaction’s performance (see Refs. [23, 29] for two examples). We thus decided to first carry out a systematic screening of the CO₂-fixation potential of all the differently functionalized catalysts shown in Fig. 1.

As a test reaction, we hereby chose the reaction of neat styrene oxide (1a) in the presence of 1 mol% of catalyst at 60 °C under an atmospheric pressure of CO₂ (balloon) for 6 h (unless otherwise stated).

First control experiments with tetraethylammonium iodide (A) and thiourea B showed that only the synergistic combination of both motives allows for notable conversion after 6 h reaction time, substantiating the need for two complementary modes of activation. Switching to our chiral cyclohexanediamine-based systems C next [27], we immediately realized that both functional groups, the (thio)urea and the quaternary ammonium iodide are crucial to reach reliable conversions. While the urea C1, which is missing in the ammonium group, did not give any product at all, the quaternary ammonium salt C2 without a urea moiety performed better, but not as good as the hybrid catalyst C3. The importance of a nucleophilic counter anion, i.e., iodide, was clearly demonstrated when using the analogous trifluoroacetate-containing C4, which did not lead to any formation of the product at all.

When changing the ammonium group from trimethylamine (C3) to benzyldimethylamine (C5) the reactions became slightly faster under standard conditions (29% conv. instead of 26%) and nearly complete conversion to the carbonate 2a could be reached by either prolonging the reaction time at 60 °C, or by raising the temperature to 120 °C. Noteworthy, the beneficial nature of both NH-groups of the urea moiety was demonstrated when testing the mono-methylated C6 instead. Changing from ureas to thioureas, next, another slight improvement in conversion could be achieved, especially when increasing the acidity of the thiourea by incorporation of electron-poor aryl groups (see catalyst C8). However, also in this case longer...
reaction times or higher temperatures were necessary to reach complete conversion.

As the bifunctional ammonium salt catalysts C have recently demonstrated their potential for asymmetric transformations of three-membered ring heterocycles (i.e., for the kinetic resolution of oxaziridines [26]), we were interested to see if we can also achieve a kinetic resolution in the CO₂-fixation of epoxides 1 (for selected recent examples by others see Refs. [16, 34–36]). We tested several epoxides 1 with different chiral catalysts C, but unfortunately in neither case any enantiomeric enrichment of the recovered starting epoxide 1 or the formed carbonate 2 could be achieved.

Because of this disappointing result we then decided to move away from the chiral catalysts and investigated analogous simple achiral bifunctional thioureas D next (for a previous report by others describing the synthesis of an analogous system see Ref. [37]). It should be clearly pointed out that some of the early results obtained with catalysts D1 and D2 were already reported in a recent collaborative publication with the Kass group [22], but they will briefly be mentioned here as well together with the new results to provide a comprehensive overview and to illustrate our motivation to carry out the detailed computational studies reported in the second part of this article. The ammonium salts D were easily accessible from the simple commercially available diamine 3 on gram-scale (Fig. 2). In general, the introduction of different ureas and thioureas, as well as different ammonium substituents is possible by this synthesis strategy. Given the observed higher activity of chiral electron-poor thioureas C (see Fig. 1), we hereby primarily focused on the achiral thiourea-containing salts D1 and D2. Both of them gave around 30% conversion at 60 °C after 6 h reaction time and it was shown that either increasing the reaction temperature to 120 °C and/or prolonging the reaction time allowed for quantitative conversion of epoxide 1a to carbonate 2a even with only 0.5 mol% of catalyst (with isolated yields higher than 90% after a short filtration over a plug of silica gel to remove the catalyst). It should be noted that we also tested the catalyst scaffold D1 with different benzyl substituents of the ammonium cation as well, but no significant difference in catalytic activity could be observed.

Very interestingly, we could show that the direct use of a mixture of the thiourea-containing amine 5 and benzyl bromide (6) allowed for the in situ generation of the active catalyst D1 (with bromide as the counter anion) under the CO₂ fixation conditions, which gave reasonable (but lower) conversions as well (for a related recent report on CO₂ fixation with an in situ prepared onium salt catalyst see Ref. [38]).

With the catalytic potential of the simple achiral bifunctional ammonium salts D1 and D2 clearly proven, we next investigated the application scope for the atmospheric pressure CO₂ fixation with different epoxides to access the carbonates 2a–2i (Fig. 3). All reactions were carried out under solvent-free conditions with 1 mol% of the catalyst by simply using a balloon of CO₂. Catalyst D1 turned out to be more reliable at 60 °C (96% conversion after 24 h) while catalyst D2 usually gave complete conversion within 4–8 h at 120 °C (which may be attributed to the better solubility of this compound at higher temperatures compared to D1).
As can be seen in Fig. 3, a variety of different aromatic and aliphatic terminal epoxides were tolerated very well (internal epoxides did unfortunately not react, which is in analogy to our recent observations with other onium salt-based systems [22]).

**Mechanistic investigations**

To obtain a better mechanistic understanding of this CO₂-fixation reaction (for three illustrative mechanistic studies of these reactions by others please see Ref. [39–41]), we carried out detailed computational studies of different possible mechanistic scenarios using DFT calculations (Fig. 4). In our previous contribution, we have already reported some of our preliminary results and observations of these mechanistic investigations [22]. Hereby kinetic isotope effects provided evidence that the reaction proceeds via opening of the H-bonding activated epoxide Int-1 on the less-substituted carbon [22]. This ring opening can either occur via addition of the iodide to the activated epoxide (pathway A, Int-2) or via addition of the sulfur of the thiourea motive (pathway B, Int-3). Interestingly, Int-3’ (which is obtained from Int-3 by a barrierless proton transfer) is energetically significantly more stable than Int-2, Int-2’ (after an almost barrierless proton transfer), or Int-2” (obtained after C=N bond rotation). In addition, Int-3’ could be isolated after stirring the catalyst D2 with epoxide 1a and also resubmitted to the reaction with CO₂ still providing the carbonate 2a [22]. However, our first computations also suggested that pathway A (iodide attack) is kinetically favored over pathway B (compare TS1 and TS 2 in Fig. 4) and we were thus wondering if we can obtain further insights by investigating the different mechanistic scenarios shown in Fig. 4 by DFT calculations.

It turned out that Int-2’ can either undergo an intramolecular iodine replacement towards Int-3’ (proceeding via the bond-rotated Int-2”), or it can directly add to CO₂ resulting in Int-5. This later pathway (TS 4) is kinetically clearly favored compared to the formation of the S-alkylated intermediate Int-3” (proceeding via TS6, Int-2” and TS7). In addition, also the final cyclization step from Int-5 to the product 2a is of lower barrier than the cyclization proceeding via Int-4 (compare TS 9 and TS 5).

Accordingly, our calculations substantiate a mechanistic scenario that proceeds predominately via pathway A (Fig. 4), while the experiment also observed Int-3’ seems to play a minor contribution to the overall reaction only.

**Conclusion**

(Thio)urea-containing quaternary ammonium salts C and D revealed their potential for the CO₂-fixation with simple terminal epoxides 1 to obtain the corresponding carbonates 2
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in high yields under operationally simple atmospheric pressure conditions. Detailed DFT calculations substantiate a mechanism involving an initial addition of the nucleophilic iodide counter anion of the ammonium salt to the H-bonding activated epoxide, followed by stepwise CO₂-fixation and cyclization.

**Experimental**

¹H and ¹³C NMR spectra were recorded on a Bruker Avance III 300 MHz spectrometer and on a Bruker Avance III 700 MHz spectrometer with TCI cryoprobe. All NMR spectra were referenced on the solvent peak. High resolution mass spectra were obtained using a Thermo Fisher Scientific LTQ Orbitrap XL with an Ion Max API Source. The catalysts C and D were synthesized as described recently starting from commercially available cyclohexane diamine [22, 28]. All epoxides 1 were purchased from commercial suppliers and the carbonates 2 are all known in literature and their NMR spectra fully matched those reported previously [16, 17, 22].

**General CO₂-fixation procedure**

A mixture of the epoxide 1 (4 mmol) and the hybrid catalyst D (0.04 mmol) was stirred at 1000 rpm at either 60 or 120 °C under one atmosphere of CO₂ (provided by using a balloon) for the time indicated in Fig. 3. After cooling to room temperature, the crude mixture was directly flushed through a short column of silica gel (heptanes/EtOAc = 10:1–3:1 as eluent) to afford the cyclic carbonates in the reported yields, fully matching the analytical data previously reported [16, 17, 22].
Computational methods

Calculations were performed using Gaussian 09 [42]: geometry optimisations were performed at the B3LYP/6–31G(d) level of theory using LANL2DZ for iodine and including an implicit description of styrene oxide as solvent by the polarized continuum model, as well as empirical dispersion as incorporated in Gaussian 09. The correct nature of the found transition states was checked by frequency calculations using the same method and basis set as the geometry optimisations. Then, the structures were reoptimised using B3LYP/6–31G(d,p)/LANL2DZ again including an implicit solvent description as well as dispersion. Gibbs free energies were obtained by vibrational frequency calculations using B3LYP/6–31+G(d,p)/LANL2DZ.

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