

CO₂-Based Alkyl Carbamate Ionic Liquids as Distillable Extraction Solvents

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S Supporting Information

ABSTRACT: A series of alkyl carbamate ionic liquids (ILs) have been prepared from CO₂ and an amine, including a number of novel members of the family, in order to provide a range of solvent properties that have the potential to improve the sustainability of natural product extractions. Whereas the dimethylcarbamate ionic liquid is a low boiling hydrophilic and water-soluble liquid, the higher homologues become water immiscible but remain easily distillable. By way of example, it is shown that the dipropylcarbamate analogue was optimal for the selective extraction of curcumins as active pharmaceutical ingredients. Product separation from these ILs can be achieved by complete distillation of the ILs.

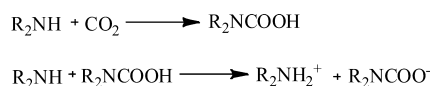
KEYWORDS: Dialkyl carbamate, Ionic liquids, Curcuminoids, Extraction, Curcumin, CO₂



INTRODUCTION

Ionic liquids (ILs) have been widely investigated as replacement solvents for many organic chemical, biochemical, and electrochemical applications.^{1–7} Some ILs belong to the protic class^{8,9} and are usually distillable due to the reversible back-transfer of the labile proton. A particularly interesting subclass of these are the ionic liquids formed by combining CO₂ and a secondary dialkylamine in an approximate 1:2 ratio.^{10–18} A Lewis acid/base reaction first takes place to form the carbamic acid adduct (Scheme 1), which then loses a proton to a second mole of amine to form the dialkyl ammonium cation and dialkylcarbamate anion.

Scheme 1



In many cases, the product is a liquid at some useful temperature. There is no fundamental reason that this reaction should be limited to symmetrical dialkylamines or to secondary amines; hence, this family of compounds is potentially very large.

The main advantage with this class of ionic liquids is its ability to dissolve a wide range of organic compounds to an appreciable extent and the ease with which they can be recovered after use. Distillation at moderate temperatures is facile due to release of CO₂ and the dialkylamine on warming. Subsequent recombination on cooling in the condenser readily reforms the ionic liquid. These materials thus offer many of the

special properties of an ionic liquid medium combined with a ready distillability.

Jessop and co-workers^{19,20} have utilized this family of liquids extensively as switchable solvents, wherein the addition of CO₂ switches the polarity from nonpolar to polar; flushing with N₂ or Ar can be subsequently used to switch the polarity back to facilitate removal and separation of products. The dimethylamine-based member of the family, known as DIMCARB, has been known since the 1950s^{10–12} for various applications. For instance, extraction of aromatic hydrocarbons and solvent extraction of oils using DIMCARB have been investigated;^{11,12} it has been shown to be a powerfully effective solvent in the extraction of valuable tannins from plant sources.¹³ It is also used in organic synthesis^{14–17} and electrochemical applications¹⁸ as a convenient solvent.

In the present study, this family of CO₂-based IL extractants has been expanded in order to provide a wider range of solvent properties ranging from distinctly hydrophilic (and water miscible) to more hydrophobic (and water immiscible). Their extraction efficiency is demonstrated by use in the selective extraction of valuable curcuminoids from plant sources.

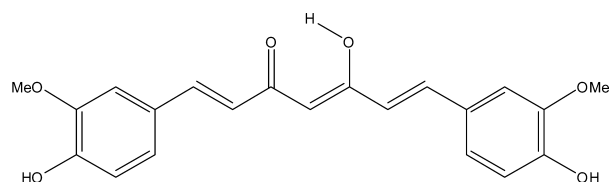
Curcumin, a polyphenol, is an active ingredient and useful compound present in *Curcuma longa* (known as turmeric).^{21–23} A range of derivatives, known as curcuminoids (Figure SI-1, Supporting Information) are present in the yellow pigmented fraction of turmeric. Curcumin, I, has been obtained in a crystalline form and identified as 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E,6E) or diferuloylme-

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thane.²⁴ It is soluble in ethanol, dimethyl sulfoxide, and acetone; is insoluble in water and ether, and can exist in enolic and β diketonic forms. It is a potent antioxidant and radical scavenger, and this ability is associated with its presence in the enolic form.²⁵



Curcumin, I

In recent years, the use of curcuminoids has gained importance in various contexts, including in the pharmaceutical industry where it is used in anti-ischemic,²⁶ anti-HIV,^{27,28} anticancer,^{29–31} antithrombosis,³² and anti-Alzheimer applications.^{33,34} Recent studies reveal that curcuminoids effectively inhibit tumor cell proliferation for malignant brain tumor cases.³⁵ They have also been shown to exhibit phyto-estrogenic activity in the treatment of breast cancers.³⁶ Despite these growing applications, widespread use is limited due to the poor extraction efficiency of the methods available at present. Conventionally, the curcuminoids are extracted as a complex mixture using molecular solvents such as acetone or ethanol via a variety of approaches including microwave-assisted methods.^{37,38} However, in spite of the use of high solvent/solid ratios and elevated temperatures (60 °C), the extraction efficiencies remain poor.³⁹ Hence, there is a need for an alternative technology that is more efficient to allow better extraction of curcuminoids for use in the pharmaceutical industry with relatively easy and milder reaction conditions.

Thus, the main objective of the present study was to synthesize a range of *N,N*-dialkyl ammonium *N,N'*-dialkylcarbamate (DialkylCARB) ionic liquids including *N,N*-dimethylammonium *N,N'*-dimethylcarbamate (DIMCARB), *N,N*-diethylammonium *N,N'*-diethylcarbamate (DECARB), *N,N*-dipropyl ammonium *N,N'*-dipropylcarbamate (DPCARB), *N,N*-diallyl ammonium *N,N'*-diallylcarbamate (DACARB), bis(2-ethylhexyl)ammonium bis(2-ethylhexyl)carbamate (DBCARB), and *N,N*-dibenzyl ammonium *N,N'*-dibenzyl carbamate (DBZCARB) and to demonstrate their use as alternate solvents. As an example of their use as extraction

solvents, we describe their use in the extraction of curcuminoids from *Curcuma longa*. While the lower members of this homologous series have been prepared previously,⁸ DACARB, DPCARB, DBCARB, and DBZCARB are described here for the first time and were included in the study specifically to introduce greater hydrophobicity into the solvent.

EXPERIMENTAL SECTION

The synthesis of the alkyl carbamate ionic liquids followed the literature procedure.⁴⁰ Typically, the synthesis of DECARB involves the slow addition and stirring of 1 mol of solid carbon dioxide to 2 mol of diethyl amine held in an ice bath. In a similar manner, the other alkylcarbamates mentioned above were synthesized via the corresponding reaction of the amine and CO₂. The target mass gain with respect to the amine starting material was confirmed. DPCARB, DACARB, DBCARB, and DBZCARB were prepared as 2:1 mixtures of amine and CO₂ and were obtained as liquids at room temperature. These therefore can be described as ionic liquids. DIMCARB and DECARB were solids at the 2:1 stoichiometry, and therefore, following the literature approach for DIMCARB, these were prepared with a substoichiometric quantity of base in order to achieve the liquid state. These two examples are therefore liquid mixtures of the salt and the parent carbamic acid. It is important to note that some of the literature concerning DIMCARB relates to this substoichiometric composition, typically 1.8 mol amine:1 mol CO₂. Nonetheless, this is still a useful solvent and, in fact, presents a degree of proton “buffering” action.⁴¹ This was also true of the DECARB made in this work (mp ~30 °C), and therefore, a 1.6:1 ratio of amine to CO₂ was used, as this was liquid at room temperature. In a similar manner, DBZCARB (mp ~35 °C) was found to only become a room temperature liquid at the 1:1 composition, which is nominally the carbamic acid.

The alkyl carbamate ionic liquids were characterized for spectral (Fourier transform infrared (FT-IR) spectroscopy) and thermal (differential scanning calorimetry (DSC)) properties. The density measurements were obtained using an Anton Parr densimeter (DMA 5000). Viscosity measurements were obtained on a Anton Paar microviscometer (Lovis 2000 M). The extracted product from turmeric was analyzed by UV/vis spectroscopy and LC-MS techniques. The details are given in SI-2 of the Supporting Information. Water miscibility was tested by mixing with an equivalent volume of water.

The extraction procedure of curcuminoids from turmeric is summarized diagrammatically in Figure SI-3 of the Supporting Information. Typically, 0.25 g of dried and powdered turmeric was added to 5 g of alkyl carbamate ionic liquid in a 50 mL round-bottomed flask, and the mixture was stirred at room temperature for a desired period of time. In a large-scale process, a filtration would be carried out at this stage; however, the extracted solute load was found

Table 1. Properties of Alkyl Carbamate Ionic Liquids

alkyl carbamate	water miscibility ^b	distillation point of carbamate (°C)	heat of distillation (kJ/mol)	density (g/cm ³ @ 25 °C ± 0.0001)	viscosity (mPa s @ 25 °C ± 0.1)
DIMCARB (1.8:1)	yes	71	128	1.034	63.2
DECARB (1.6:1)	yes	69	126	0.924	62.8
DPCARB	yes	52	123	0.8804	31.0
DIPCARB ^a	–	–	–	–	–
DACARB	yes	59–113	127	0.9341	5.3
DBCARB	no	59–176	128	0.8106	33.9
DBZCARB (solid)	no	36–198	267	–	–
DBZCARB (1:1)	no	63–204	250	1.0915	54.1

^aSynthesis of diisopropyl carbamate (DIPCARB) was not successful; CO₂ remained highly volatile over this reaction mixture. ^bWater miscibility refers to a drop by drop addition of water at room temperature to the alkyl carbamate ionic liquids to form a homogeneous solution.

here to be sufficiently high that the room temperature viscosity of the mixture was elevated to the point that *quantitative* filtration and separation of the undissolved material was not facile. Therefore, samples were collected at different time intervals by allowing the mixture to settle and then pipetting out an aliquot. The ionic liquid was distilled from these aliquots, and the residue was mixed with ethanol and immediately filtered (contact time was less than 1 min) to remove the undissolved solids. Control experiments indicate that ethanol extracts insignificant amounts of curcuminoids under these short contact time conditions. The ethanol fraction, containing the curcuminoids, was evaporated and dried, and the yield was computed. In the case of the lighter dialkylcarbamates, the liquid was condensed using a water-cooled condenser. In the cases of DBCARB, DACARB, and DBZCARB, for reasons evident in the DSC traces discussed further below (Figure SI-4, Supporting Information), a liquid nitrogen trap is necessary to ensure that CO₂ is not lost.

RESULTS AND DISCUSSION

The properties of the alkyl carbamate ionic liquids are summarized in Table 1. It is clear from Table 1 that DBCARB and DBZCARB are hydrophobic in nature, as evidenced in the water miscibility data. CO₂ evolution was not observed in this process. In the miscible cases, it is likely that the bicarbonate ion is formed to some extent.

Thermal traces are shown in Figure SI-4 of the Supporting Information. It is shown from these that in the cases of DECARB, DPCARB, and DIMCARB a single endothermic transition appears in the range between 30 and 70 °C, indicating their distillation temperatures under these conditions. Complete distillation of the liquid was confirmed in the extraction studies. In the cases of DACARB, DBCARB, and DBZCARB, two endothermic transitions were observed. The first corresponds to the loss of CO₂ from the mixture, and the second is due to the distillation of the amine. FT-IR spectroscopic measurements showed the presence of symmetric carbamate (1408 cm⁻¹) and carbamate C–O stretching (1621 cm⁻¹) peaks, indicating the formation of the adduct as these peaks are absent in the corresponding amines.

The yield of crude curcuminoid extract was determined by mass of the dried product. The results (Table 2) indicate that

Table 2. Extraction of Curcuminoids Using Different Solvents

sample no.	extraction solvent	extraction yield (wt %) (± 1%)		
		1 h	2 h	24 h
1	conventional EtOH process	1.0	1.6	6.0
2	DIMCARB (2:1) extraction	17.0	20.0	22.0
3	DECARB (1.6:1) extraction	7.2	12.6	13.4
4	DPCARB (2:1) extraction	10.4	12.0	15.2
5	DACARB (2:1) extraction	12.0	14.5	16.4
6	DBCARB (2:1) extraction	–	–	15.8
7	DIMCARB (2:1)+ EtOH (50/50 wt %) extraction	–	–	20.0
8	DECARB (1.6:1)+ EtOH (50/50 wt %) extraction	–	–	12.8

higher yields (approx 2.5 times) were obtained from the carbamate liquid extractions, as compared to the conventional ethanol-based method (entry 1) under similar reaction conditions. The maximum content of curcuminoids thought to be typically present in turmeric is around 15%,³⁹ similar to the yields obtained in the all of the cases except DIMCARB.

The DIMCARB yield is higher than expected and hence is thought to contain some IL component or additional plant materials (as discussed further below). Maximum extraction yield was achieved in about 2 h in the IL cases, considerably faster than the ethanol extraction. This demonstrates the superior nature of the carbamate liquid in the extraction of curcuminoids from the cellular structure of the plant material. A similar trend was obtained in our previous study for the extraction of tannins.¹³ The higher extraction efficiency in the carbamate liquid could be due to the high solvency toward the curcuminoids and/or the ability of the carbamate liquid to deprotonate them as part of the dissolution reaction. The role of the solvent in disrupting and opening the cellular structure of the substrate is also critical; however, the chemical mechanisms of this are not known at this stage.

The extracted samples were analyzed by UV/vis spectroscopy and LC-MS for identification of the curcuminoids. The LC-MS data and a typical LC-MS spectrum of curcumin extracted by DPCARB are respectively presented in Table SI-1 and Figure SI-5 of the Supporting Information. The LC-MS results are very similar in the cases of DPCARB, DECARB, the authentic curcumin sample, and the ethanol extracted samples, verifying that the same profile of compounds is extracted in these cases. However, in the case of the DIMCARB extract, the LC-MS showed a range of products with only a minor signal at the 369 mass number for curcumin.

It was reported in the literature that the **neutral form** of curcumin absorbs between 420 and 430 nm in various organic solvents;^{23,42} the basic form produces a shoulder at 480 nm on the main absorption peak.⁴³ Figure 1 shows that the **neutral**

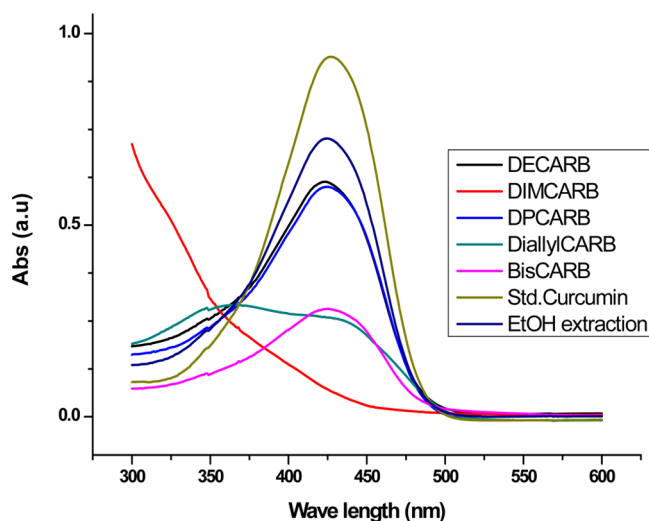


Figure 1. UV spectra of curcuminoids from extracted samples (1 mg/mL in ethanol).

curcuminoids were present in all of the extracted samples (presence of peak at 430 nm) to varying extents, but only a small amount is present in the DIMCARB extract. In the case of DIMCARB, there is a substantial extract (Table 2) that does not have any strong absorption in the 430–480 nm range. In combination with the LC-MS data above, this confirms that the DIMCARB extract contains only a small curcuminoid fraction; instead, more hydrophilic components appear to have been extracted in this case. To investigate this further, another set of extraction experiments were carried out to change the polarity of DIMCARB by adding 50 wt % ethanol to it. The extraction

efficiencies are shown in Table 2, while the UV studies are illustrated in Figure SI-6 of the Supporting Information. However, the yield of curcuminoids was not increased. Thus, it appears that the DPCARB system expresses the optimum balance of solvent properties for this extraction, selectively extracting a larger fraction of the valuable material against a background of other partially soluble components.

In order to demonstrate the recyclability and reuse of these ionic liquids, experiments were carried out on neat and recycled DPCARB to extract curcuminoids (Table SI-2, Supporting Information). The results show that the recycled ionic liquid can be successfully used to extract curcuminoids from neat turmeric.

There are aspects of the behavior of these carbamate ILs that offers the properties of a switchable solvent as described by Jessop et al.^{19,20} In the higher homologues of the series (all but DIMCARB), it is possible to remove the CO₂ from the mixture at relatively low temperatures and thereby switch the solvent from “ionic” to a “molecular liquid” base. Under some circumstances, this may cause precipitation of the extract providing an overall low energy cost process.

CONCLUSION

In summary, we have described a number of alkyl carbamate distillable ionic liquids of varying hydrophilicity and hydrophobicity, several being water-immiscible liquids. We have shown these to be able to extract valuable curcuminoids in substantial quantities, in contrast to conventional extraction methods. We have also shown that the ionic liquids can be successfully recycled.

ASSOCIATED CONTENT

Supporting Information

Chemical structures of curcuminoids, details of DSC analysis and LC-MS analysis, flowchart of extraction of curcumin from turmeric using dialkyl carbamate ionic liquids, DSC traces of dialkyl carbamate ionic liquids, UV spectra of curcumin extracted using mixed solvents, LC-MS data of curcuminoids extracted from different solvents, and extraction results using recycled ionic liquids. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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