Mixed Anhydrides: Key Intermediates in Carbamates Forming Processes of Industrial Interest[+]

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Abstract: Mixed anhydrides of carbonic acid with phosphonic or carbamic acid, are mimic of relevant biological systems, and behave as key intermediates in transesterification processes that afford carbamates of industrial interest. They are formed in the phosphonic acids mediated or direct transesterification reaction of organic carbonates with amines to afford carbamates and have been isolated and characterised in the solid state and solution. Their conversion into the products has been demonstrated to occur with high regioselectivity. The application of such intermediates in some synthetic processes is discussed.

Keywords: anhydrides · carbamates · carbonates · industrial processes · intermediates

Introduction

Mixed anhydrides, compounds of general formula $X_n(O)EOE'(O)Y_m$, play an important role as intermediates in biological[1] and chemical processes.[2] According to the nature of E and E′ they can be categorized as reported in Figure (1).

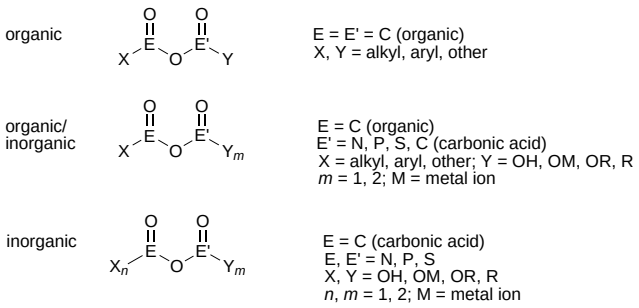
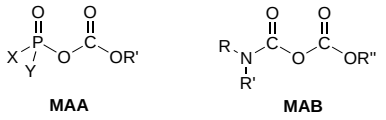


Figure 1. Categorization of mixed anhydrides.

Although they are common intermediates in organic,[3] organometallic,[4] and inorganic[5] reactive processes, they have only seldom been used for solving synthetic problems. Their role is rarely emphasized and the only review available in the literature dates back to early sixties.[2a] In biochemical systems, mixed anhydrides play a key role in synthetic processes as active form of otherwise much less reactive species. However, one of the most interesting compounds is carboxyphosphate (see below) which represents the active form of hydrogencarbonate anion, HCO_3^-, used instead of CO_2 in some natural carboxylation reactions.[1]

In this paper we report the characterisation and reactivity of mixed anhydrides of formula MAA and MAB which have a key role in transesterification reactions which convert amines and organic carbonates into organic carbamates.



The conversion of the mixed anhydride into the final product is 100% regioselective, which ensures that mixed anhydrides react in very selective processes in vitro as they do in biosystems.

Results and Discussion

Organic carbamic esters, RR′NCOOR″, find a large utilisation in the chemical,[6] pharmaceutical,[7] and agrochemical[8] industry. Presently, they are synthesized from phosgene, mainly as in Equation (1), but also by alternative synthetic routes if necessary to meet environmental and raw material diversification issues.

$$ROH + COCl_2 \xrightarrow{B} ROCOCl + BHCl \quad (1a)$$

$$ROCOCl + R'R''NH \xrightarrow{B} R'R''NCOOR + BHCl \quad (1b)$$

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Innovative synthetic pathways are reported in Equations (2) and (3).

$$RR'NH + CO_2 + R''X \xrightarrow{B} RR'NC(O)OR'' + BHX \quad (2)$$

$$RR'NH + (R''O)_2C{=}O \longrightarrow RR'NC(O)OR'' + R''OH \quad (3)$$

which also correspond to the atom economy principle and reduction of waste.[9] These reactions could find an industrial exploitation, given that fast and selective reactions were to be developed.

In particular, Reaction (3) is attractive, as routes alternative to phosgene are now available for the synthesis of organic carbonates as the ENIChem[10] [Eq. (4)] and Ube[11] processes [Eq. (5)]:

$$2\,CH_3OH + CO + 1/2\,O_2 \xrightarrow{Cu^I/Cu^{II}} (CH_3O)_2CO + H_2O \quad (4)$$

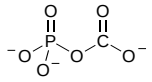
$$2\,CH_3OH + CO + 1/2\,O_2 \xrightarrow{Pd^{II}/NO} (CH_3O)_2CO + H_2O \quad (5)$$

Reaction (3) requires a catalyst which is often a transition metal system.[12] The major drawback is the concurrent alkylation/arylation reaction of the amine [Eq. (6), R″ = alkyl, aryl].

$$RR'NH + (R''O)_2CO \rightleftharpoons RR'R''N + R''OH + CO_2 \quad (6)$$

Therefore, the ideal catalyst should not promote the amine alkylation/arylation [Eq. (6)], while enhancing the carbamation reaction, at moderate temperature, as this parameter may also play an important role in the byproduct formation.

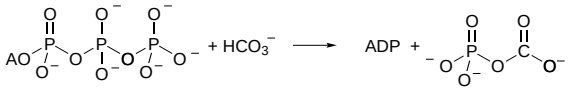
As we have anticipated, biological systems use mixed anhydrides in processes related to those described above. A relevant case is represented by the enzyme carboxyphosphate (CP)[13] in the carbamation of ammonia or amines [Eq. (7)].



CP

$$\xrightarrow[+\,RNH_2]{+\,NH_3} \begin{matrix} (^-O)_2P(O)OH + H_2NCOO^- \\ (^-O)_2P(O)OH + RHNCOO^- \end{matrix} \quad (7)$$

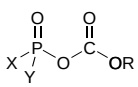
CP represents the active form of HCO_3^- from which it is generated by reaction with ATP [Eq. (8a)].



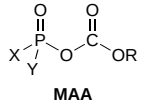
$$+ HCO_3^- \longrightarrow ADP + \quad (8a)$$

Despite several attempts, CP has not yet been synthesized in vitro starting from phosphate and HCO_3^- or CO_2. Thus, it has not been possible to demonstrate so far and exploit its peculiar properties [Eq. (7)] nor those of relevant species. Mixed anhydrides (MAA) derived from phosphoric/phosphonic acids and organic carbonates have structural properties similar to CP. They can be easily synthesized starting from the sodium salt of the commercial phosphonic acid, XYP(O)OH, and an alkyl ester of the chlorocarbonic acid,[14] ClC(O)OR [Eq. (8b)].

$$XYP(O)ONa + ClCOOOR \longrightarrow \quad (8b)$$



However, in order to evaluate the potential of such mixed anhydrides in synthetic chemistry, we have prepared such compounds and treated them with amines. XYP(O)ONa, the sodium salts of the commercially available acids $Ph_2P(O)OH$, $(PhO)_2P(O)OH$, $(BuO)_2P(O)OH$, promptly react with organic chloroformates ClC(O)OR to afford mixed anhydrides of general formula MAA [Eq. (8b)]. The latter then easily reacts with aliphatic and aromatic amines to afford organic carbamates [Eq. (9)] and ammonium phosphonate:



MAA

$$+ 2\,R'R''NH \rightleftharpoons XYP(O)OR'R''NH_2 + R'R''NC(O)OR \quad (9)$$

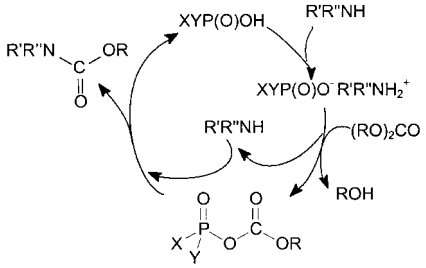
Thus, MAA acts as an active organic carbonate in a transesterification process, a reaction of great potential interest [Eq. (3)] that can be implemented as alternative to the phosgene amination/alcoholation for the synthesis of carbamates. However, the synthetic strategy based on the use of sodium salts of phosphonic acids and chloroformates [Eq. (8b)] is not economically viable, although it is interesting for the easy synthesis of MAA. Therefore, we have investigated alternative ways to the synthesis of the mixed anhydride MAA. As the acid XYP(O)OH itself promptly reacts with amines to afford the corresponding ammonium salt [Eq. (10)], the question arose whether the latter would efficiently substitute the sodium salt used in our first attempts or not.

$$XYP(O)OH + R'R''NH \rightleftharpoons XYP(O)O^- R'R''NH_2^+ \quad (10)$$

The discovery that the ammonium salts of phosphonic and phosphinic acids react with organic carbonates [Eq. (11)]

$$XYP(O)O^- R'R''NH_2^+ + (RO)_2CO \rightleftharpoons XYP(O)OC(O)OR + ROH + R'R''NH \quad (11)$$

opened the way to the exploitation of phosphonic acids as catalysts in the transesterification reaction described in Scheme 1, which shows how a catalytic cycle can be run based



Scheme 1. Use of phosphonic acids as catalysts in transesterification reactions for the selective synthesis of carbamates from amines and organic carbonates.

on the reactions described in Equations (10), (11) and (9), respectively.

However, the net reaction is represented by Equation (12):

$$(RO)_2CO + R'R''NH_2 \rightleftharpoons R'R''NC(O)OR + ROH \quad (12)$$

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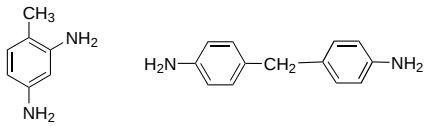
The practical interest of such a reaction is demonstrated by the fact that phosphonic acids have been used as efficient catalysts in the carbamation of industrially relevant amines such as TDA and MDA.[15, 16]

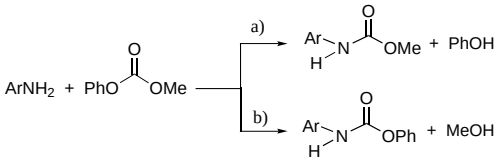


TDA **MDA**

The transesterification reaction is carried out treating the diamine with the organic carbonate under mild conditions (360 K) using the carbonate itself as the solvent. The reaction seems to be of general application. In fact, we have used either dimethylcarbonate (DMC) or diphenylcarbonate (DPC) or methylphenylcarbonate (MPC) for the carbamation of both mono-aromatic amines as aniline or naphthylamine, and the diamines reported above.

The reaction is very selective (see Experimental Section) and the alkylation/arylation of the amine is not observed under the experimental conditions reported above. The reactivity of carbonates is in the order DPC > MPC > DMC.

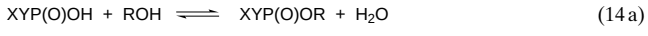
Interestingly, MPC behaves as a very selective carboxymethylating reagent for aromatic amines with selective release of phenol instead of methanol [Eq. (13)].



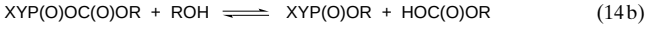
(13)

Thus, MPC is more reactive and selective than DMC[16] in the synthesis of the methylcarbamate, and neither the alkylation nor the arylation of the substrate is observed. The fact that the carbonate itself can be used as solvent, either liquid or low melting solid, makes the reaction and recycling of the catalyst easier as the phosphonic acid can be easily separated as ammonium phosphate and, thus, does not contaminate the product.[9a, 15]

The catalyst runs for hours, with a 1–3% load with respect to the amine, the carbonate being both reagent and solvent. The intermediacy of the mixed anhydride is of crucial importance in the overall reaction. The deactivation of the catalyst is caused by the formation of esters of the acid which can, in principle, be produced either by an intramolecular rearrangement of the mixed anhydride as in Reaction (14c) or by reaction of the acid or the mixed anhydride with the alcohol present in the reaction medium as in Reactions (14a, b)].



(14a)



(14b)

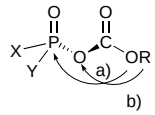
(14b')

(14c)

Although all routes described in Reactions (14a–c) have been proven to occur independently, Reaction (14c) is most likely to be operative under the reaction conditions at least until a low concentration of free alcohol is present in the reaction medium. The direct deactivation of the MAA undergoes an intramolecular rearrangement, and the rate of deactivation depends on the alcohol used. In the case of PhOH or MeOH, we have observed that it occurs that the rate is MeOH > PhOH. It may be worth to note that the rate of the intramolecular rearrangement reaction follows the trend of the acidity of the alcohol (pKa_{PhOH} 9.89, pKa_{MeOH} 16), that means that Reaction (14b) may be operative when the concentration of free alcohol increases in the medium.

We have found that the species XYP(O)OR is not active in catalysis when R = Me, while with R = Ph it still has a catalytic activity. However, the deactivation of the catalyst has been observed essentially when DMC or MPC is used, while DPC does not produce any negative effect on the catalyst.

Reaction (14c) is an example of CO_2 elimination from a mixed anhydride. The process takes place with high regioselectivity. Two pathways are possible for the CO_2 expulsion, as depicted in Scheme 2: a) nucleophilic attack at the P atom by the RO group; b) electrophilic attack by R at the bridging O atom. Path a) is actually observed as was demonstrated by labeling the O atoms.



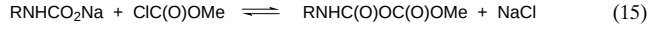
Scheme 2. Possible pathways for CO_2 elimination from the mixed anhydrides.

Carbamates of TDA and MDA find an industrial use as precursor of isocyanates (TDI and MDI) which are formed upon controlled thermal treatment of the relevant carbamates.

The purity of the carbamates is, thus, of crucial importance in order to avoid side reactions (for example, ureas formation) and the reaction based on mixed anhydrides has a good potential for application purposes.[17]

The high regioselectivity of CO_2 elimination has been also demonstrated using mixed anhydride MAB, which is formed by reacting ammonium carbamates with organic carbonates. Mixed anhydrides of the MAB type are known since time.[18] According to the amine used, they have been shown to have a different stability at room temperature, undergoing CO_2 elimination.[19]

For a complete characterisation of the system we have synthesized[19] MAB by reacting sodium *N*-alkylcarbamates with ClC(O)OMe [Eq. (15), R = benzyl, cyclohexyl, allyl].



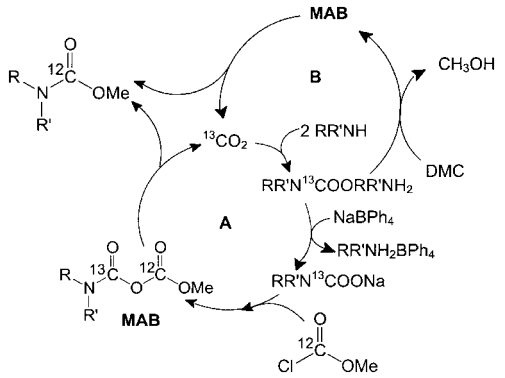
(15)

Either aliphatic or aromatic amine derivatives can be synthesized in this way and characterized.[19] The subsequent elimination of CO_2 affords organic carbamates as in Equation (16).

(16)

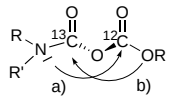
Again, the reaction per se may have a synthetic interest, but the reagents used in Reaction (15) render it of no economic interest.

However, Reaction (15) provides a means for the isolation of various MAB, which have been studied for the elimination mechanism. By using labelled $*CO_2$, the reaction has been shown to occur according to the mechanism presented in Scheme 3a, which represents a quite unique CO_2-catalyzed transesterification process. In fact, $^{13}CO_2$ has been recovered



Scheme 3. CO_2 catalysis in the formation of mixed anhydrides and their reactivity.

at the end of the cycle and ^{13}C NMR experiments have clearly shown that no ^{13}C was incorporated into the methylcarbamate isolated in quantitative yield. This estimate is easily done by comparing the intensity of the peaks for the carbamic C in reactions with labelled and unlabelled CO_2 by allowing the decomposition reaction to occur in an NMR tube. The reaction clearly takes place through a nucleophilic attack of carbamic N at carbonic C (path a), Scheme 4) with expulsion of $^{13}CO_2$. The nucleophilic attack by OR at ^{13}C would also have generated the carbamate, but with ^{13}C incorporation. The global reaction is represented in Scheme 3a. A better exploitation of this reaction to a synthetic end is achieved by performing the reaction of amines with organic carbonates under a CO_2 atmosphere. As shown in Scheme 3b, CO_2 behaves as a catalyst and mixed anhydride MAB has a crucial importance in the formation of the carbamates from amines and organic carbonates. The catalytic property of CO_2 is clearly demonstrated by kinetic studies which have shown that in absence of CO_2 the reaction of amines with organic carbonates has an induction time (Figure 2) of a few hours (c). The marked difference of reactivity in presence (a) and absence of CO_2 (c) stimulated us to investigate and explain the reason for such behaviour.



Scheme 4. Elimination of CO_2 from the mixed anhydride to afford an organic carbamate.

We have shown that in absence of CO_2, the organic carbonate primarily acts as an alkylating/arylating (depending on the nature of R) agent for the amine [Eq. (6)].[19]

This reaction eventually releases CO_2, which is formed and can be detected in the reaction medium. Once CO_2 is formed, it reacts with the amine and generates the carbamate, which, in turn, produces MAB according to Scheme 5b. This explains why the carbamation reaction starts with a long delay under N_2 with respect to the case of the reaction carried out under

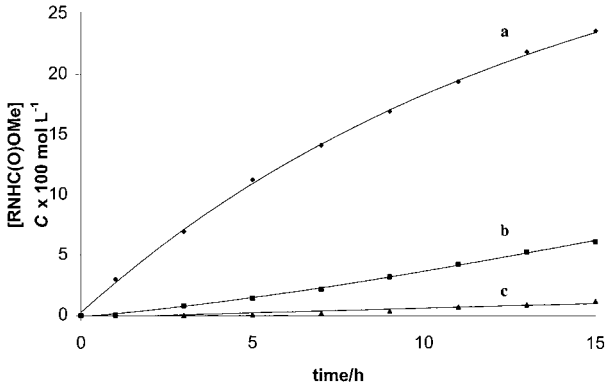


Figure 2. Formation trend of aliphatic carbamates.

CO_2 and why it can be accelerated under nitrogen by using ammonium salts, which can speed up the formation of CO_2 according to Reaction (17).

$$RNH_3Cl + (R'O)_2CO \longrightarrow RNH_2 + R'OH + CO_2 + R'Cl \quad (17)$$

However, also if CO_2 is not added to the amine/carbonate system, there may be a CO_2 catalysis, but obviously much less important, due to the limited amount of CO_2 formed concurrently with the alkylation/arylation of the amine by the organic carbonate.

Noteworthy under CO_2 catalysis the alkylation/arylation of the amine proceeds at a much less extent with respect to a metal catalysed reaction, with a benefit for the whole process. The usefulness of such synthetic methodology is demonstrated by the fact that it can be applied to the conversion of functionalized amines, such as silylamines, into carbamates. We have reported in a preliminary note[20, 21] that silylamines of formula $H_2N(CH_2)_3Si(OMe)_3$, $H_2N(CH_2)_3Si(OEt)_3$, $H_2N(CH_2)_2NH(CH_2)_3Si(OMe)_3$, and $H_2NC(O)NH(CH_2)_2NH(CH_2)_3Si(OMe)_3$ can be selectively converted into the corresponding carbamates $MeO(O)CNH(CH_2)_3Si(OMe)_3$, $MeO(O)CNH(CH_2)_3Si(OEt)_3$, $MeO(O)CNH(CH_2)_2NH(CH_2)_3Si(OMe)_3$, $MeO(O)CNHC(O)NH(CH_2)_2NH(CH_2)_3Si(OMe)_3$ under mild conditions. The CO_2 catalysis, which bears to the formation of mixed anhydrides, appears to be useful for substituting more drastic conditions and harsh catalysts.

Mixed anhydrides MAA and MAB are, thus, quite useful intermediates in a chemistry which is relevant to industrial processes. They can be used for developing innovative synthetic methodologies with both waste elimination at the source and energy-saving costs.

Conclusion

We have shown that mixed anhydrides of formula XYP(O)O-C(O)OR and RR′NC(O)OC(O)OR″ can be easily formed under different conditions in which amines, an organic carbonate and a phosphonic acid and/or CO_2 are present. They have an important role as intermediates in chemical

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syntheses, recalling the role of similar compounds in biological systems. Their formation represents the key step for evolving selective synthesis of organic carbamates from amines and organic carbonates in transesterification reactions to be useful in obtaining industrially relevant compounds.

Experimental Section

All reactions and manipulations were carried out under an inert atmosphere, by using vacuum line techniques. All solvents were dried as described in the literature[22] and stored under N_2.

IR spectra were obtained with a Perkin–Elmer 883 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with a Varian XL-200 spectrometer. ^{31}P NMR shifts were referenced to the peak of H_3PO_4 (85%, ext. ref). GC/MS analyses were carried out with a gas chromatograph Shimadzu 17A (capillary column: 1000 (30 m × 0.00025 m, 0.25 μm thickness) detector linked to a Shimadzu GCMS-QP 5050 mass. HPLC analyses were performed with a Perkin Elmer Series 4LC connected with a LC 290 UV/Vis spectrophotometer detector.

The synthesis of Group 1 carbamates by using $MBPh_4$, CO_2 and amines has been described in ref. [23].

Synthesis of the mixed anhydride $Ph_2P(O)OC(O)OMe$: a) A solution of $Ph_2P(O)Cl$ (0.39 mL, 2.05 mmol) in THF (10 mL) was added to NaO(O)COMe (0.201 g, 2.05 mmol), dispersed in THF (20 mL). The reaction solution was stirred at 253 K for 24 h, then concentrated to half volume and filtered at 273 K. The solvent was evaporated in vacuo and the residue, a colorless oil, was identified as $Ph_2P(O)OC(O)OMe$ (396 mg, 70%). IR (Nujol, KBr disks): $\tilde{\nu} = 1770$ (s, br, ν_{CO}), 1591 (m), 1440 (s), 1250 cm^{-1} (s, br); ^1H NMR ($CDCl_3$, 200 MHz, 293 K): $\delta = 7.9-7.3$ (10H, Ar), 3.76 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 50.3 MHz, 293 K): $\delta = 149.27$ (br d, $^2J_{COP} = 5.6$ Hz, O*C*(O)O), 132.99 (d, $J_{CP} = 2.8$ Hz, C_{para}), 131.59 ($J_{CP} = 10.8$ Hz, C_{ortho}), 128.71 ($J_{CP} = 14.2$ Hz, C_{meta}), 56.03 (CH_3); ^{31}P NMR ($CDCl_3$, 50.3 MHz, 293 K): $\delta = 31.7$; elemental analysis calcd (%) for $C_{14}H_{13}PO_4$: C 60.86, H 4.74, P 11.22; found: C 60.76, H 4.66, P 11.15.

b) ClC(O)OMe (0.201 g, 2.05 mmol) was added to a solution of $Ph_2P(O)ONa$ (0.39 mL, 2.05 mmol) in THF (10 mL). The reaction solution was stirred at 253 K for 24 h, then concentrated to half volume and filtered at 273 K. The filtered solvent was evaporated in vacuo and the residue, a colorless oil, was identified as $Ph_2P(O)OC(O)OMe$ (396 mg, 70%). The ^1H, ^{13}C, ^{31}P NMR spectra were identical with those obtained for the sample isolated according to procedure a). Elemental analysis calcd (%) for $C_{14}H_{13}PO_4$: C 60.86, H 4.74, P 11.22; found: C 60.81, H 4.72, P 11.20.

Deactivation of the mixed anhydride $Ph_2P(O)OC(O)OMe$: $Ph_2P(O)OC(O)OMe$ was prepared as described above in the paragraph a). At 293 K, both in the pure state and in THF solution, the mixed anhydride slowly decarboxylates and converts into $Ph_2P(O)OMe$ and CO_2. The GC/MS of the reaction solution shows the presence of the diphenylphosphinic acid methyl ester (*m*/*z* 232) in the reaction mixture. At 373 K the decarboxylation reaction is much faster and completed within a few minutes. The same behaviour has been observed when $Ph_2P(O)C(O)OPh$ is used. Both $PhP(O)OMe$ and $Ph_2P(O)OPh$ have been used as catalysts in the transesterification reactions replacing the free parent acid (see the following paragraphs) and shown to have a quite different reactivity. $Ph_2P(O)OPh$ still has good catalytic properties, while $Ph_2P(O)OMe$ is totally inactive.

Reaction of $Ph_2P(O)OC(O)OMe$ with aniline: The mixed anhydride $Ph_2P(O)OC(O)OMe$ (1.57 g, 5.7 mmol) was treated with aniline (0.5 mL, 5.7 mmol) in THF at room temperature. The reaction immediately took place and the phosphinic acid $Ph_2P(O)OH$ and the carbamate PhHNCOOMe were formed. The aniline carbamate was isolated by column chromatography, and shown identical with an authentic sample synthesized by a different procedure.

Reaction of DPC with aniline in the presence of $Ph_2P(O)OH$—Synthesis of *N*-phenylcarbamate: $Ph_2P(O)OH$ (0.118 mg, 0.54 mmol) was added to a solution of aniline (1 mL, 11.4 mmol) and DPC (2.335 g, 10.9 mmol) in THF (20 mL). The reaction mixture was stirred for 20 hours at 363 K, then cooled to room temperature and concentrated under reduced pressure. After addition of hexane (30 mL) the pure carbamate was isolated (1.170 g, 50%). IR (Nujol, KBr disks): $\tilde{\nu} = 3321$ (ms, br, ν_{NH}), 1715 (s, ν_{CO}), 1597 (m-s), 1590 (m), 1530 (s), 1488 (m-s), 1443 (s), 1317 (m-s), 1260 (m), 1223 (s), 1201 (s), 790 (m-s), 755 (s), 724 (m), 694 cm^{-1} (s); ^1H NMR (CD_2Cl_2, 200 MHz, 293 K): $\delta = 7.46$ (m), 7.42 (m), 7.38 (m), 7.34 (m), 7.29 (m), 7.26 (m), 7.21 (m), 7.18 (m), 7.15 (tt). Addition of D_2O reveals the NH proton at around $\delta = 7.1$; ^{13}C ATP NMR ($CDCl_3$, 50.3 MHz, 293 K): $\delta =$ 151.79 (br, *C*(O)O), 150.53 (C_{ipso}, OPh), 137.36 (br, C_{ipso}, NHPh), 129.43/129.15 (C_{meta}, OPh/C_{meta}, NHPh)), 125.74 (C_{para}, OPh), 123.91 (br, C_{para}, NHPh), 121.68 (C_{ortho}, OPh), 118.78 (br, C_{ortho}, NHPh); elemental analysis calcd (%) for $C_{13}H_{11}NO_2$: C 73.22, H 5.20, N 6.57; found: C 73.52, H 5.24, N 6.40.

The same methodology has been used for the synthesis of mono- and dicarbamates of MDA and TDA.[15]

Synthesis of $PhCH_2NHC(O)OC(O)OMe$: A solution of $PhCH_2NH_2$ (1.0 mL, 0.981 g, 9.15 mmol) in diethyl ether (40 mL) was saturated with CO_2 at 233 K to afford benzylammonium carbamate, $PhCH_2NHCOO^{-+}H_3NCH_2Ph$. ClC(O)OMe (0.35 mL, 0.432 g, 4.57 mmol) was added to the suspension. The reaction mixture was stirred for 4 h at 233 K under CO_2, then filtered. The mother solution was collected and evaporated in vacuo. A white powder was obtained and identified as $PhCH_2NHC(O)OC(O)OMe$. IR (Nujol, KBr disks): $\tilde{\nu} = 3360$, 1805, 1740 cm^{-1} (s, br, ν_{CO}); elemental analysis calcd (%) for $C_{10}H_{11}NO_4$: C 57.41, H 5.30, N 6.69; found: C 58, H 5.87, N 7.01.

Synthesis of *N*-benzylmethylcarbamate: A solution of $PhCH_2NH_2$ (1.0 mL, 0.981 g, 9.15 mmol) in DMC (10 mL) was prepared under N_2 and then saturated by bubbling CO_2. A white precipitated identified as $PhCH_2NH_3^+PhCH_2NHCO_2^-$ was obtained. The reaction mixture was heated at 363 K for 24 h. After cooling to room temperature, a small amount of a white solid was isolated by filtration, which analyzed as $PhCH_2NH_3^+PhCH_2NHCO_2^-$. The solution was collected and fractionated on a silica gel column with diethyl ether/hexane (2:1 v/v) mixture as eluent. After evaporation of the solvent, the pure carbamate was isolated (1.07 g, 71%). IR (Nujol, KBr disks): $\tilde{\nu} = 3374$ (ms), 3350 (m, sh), 1715 (ms, sh), 1690 (vs), 1527 (vs), 1274 cm^{-1} (vs); ^1H NMR ($CDCl_3$, 200 MHz, 293 K): $\delta = 7.27$ (m, 5H, $H_{aromatic}$), 5.44 (br, 1H, N*H*), 4.31 (d, 2H; $^3J_{HCNH} = 5.32$ Hz, CH_2), 3.64 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 200 MHz, 293 K): $\delta = 157.16$ (sept, *C*(O)O; $^3J_{COCH} = {}^3J_{CNCH} = 3.8$ Hz); 127.43, 127.41, 128.61, 138.60 (C_{Ar}); 52.20 (q; $^1J_{CH} = 146.58$ Hz, CH_3); 45.07 (br t, $^1J_{CH} = 137$ Hz, CH_2); elemental analysis calcd (%) for $C_9H_{11}NO_2$: C 65.45, H 6.67, N 8.48; found: C 65.70, H 6.87, N 8.37; GC/MS: *m*/*e*: 165 $[M]^+$, 150, 133, 121, 106, 91, 79, 77, 28.

Reaction of DMC with cyclohexylamine in the presence of $^{13}CO_2$: A solution of $CyNH_2$ (2 mL, 1.734 g, 1.75 mmol) in DMC (20 mL) was prepared under N_2 and then saturated with $^{13}CO_2$ to give $CyNH_3^+CyNH^{13}CO_2^-$. The reaction mixture was heated to 343 K. The pathway of the reaction was monitored by GC/MS and IR spectroscopy. After 2 h the main product was the cyclohexyl carbamate. IR (Nujol, KBr disks): $\tilde{\nu} =$ 3350 (s), 3320 (ms, sh), 1710 (s, sh), 1685 (vs), 1529 (vs), 1450 (vs), 1317 (v), 1275 (s), 1250 (s), 1228 (s), 1052 cm^{-1} (vs); GC/MS: *m*/*e*: 157 $[M]^+$, 142, 114, 101, 82, 76, 59, 28.

The related mass spectrum showed the I(*M*+H)/I(*M*) isotope ratio which is in agreement with the value expected for unlabelled carbamate. Moreover, the IR spectrum of the isolated carbamate showed that $^{13}CO_2$ was not incorporated into the product.

In a similar manner several other aliphatic amines[24] and aminofunctional silanes[20] were converted into their respective carbamates using organic carbonates.

Kinetic studies to demonstrate the catalytic role of CO_2: The reaction flask was a 30 mL tube sealed with a two-way valve which allowed withdrawing of the solution with a chromatography syringe without no air contact. The reaction was carried out using three different conditions.

1) $PhCH_2NH_3^+PhCH_2NHCO_2^-$ (9.15 mmol) obtained from $PhCH_2NH_2$ and CO_2; $p_{CO_2} = 0.1$ MPa; DMC (20 mL);
2) $PhCH_2NH_2$ (18.3 mmol); $PhCH_2NH_3Cl$ (9.06 mmol); $p_{N_2} = 0.1$ MPa; DMC (20 mL);
3) $PhCH_2NH_2$ (18.3 mmol); $p_{N_2} = 0.1$ MPa; DMC (20 mL).

In all cases the reaction vessel was heated to 393 K. At fixed times, the reaction mixture was cooled to room temperature and a sample analyzed by HPLC. Data are represented in Figure 3. The complete kinetic study

with evaluated ΔG^{+} and isokinetic temperature estimation can be found in ref. [24].

Kinetic measurements to study the formation trend of mono- and dicarbamate of MDA and TDA in the presence of P acids: The reaction was performed into a 25 mL tube equipped with a two-way valve as reported above. Amine (0.267 g, 1.35 mmol) was added into the reactor containing $Ph_2P(O)OH$ (0.0299 g, 0.135 mmol). The carbonate (DPC) or THF (when the carbonate was MPC) were used as solvent. The reaction was carried out at 363 K. At intervals of time a sample was withdrawn and analyzed by HPLC.

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