ChemComm

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Journal:	*ChemComm*
Manuscript ID	CC-COM-08-2019-006429.R1
Article Type:	Communication

COMMUNICATION

Unorthodox crystalline drug salts via the reaction of amine-containing drugs with CO_2

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

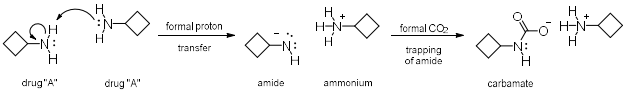
Mohammad Soltani,[a] Brandon L. Mash,[b] Julian Henseler,[c] Sharhzad Badri,[a] Matthias Zeller,[b] E. Alan Salter,[a] Andrzej Wierzbicki,[a] Alexandra C. Stenson,[a] and James H. Davis, Jr.[a]*

Drugs containing amine groups react with CO_2 to form crystalline ammonium carbamates or carbamic acids. In this approach, both the cation and anion of the salt, or the neutral CO_2 adduct, are derived from the parent drug, generating new crystalline versions in a 'masked' or prodrug form. It is proposed that this approach may serve as a valuable new tool in engineering the physical properties of drugs for formulation purposes.

Our experience with the use of amine-functionalized ionic liquids for CO_2 capture,[1] and familiarity with the general characteristics of carbamic acids and ammonium carbamate salts, the usual products of amine-CO_2 reactions,[2] leads us to propose that there may be utility in creating new forms of amine-containing drugs via their reaction with CO_2. It has been suggested in recent reviews that devising new ways to alter the physical forms (polymorphs, co-crystals, ionic liquid forms[3], etc.) of drugs is increasingly central to the future of drug development.[4]

To better appreciate why the possibility of creating ammonium carbamate salts of drugs is appealing, consider the fact that more than 50% of drugs are administered as salts,[5] and this is often because the ionic form of an active pharmaceutical ingredient (API) has superior physicochemical properties (solubility, etc.) from a formulation standpoint compared to the neutral substance. Further, ionic forms are often more readily purified due to a propensity to crystallize; in fact, crystallization is the last step in the manufacture of 70% of small-molecule drugs.[6]

Classically, drug salts are often generated by protonation of an amine group that is a part of the native drug structure. Naturally, the anion of any such salt comes from the donor acid. These anions are predominantly simple inorganic species such as chloride or sulphate, and arise from the strong acids used to protonate the API.[5] In other cases, weak acids such as succinic or malonic acid may be used instead to accomplish the API protonation.[5] In those instances, the accompanying anion is more elaborate. For example, both succinic and malonic acid incorporate a second carboxylic acid group in addition to that which supplies the cation-generating proton, and this group likewise becomes a part of the overall salt composition.



Scheme 1. In the presence of CO_2, one molecule of an amine-containing drug functions as an acid toward another molecule of the same drug, formally generating amide- and ammonium variants. The formal amide is then (conceptually speaking) trapped and stabilized by CO_2 as a carbamate.

The generation of salts by the reaction of CO_2 with amine-containing drugs differs in both conceptually significant and practically exploitable ways from the established practise of using Brønsted acids, whether strong or weak. Specifically, we note that the formation of drug carbamate salts would be accomplished by (formally) inducing one molecule of the drug to transfer a proton to another, creating both the cation and the anion of the salt *from the same drug* (Scheme 1). Half of the salt would be an ammonium prodrug version of the API, identical to that produced by the classic salt-forming approach. The anion half, however, would be a different prodrug form of the API; rather than being 'unmasked' *in vivo* by deprotonation, it would be 'unmasked' instead by CO_2 elimination to restore the native API. Depending upon the rate with which this would occur, the anion could even be (on a case-by-case basis) a delayed or slow-release form of the API. It also bears note that the species which induces the salt formation, CO_2, is a neutral molecule with a very low potential for causing unwanted side reactions. That is to say, in contrast to HCl or H_2SO_4, it is highly unlikely to foster any rearrangements, hydrolyses, etc. that could alter other portions of a drug molecule's structure or composition during its formulation. And, unlike many of the weak acids used in API

[a] *Department of Chemistry, University of South Alabama, Mobile, Alabama 36688.*
[b] *Department of Chemistry, Purdue University, West Lafayette, Indiana 47907.*
[c] *Department of Chemistry, Hochschule Aalen, 73430 Aalen, Germany.*
Electronic Supplementary Information (ESI) available: [NMR spectra; Elemental analyses; Thermogravimetric analyses (TGA); Additional crystallographic information]. CCDC 1947399-1947402 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See DOI: 10.1039/x0xx00000x

salt formulations, CO_2 carries with it no possibly complicating secondary functionality. Each of these considerations would seem to be advantageous in drug formulation.

When we surveyed the literature to ascertain the scope and character of prior research at the nexus of drugs and CO_2, we discovered a substantial body of work, but the majority of it pertains to the use of supercritical CO_2 in drug processing.[7] Also, there are reports concerning the formation and use of carbamate anions (formed by amine-CO_2 reactions) as intermediates in the synthesis of drugs containing carbamate ester moieties.[2b] However, we only found two reports describing the reaction of extant drugs with CO_2 in anticipation of forming discrete compounds. The first, from 1948, reported there to be no reaction between CO_2 and ephedrine; that result was detailed within the context of a general study of arylalkyl amine reactions with the gas.[8] In the second, Mezei, *et al.* showed that CO_2 can be used to aid in the separation of desloratidine from contaminants during its synthesis.[9] A new compound was generated in the process that was then used as a precursor of various loratidine derivatives, and which they suggested might be interesting as a drug in its own right.[9] However, while the composition of the compound was unambiguously established by elemental analysis, its structure was not. Instead, it's 'structure' was depicted in the non-standard fashions shown in Figure 1, and the material was simply described as a "2:1 addition compound." It was further noted that the material "immediately" lost CO_2 upon dissolution "in any solvent," which precluded re-crystallization for analysis by single-crystal X-ray diffraction.[9a] We speculate that its solution-state instability may account for the apparent lack of any clarifying follow-up report.

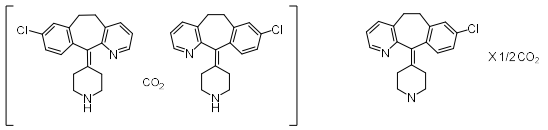


Figure 1. Depictions of the proposed product of desloratidine combined with CO_2, as duplicated from References 9a (left) and 9b (right). Note that while the depiction on the left reflects a composition ($C_{39}H_{38}N_4O_2Cl_2$) that matches the experimental elemental analysis (the depiction on the right does not), neither constitutes an unambiguous representation of a specific structure.

Here, we examined the reactivity of CO_2 with seven currently-used drugs (Figure 2): desipramine (Norpramin™), nortriptyline (Pamelor™), maprotiline (Ludiomil™), tranylcypromine (Parnate™), betahistine (Veserc™), ephedrine (Primatene™), and pramipexole (Mirapex™). These candidates were chosen based on three factors. First, each incorporates a primary or secondary amine group, features known to be amenable to the generation of ammonium carbamate salts on exposure to CO_2. Second, each drug is relatively small and structurally simple, something we thought potentially advantageous, keeping potential chemical and structural 'complications' to a minimum in this pilot study. The final factor was also pragmatic, but not chemical in character – each of these drugs may be purchased without a license. As an aside, we note that there are a number of other amine-containing small drugs that are very interesting candidates, but which require particular licenses to acquire.

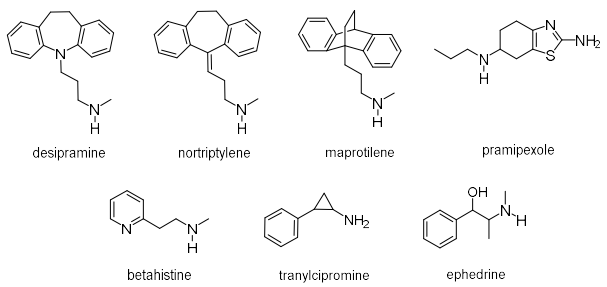


Figure 2. Structures of the drugs evaluated in the present study.

The synthesis of the CO_2-modified drugs is straightforward. The hydrochloride or hydrobromide salt of each material (the form in which they are commercially available) was first neutralized in a biphasic system consisting of aqueous NaOH and Et_2O, the latter phase being the one into which the neutral parent drug partitioned. The organic layer was then isolated and dried using anhydrous $MgSO_4$. After removal of solid by gravity filtration, the ethereal solution containing the free-amine drug molecule was transferred to a small round-bottomed flask that was then fitted with a rubber septum. The flask was then flushed with CO_2 (admitted via a syringe-needle-fitted hose and vented via a second syringe needle) for approximately one minute. The inlet and outlet needles were removed, the septum sealed with parafilm, and the flask set aside. Depending on the exact conditions of a given experiment, solids formed within a few minutes to a day. We note here that we also think their formation could be achieved by ball-milling the neutral drugs under an atmosphere of CO_2, a prospect we plan to evaluate.

The products were isolated by decanting the supernatant, then dried using a stream of CO_2. Except for the betahistine product, the solids were non-hygroscopic. Five of the seven appear to be thermally stable towards CO_2 loss at room temperature. The exceptions to that, tranylcypromine-CO_2 and ephedrine-CO_2, lose CO_2 over the course of a few days if not stored under a CO_2 atmosphere. In turn, pramipexole-CO_2 is stable as a solid, but CO_2 dissociates in solution (free CO_2 observed by ^{13}C-NMR at 124 ppm).

Each material was analysed using ^{1}H- and ^{13}C-NMR, elemental analysis, and TGA. Excepting the betahistine product (which manifested a slightly low value for carbon) the C, H, N analysis of each fell within standard parameters. Likewise, the NMR spectra of each comports with the structure expected and as established by single-crystal X-ray diffraction (*vide infra*). Particularly notable insofar as the NMR data are concerned is the presence in the ^{13}C spectrum of each (except from pramipexole, *vide supra*) of a peak at ca. 158-162 ppm, consistent with the presence of a carbamate or carbamic acid carbon. Unfortunately, electrospray mass spectrometry proved to be fruitless for detecting the CO_2-bearing anions, these apparently being unstable in the high-energy, high-vacuum

conditions of the instrument. However, the TGA of each compound shows a clear loss of mass (generally beginning between 50°C-70°C, depending on the compound) that, on a percentage basis, comports with the extrusion of CO_2 from the material; this has previously been shown by others to be a hallmark of the thermal behaviour of ammonium carbamate salts and carbamic acids.[10] Significantly, the materials also evolve CO_2 and revert to their parent drug form upon dissolution in water the pH of which correlates to that of gastric fluid, validating our proposal that the carbamate anions of the salts constitute prodrug forms of the parent pharmaceuticals (Figure 3).

Figure 3. Left: Crystals of the desipramine-CO_2 ammonium carbamate salt. Right: Same salt upon addition of water at pH = 2.0, within the normal gastric pH range. The evolution of CO_2 is apparent. Subsequent evaporation of water and analysis by ^{1}H- and ^{13}C-NMR revealed the re-formation of desipramine hydrochloride, the form of the drug currently in clinical use.

Four of the products formed crystals suitable for study by single-crystal X-ray diffraction (XRD): desipramine-CO_2, nortriptyline-CO_2, maprotiline-CO_2, and betahistine-CO_2. The desipramine-CO_2 and nortriptyline-CO_2 structures were uncomplicated; the materials proved to be carbamate salts (as expected), the primary crystallographic characteristic of note being extensive H-bonding between the ammonium group of the cations and the carbamate group of the anions (Figure 4). However, as maprotiline-CO_2 deposited from solution, two visibly distinguishable (Figure S1) types of solids – in approximately equal amounts – were found to be present. One consisted of polycrystalline aggregates, the individual components of which were too small for study by single-crystal XRD. The second also consisted of clusters of crystals, but of sufficient size for study by X-ray diffraction. These proved to be a hemihydrate of the expected salt. Interestingly, the C,H,N analysis of the bulk sample was consistent with the overall ('average') material being a 1.5 hydrate, and likewise the TGA of the bulk material evidenced two mass loss events. The first, lower-temperature event was consistent with a stoichiometric loss of CO_2; the second, occurring at ca. 100 °C, was consistent with a loss of ≈1.5 waters per ion pair. Consequently, it is our conjecture that the other form of the maprotilene-CO_2 from the reaction deposits as a higher-order hydrate. However, it is important to note here that NMR analysis of the bulk material gives no evidence of more than one structural type of cation or anion.

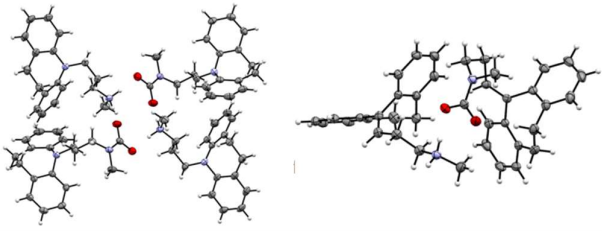


Figure 4. ORTEPs of the carbamate salt of desipramine (top) and nortryptilene (bottom). ORTEPs of the other materials are provided in the Supporting Information.

The fourth single-crystalline material – betahistine-CO_2 – proved to be something of a surprise. In contrast to the previous products, its crystalline form is that of a carbamic acid, a neutral one-component material, not a salt as was the case with the other compounds. Betahistine differs from the other materials in possessing a second nitrogen site (the pyridyl sp^2-N atom) that can act as a ready acceptor for a hydrogen bond, but that is unable to react with CO_2 itself to form a carbamate. Hence, rather than transferring the acidic proton of the carbamic acid to the amine functionality of a second drug molecule and creating a carbamate salt, the carbamic acid in the betahistine framework stabilizes itself by forming a strong O-H···N_{py} hydrogen bond, which allows all betahistine molecules to be transformed into a carbamic acid rather than half of the amine moieties being utilized to stabilize the carbamates formed by the other half. This difference between the betahistine-CO_2 compound on the one hand, and the three carbamate-forming materials on the other, is also reflected in their packing arrangements in the solid state. The arrangement of the betahistine-CO_2 molecules in the solid state is one of strings aligned in thin sheets, one molecule deep (see Supporting Information).

In contrast, the three previously-mentioned crystals are made of layers two-molecules-deep that are segregated into polar versus nonpolar regions. The polar groups reside on the layer surfaces in the case of the despiramine-CO_2 product, while they are embedded within the layers of the maprotiline-CO_2 and nortriptyline-CO_2 products. The lattices of the despiramine- and nortriptyline-based salts are shown in Figure 5.

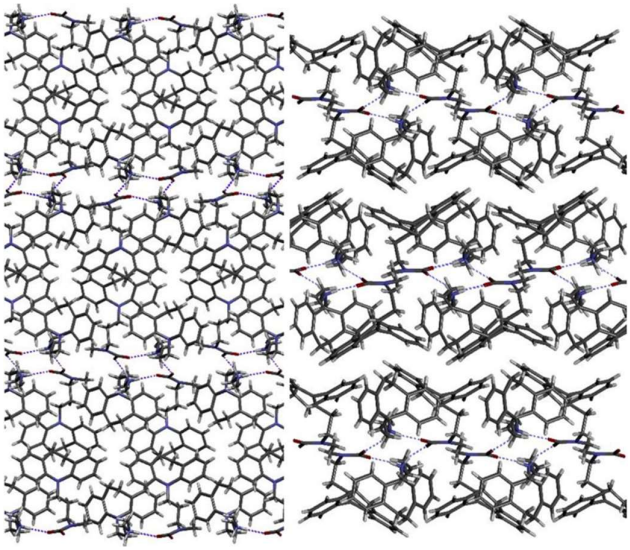


Figure 5. Desipramine-CO_2 (left) and nortriptyline-CO_2 (right) crystalline products. Three layers shown; H-bonds indicated by green dashed lines. Desipramine-CO_2: The layers have an all-hydrocarbon interior, save for the tertiary amine centres. H-bonding occurs on the layer surfaces between carbamate and amine groups; also, the gap

between layers is spanned by H-bonds. Nortriptyline-CO_2: The layer surfaces are nonpolar, populated by π faces of inclined phenyl groups of the carbamate species and by hydrogens of the amine species; each layer is made of distinct upper and lower sublayers joined at an interior seam where the ionic functional groups are located and H-bonding occurs.

Overall, the present results make clear several points with regard to forming drug-based ammonium carbamate salts for potential pharmacological use. First, as is apparent from the tranylcypromine and ephedrine results, the approach will not work for all amine-containing drugs; some will simply prove too unstable towards decarboxylation in the solid state for processing and long-term storage. The hygroscopicity of others, such as the betahistine derivative, could prove to be an impediment (but not necessarily an outright barrier) to commercial development. But more importantly, five of the drugs (including pramipexole) presently evaluated form salts that are sufficiently well-behaved as solids to consider worthwhile candidates for further development.

In light of the foregoing, we venture to suggest that the modification of existing drugs as well as new drug candidates through reactions with CO_2 may be an especially attractive tool for those seeking to evaluate an expanded scope of property-modification strategies, especially given the simplicity with which it can be tested. Note that the generation of the ammonium carbamate salts involves only one step, and there are no associated energy costs from needing to heat or cool the reaction. Better still, the only reagent required – CO_2 – is cheap, abundant, easily handled, non-corrosive, and completely non-toxic. Furthermore, no waste is generated by the process – it is, in principle, 100% atom-efficient. Finally, in the event the modified drug is subsequently found to be unsatisfactory from a pharmacological/formulation standpoint, the parent can be readily recovered from unused portions by heating gently in an inert gas flow or by treatment with dilute aqueous acid. The latter consideration might be especially important when working with investigational drugs that are expensive or of which only small quantities are available.

Acknowledgments

JHD thanks the National Science Foundation for support under grant number CHE-1464740. This material is also based upon work supported by the National Science Foundation through the Major Research Instrumentation Program under Grant No. CHE 1625543. (Funding for the single crystal X-ray diffractometer). We also thank a reviewer of the initial manuscript for suggesting the possibility of CO_2-solid reactions.

Conflicts of interest

There are no conflicts to declare.

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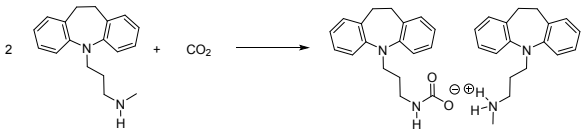

Exposing amine-containing drugs to CO_2 results in new crystalline salts comprised of two different prodrug forms of the original drug.