Organic &
Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2016, **14**, 6554

S_N1 reactions in supercritical carbon dioxide in the presence of alcohols: the role of preferential solvation†

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Received 19th May 2016,
Accepted 7th June 2016

DOI: 10.1039/c6ob01097k

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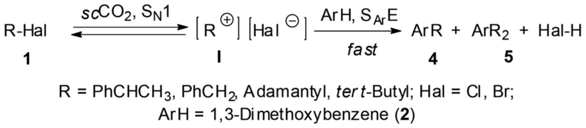
Ethanol (**3b**) inhibits S_N1 reactions of alkyl halides **1** in supercritical carbon dioxide (*sc*CO_2) and gives no ethers as products. The unexpected behaviour of alcohols **3** in the reaction of alkyl halides **1** with 1,3-dimethoxybenzene (**2**) in *sc*CO_2 under different conditions is rationalised in terms of Brønsted and Lewis acid–base equilibria of reagents, intermediates, additives and products in a singular solvent characterised by: (i) the strong quadrupole and Lewis acid character of carbon dioxide, which hinders S_N2 paths by strongly solvating basic solutes; (ii) the weak Lewis base character of carbon dioxide, which prevents it from behaving as a proton sink; (iii) the compressible nature of *sc*CO_2, which enhances the impact of preferential solvation on carbon dioxide availability for the solvent-demanding rate determining step.

Introduction

Supercritical carbon dioxide (*sc*CO_2) is an alternative solvent for green chemistry[1] characterised by zero dipole moment, very low dielectric constant, and no hydrogen-bonding behaviour,[2] yet is suitable for performing uncatalysed S_N1 reactions of alkyl halides **1**[3a] and electrophilic brominations of weakly activated aromatics.[3b] The strong quadrupole and the Lewis acid but non-basic character of carbon dioxide[3,4] accounts for the ability of *sc*CO_2 to solvate ionic species and to avoid capture by acidic intermediates.

In the course of our study[3a] on the reaction of alkyl halides **1** with 1,3-dimethoxybenzene **2** in *sc*CO_2, which proceeds through the solvent-promoted ionisation of **1** and capture of carbenium ion **I** by the aromatic (Scheme 1), we noticed that alcohols **3** inhibited the formation of Friedel–Crafts adducts, **4** and **5**, and no ethers **6** formed as products.[3a] This unexpected behaviour[5] for a polar, protic and nucleophilic additive prompted us to further explore S_N1 reactions as sensitive probes for solvation in *sc*CO_2.[6] Herein we report on reactions of alkyl halides **1**, 1,3-dimethoxybenzene (**2**), and alcohols **3** in *sc*CO_2 under different conditions, and disclose the reaction paths involved, as well as the impact of solvation on the product distribution and ionising ability of *sc*CO_2. The results revealed that solute–carbon dioxide interactions modify the course of these reactions in relation to conventional solvents, and stressed the relevance of solvation by *sc*CO_2 when designing applications of this medium as a solvent for green chemistry.



Scheme 1 Reaction of alkyl halides **1** with aromatic **2** in *sc*CO_2.

Results and discussion

The model systems selected for exploring S_N1 reactions in *sc*CO_2 were 1-chloro-1-phenylethane (**1a**) and benzylbromide (**1c**) as ionogens, 1,3-dimethoxybenzene (**2**) as the aromatic, and 1-phenylethanol (**3a**) and ethanol (**3b**) as additives. The reactions were performed and analysed following reported procedures.[3a] The experiments performed in view cells showed homogeneous reaction mixtures in all cases. Styrene and products derived from CO_2-capture (carbonates or carboxylic acids) were not detected in the reaction mixtures. The ESI† provides a detailed description of the experimental procedure and the balance of products for the isotopic tracer experiments (Table S1†).

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† Electronic supplementary information (ESI) available: Experimental procedures and spectra. See DOI: 10.1039/c6ob01097k

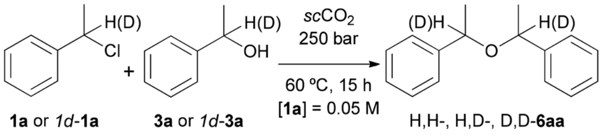
S_N1 reactions of alkyl halides 1 and alcohols in *sc*CO_2: reaction pathways

The absence of ethers **6** as products from the reactions of alkyl halides **1** with aromatic **2** in *sc*CO_2 in the presence of ethanol (**3b**) was firstly attributed to solvation by *sc*CO_2, which would either prevent alcohol **3b** to react with carbocations **I**, or would modify the reaction paths of the intermediate species in relation to those observed in conventional solvents. In order to explore these possibilities, we designed isotopic tracer experiments with 1-chloro-1-phenylethane (**1a**) and 1-phenylethanol (**3a**) in *sc*CO_2 in order to open alternative reaction channels to the intermediate species and track the reaction components under these conditions. Scheme 2 depicts the ionisation and proton-transfer equilibria, and the irreversible aromatic electrophilic substitution paths involved in these reactions.

Reaction of 1-chloro-1-phenylethane (1a) with 1-phenylethanol (3a). Isotopic tracer experiments

The reaction of equimolar amounts of 1-chloro-1-*deutero*-1-phenylethane (1*d*-**1a**) 80 D-atom% and 1-phenylethanol (**3a**) in *sc*CO_2 at 250 bar and 60 °C for 15 h gave 36% of the corresponding ether **6aa** as a mixture of *syn*- and *anti*-diastereomers (run 1, Fig. 1). This result shows that solvation by *sc*CO_2 does not prevent alcohol **3a** from capturing carbocation intermediates 1*d*-**Ia** formed by the solvent-promoted ionisation of alkyl halide 1*d*-**1a** (Scheme 2). The reaction of 1-phenylethanol (**3a**) with alkyl halide **1a** to give ether **6aa** contrasts with the reluctance of ethanol (**3b**) to undergo an analogous transformation, and suggests that the ability of alcohol **3** to ionise under these conditions may determine the reaction course.

The formation of ether H,H-**6aa** in amounts larger than ether H,D-**6aa** (entry 1, Fig. 1), and the higher conversion rate of alcohol **3a** (81%) compared to alkyl halide 1*d*-**1a** (25%) (Table S1†), indicate the involvement of acid catalysed dehydration of alcohol **3a** under these conditions (Scheme 2).[7] The formation of symmetrical ether D,D-**6aa** (entry 1, Fig. 1) suggests that protonated ether H,D-**6aaH**$^+$ ionises in the reaction medium to release alcohols **3a** or 1*d*-**3a** and carbocation intermediates **Ia** or 1*d*-**Ia** (Scheme 2).

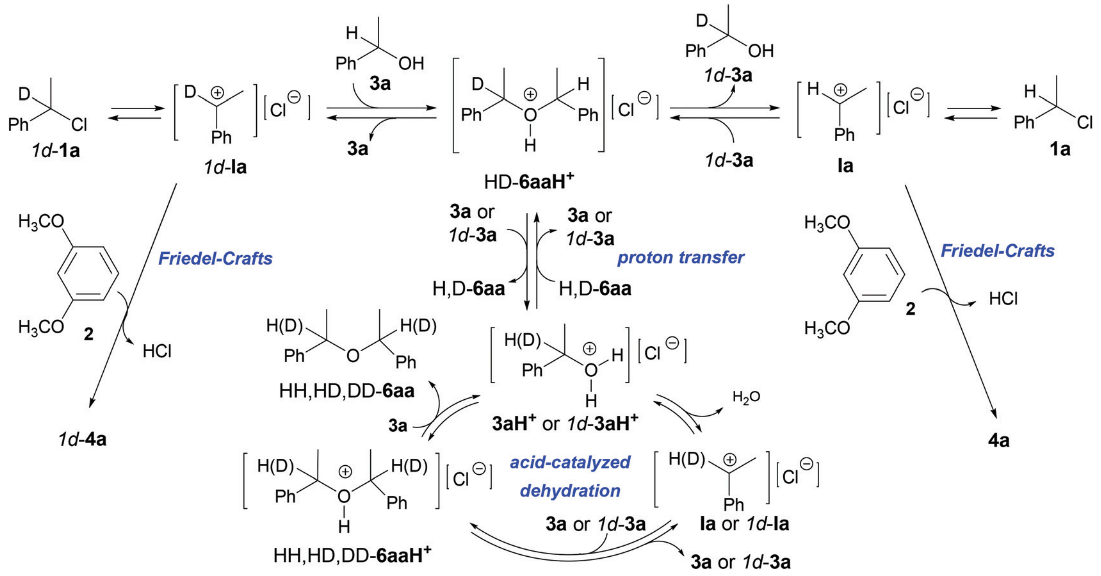


			Product distribution (%) *D-label distribution H:D or H,H:H,D:D,D (%)*			
Run	1	3 (equiv)	1a	3a	*syn*-6aa	*anti*-6aa
1	1*d*-1a	3a (1)	51	13	20	16
	80 D-atom %		*23:77*	*84:16*	*50:33:17*	*41:38:21*
2	1a	1*d*-3a (2)	37	42	11	10
		88 D-atom %	*79:21*	*12:88*	3:40:57	*<1:39:61*

Fig. 1 Isotopic tracer experiments for reactions of 1-chloro-1-phenylethane (**1a**) (0.05 M), and 1-phenylethanol (**3a**) in *sc*CO_2 at 250 bar and 60 °C for 15 h. Isotopic labels were obtained from the relative intensities of the ions [M^+] for 1*d*-**1a**, **3a**, and [$M - 15^+$] for **6aa**. The figures are the average of at least three independent experiments within standard deviation of ±15%.

The reaction of 1-chloro-1-phenylethane (**1a**) with a twofold excess of 1-*deutero*-1-phenylethanol (1*d*-**3a**) in *sc*CO_2 under the same conditions (entry 2, Fig. 1) followed the same trends. In this case, symmetrical ether D,D-**6aa** was the major product with conversions of alkyl halide **1a** and alcohol 1*d*-**3a** of 8% and 48%, respectively (Table S1†).

Finally, the low isotopic dilution observed for unreacted alkyl halide 1*d*-**1a** and alcohol 1*d*-**3a** (4–13% and 7–0%, respectively, Table S1†) compared to the relatively high extent of ethers **6aa** formed (entries 1 and 2, Fig. 1) indicates that the



Scheme 2 Reaction paths proposed for 1-chloro-1-*deutero*-1-phenylethane (1*d*-**1a**), 1-phenylethanol (**3a**), and 1,3-dimethoxybenzene (**2**) in *sc*CO_2.

chloride anion does not compete efficiently with alcohols **3a** to trap carbocation intermediates **Ia** in *sc*CO$_2$.

Reaction of 1-chloro-1-phenylethane (1a) with 1,3-dimethoxybenzene (2) in the presence of 1-phenylethanol (3a). Isotopic tracer experiments

1-Chloro-1-phenylethane (**1a**) reacts quantitatively with aromatic **2** (4 equiv.) in *sc*CO$_2$ at 60 °C and 250 bar for 5 h to give mono- and di-substituted Friedel–Crafts adducts **4a** (82%) and **5a** (18%) as mixtures of regioisomers (**4a**$_{o,p}$ and **4a**$_{o,o}$) and diastereomers (**5** and **5′**), respectively (entry 1, Fig. 2).[3a] Conversely, the reaction of equimolar 1-chloro-1-*deutero*-1-phenylethane (1*d*-**1a**) 80 D-atom% and 1-phenylethanol (**3a**) with a 4-fold excess of 1,3-dimethoxybenzene (**2**) in *sc*CO$_2$ for 15 h under the same conditions (entry 2, Fig. 2) gave monosubstituted Friedel–Crafts adducts **4a** (38%) with 44–47 D-atom% and disubstituted adducts **5a** (6%) with a nearly statistical (1 : 2 : 1) H,H : H,D : D,D distribution (entry 2, Fig. 1). Substrate conversions were 42% and 72% for 1*d*-**1a** and **3a**, respectively (Table S1†).

These data evidence that the Friedel–Crafts reaction involves nearly equivalent amounts of carbocations 1*d*-**Ia** and **Ia**, and indicate that protonated ether H,D-**6aaH**$^+$ is the major source of electrophilic intermediates for this reaction. Therefore, carbocations 1*d*-**Ia**, formed by the ionisation of alkyl halide 1*d*-**1a**, react with alcohol **3a** faster than with 1,3-dimethoxybenzene (**2**) (Scheme 2).

The isotopic traces provide further information on the reaction course in *sc*CO$_2$. Thus the preferential formation of symmetrical H,H-ethers **6aa** (entries 2 and 3, Fig. 2), and the conversions of alkyl halide 1*d*-**1a** (42%) and alcohol **3a** (7%) (Table S1†), once again indicate the involvement of the acid catalysed dehydration of alcohol **3a** under these conditions. However, the isotopic labels found for Friedel–Crafts adducts **4a** (44–47 D-atom%) and **5a** (H,H : H,D : D,D *ca.* 1 : 2 : 1) (entry 1, Fig. 2) suggest that protonated alcohol **3aH**$^+$ and ethers **6aaH**$^+$ from the acid-catalysed dehydration path (Scheme 2) do not play a significant role in the Friedel–Crafts reaction, otherwise the D-labelling for adducts **4a** and **5a** would be lower than those observed. The results hence suggest that hydrogen chloride formed in the Friedel–Crafts reaction competes efficiently with carbocations **Ia** and 1*d*-**Ia** to trap alcohol **3a** and that the H-bonding interactions[8] of protonated species **3aH**$^+$ and **6aaH**$^+$ with alcohol **3a** facilitate the acid-catalysed dehydration pathway. These interactions are enhanced by the low basicity of carbon dioxide,[9] which prevents the solvent from behaving as a proton sink in these reactions.

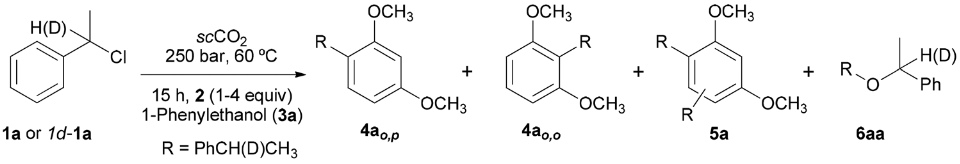
The reactions performed with equimolar amounts of ionogen 1*d*-**1a**, alcohol **3a** and 1,3-dimethoxybenzene (**2**) (entry 3, Fig. 2) led to Friedel–Crafts adducts **4a** with 37–35 D-atom%, respectively, and disubstituted adducts **5a** in the *ca.* 2 : 2 : 1 H,H : H,D : D,D distribution. The conversions of 1*d*-**1a** and **3a** were 40% and 95%, respectively (Table S1†). These isotopic traces reveal the increased competitiveness of alcohol **3a** in relation to 1,3-dimethoxybenzene (**2**) to trap carbocations 1*d*-**Ia** and **Ia** compared to the reactions performed with a 4-fold excess of **2** (entry 2, Fig. 2).

The isotopic dilutions found for the unreacted substrates in these reactions (entries 2 and 3, Fig. 2) were 4–13% for alkyl halide 1*d*-**1a**, and were negligible for alcohol **3a** (Table S1†).

Friedel–Crafts reactions of alkyl halide 1a in the presence of ethanol (3b)

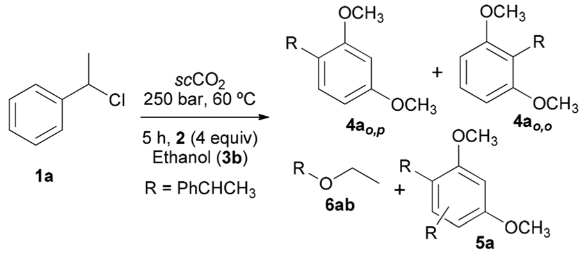
The Friedel–Crafts reactions of alkyl halide **1a** with aromatic **2** in *sc*CO$_2$ in the presence of ethanol (**3b**) followed a different course (Fig. 3). Thus increasing amounts of ethanol (**3b**) above 0.5 equiv. progressively inhibited the conversion of alkyl halide **1a** (entries 2–5, Fig. 3). Ethyl 1-phenylethyl ether (**6ab**), 1-phenylethanol (**3a**), and ethyl-substituted Friedel–Crafts adducts **4b** and **5b** were not found as products under these conditions. These results can now be interpreted with the information collected from the isotopic tracer experiments (Scheme 3).

Protonated ether **6abH**$^+$ is the source of carbocation intermediates **Ia** for Friedel–Crafts reactions in the presence of ethanol (**3b**) (Scheme 3). The absence of 1-phenylethanol (**3a**)



			Product distribution (%) / *D-label distribution H:D or H,H:H,D:D,D (%)*							
Run	**1**	**2** (equiv)	**1a**	**3a**	**4a**$_{o,p}$	**4a**$_{o,o}$	**5a**	**5a'**	*syn*-**6aa**	*anti*-**6aa**
1	**1a**	4	--	--	73	9	9	9	--	--
2	*1d*-**1a**	4	33	16	32	6	3	3	4	3
	80 D-atom %		*23:77*	*90:10*	*56:44*	*53:47*	*30:47:23*	*32:40:28*	*50:38:12*	*50:45:5*
3	*1d*-**1a**	1	40	3	20	4	10	10	10	3
	80 D-atom %		*30:70*	*90:10*	*63:37*	*65:35*	*41:42:17*	*41:42:17*	*50:33:17*	*52:35:13*

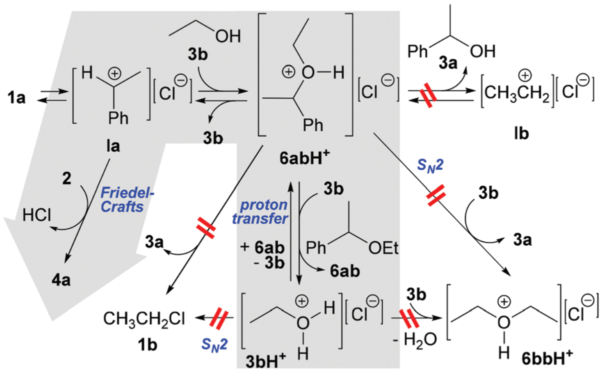
Fig. 2 Reactions of 1-chloro-1-phenylethane (**1a**) (0.05) M, 1,3-dimethoxybenzene (**2**), and 1-phenylethanol (**3a**) in *sc*CO$_2$ for 5 h (run 1)[3a] and 15 h (runs 2 and 3). Isotopic labels were obtained from the relative intensities of the ions [M$^+$] for 1*d*-**1a**, **3a**, **4a**, and **5a**, and [M − 15$^+$] for **6aa**. The figures are the average of at least three independent experiments within standard deviation of ±15%.



Product distribution (%)

Run	3b (equiv)	1a	3a	$4a_{o,p}$	$4a_{o,o}$	5a	5a'
1	--	--	--	73	9	9	9
2	0.5	--	--	74	9	8	9
3	0.7	3	--	64	9	12	12
4	1	47	--	39	7	3	4
5	2	86	--	12	2	--	--

Fig. 3 Reactions of 1-chloro-1-phenylethane (**1a**) (0.05) M and ethanol (**3b**) with 1,3-dimethoxybenzene (**2**) (4 equiv.) in *sc*CO_2. The figures are the average of at least three independent experiments within standard deviation of ±15%.



Scheme 3 Prevailing reaction path for 1-chloro-1-phenylethane (**1a**), 1,3-dimethoxybenzene (**2**) and ethanol (**3b**) in *sc*CO_2.

as a product in these reactions (Scheme 3) shows that S_N2 nucleophilic displacements on the highly electrophilic primary carbon atom of **6abH**$^+$ by either alcohol **3b** or the chloride anion do not compete with unimolecular pathways under these conditions (Scheme 3). Solvation by carbon dioxide probably hinders nucleophiles approaching electrophilic sp^3 carbon atoms in an S_N2 fashion.

This fact limits the reaction paths available for protonated ether **6abH**$^+$ to the back-ionisation and proton transfer to ethanol (**3b**), and those for **3bH**$^+$ to the back proton transfer to ether **6ab** (Scheme 3) since neither **6abH**$^+$ nor **3bH**$^+$ undergoes S_N2 or S_N1 reactions at the primary carbon atom under these conditions (Scheme 3). Accordingly, the reaction progresses towards the irreversible electrophilic aromatic substitution with aromatic (**2**) (Scheme 3), which makes ethyl 1-phenylethyl ether (**6ab**) formation unfeasible. Conversely, the reactions with 1-phenyl-1-ethanol (**3a**) as an additive (Fig. 2) have unimolecular paths available to deplete protonated alcohol **3aH**$^+$ from the solution due to the stability of secondary benzylic carbocation **Ia** (Scheme 2).

S_N1 reactions of alkyl halides 1 and alcohols in *sc*CO_2: preferential solvation

The results reported in Fig. 1–3 have shown that alcohols **3** react with carbocation intermediates **Ia** formed by the *sc*CO_2-promoted ionisation of **1a** faster than 1,3-dimethoxybenzene (**2**), and that the irreversible Friedel–Crafts reaction with 1,3-dimethoxybenzene (**2**) involves carbocations **Ia** formed from a series of competitive ionisation and proton-transfer reversible processes (Schemes 2 and 3). The reaction paths depicted in Schemes 2 and 3 do not account, however, for the low isotopic dilution found for unreacted substrates 1*d*-**1a** and **3a** (Table S1†), the low conversions of alkyl halide **1a** (Fig. 1 and 2; Table S1†), nor for the progressive reaction inhibition promoted by increasing amounts of ethanol (**3b**) (Fig. 3). These results rather suggest that alcohols **3** inhibit the ionisation of alkyl halide **1a** in *sc*CO_2, a notion which apparently contradicts the well-established behaviour of alcohols **3** as solvents for S_N1 reactions.[2,5] Nevertheless, it is known that ethanol (**3b**) behaves as an electrophilic catalyst for S_N1 reactions in non-polar and non-protic solvents,[5c] yet inhibits S_N1 reactions in solvents which are stronger H-bond donors than itself.[10] For instance, the solvolysis of alkyl halides **1** in binary mixtures water : **3b**[10a] and fluorinated alcohols : **3b**,[10b] become progressively slower with increasing amounts of ethanol (**3b**). The same trend is known for acetone, dimethylsulfoxide, and for dioxane as cosolvents for S_N1 reactions in aqueous medium.[11]

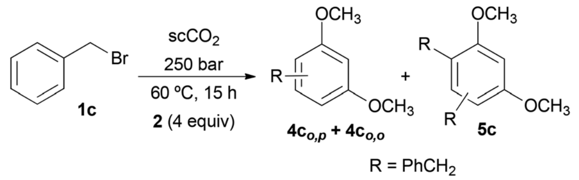
The changes in the reaction rates and equilibria promoted by additives or cosolvents are generally attributed to competitive substrate–solvent, substrate–cosolute, and cosolute–solvent interactions.[12] This concept suggests that alcohols **3** may hinder the highly solvent-demanding rate-determining step of S_N1 reactions in *sc*CO_2 by competing with alkyl halides **1** for solvation. The properties of *sc*CO_2, such as compressibility, densities lower than those for liquid solvents within the 75–250 bar range,[13] and density inhomogeneities promoted by specific solute–solvent and solvent–solvent interactions,[14] would enhance the effect of alcohols **3** on these reactions. In order to explore this possibility, we performed the reaction of benzyl bromide (**1c**), 1,3-dimethoxybenzene (**2**) and ethanol (**3b**) in *sc*CO_2 under different conditions (eqn (1), Table 1).

Friedel–Crafts reactions of alkyl halide 1c in the presence of ethanol (3b)

Benzyl bromide (**1c**) was proved to be more sensitive to ethanol (**3b**) than 1-chloro-1-phenylethane (**1a**) (Table 1). Thus 0.7 equivalents of ethanol (**3b**) sufficed to suppress the reaction for **1c** (entry 9, Table 1), while more than 2 equiv. were required to achieve the same effect for **1a** (entry 5, Fig. 3). This result suggests a stronger solvent-demand in the rate-determining step for benzyl bromide (**1c**) than for 1-chloro-1-phenylethane (**1a**), in agreement with the different stabilities of primary and secondary benzylic carbocations, **Ic** < **Ia**.

The results showed that reaction efficiency was dependent on both ethanol (**3b**) and benzyl bromide (**1c**) concentrations (Table 1). Thus reactions with a molar ratio of **1c** : **3b** of 1 : 0.5

Table 1 Reaction of benzyl bromide (**1c**) with 1,3-dimethoxybenzene (**2**) in *sc*CO_2, in the presence of ethanol (**3b**)[a]



Run	Molar ratio of **1c** : **3b**	[**1c**] (M)	[**3b**] (M)	Conv. (%)
1[b]	—	0.1	—	98
2[b]	—	0.05	—	98
3[b]	—	0.025	—	99
4[b,c]	—	0.05	—	99
5	1 : 1	0.1	0.1	—
6	1 : 0.5	0.1	0.05	—
7	1 : 0.25	0.1	0.025	76
8	1 : 1	0.05	0.05	—
9	1 : 0.7	0.05	0.035	—
10	1 : 0.6	0.05	0.03	76
11	1 : 0.5	0.05	0.025	77
12	1 : 0.25	0.05	0.0125	83
13	1 : 1	0.025	0.025	—
14[d]	1 : 0.5	0.025	0.0125	59

[a] Reactions were performed with the molar ratio of **1c** : **2** of 1 : 4, for 15 h. The figures are the average of at least three independent experiments within standard deviation of ±15%. [b] Typical product distribution: **4c**$_{o,p}$ 82%, **4c**$_{o,o}$ 6%, **5c** 6%, and **5c′** 6%. [c] Reaction at 90 bar. [d] Molar ratio **1c** : **2** 1 : 8.

proceeded for [**3b**] = 0.025 M, but not for [**3b**] = 0.05 M (entries 6 and 11, Table 1), while the reactions with a molar ratio of **1c** : **3b** of 1 : 1 did not proceed at all, not even for [**3b**] = 0.025 M (entries 5, 8 and 13, Table 1). These trends strongly suggest that ethanol (**3b**) competes with alkyl halide **1c** for solvation.[15]

Scheme 4 illustrates the solvation equilibria[15] for alkyl halide **1** and ethanol (**3b**) (steps 1 and 2), the exchange of carbon dioxide molecules clustered around **1c** and **3b** (step 3), and the integration of further carbon dioxide molecules into the solvation shell of alkyl halide **1** (step 4) required in the rate-determining step (step 5). Steps 4 and 5 are expected to be strongly sensitive to the cosolutes that compete with alkyl halide **1c** for solvation. By assuming that the concentration of carbon dioxide available for alkyl halide **1** is roughly that which remains after the solvation of alcohol **3b**, the rate law for a simplified scheme with eqn (1), (2), (4) and (5) (Scheme 4) shows that the order for ethanol (**3b**) depends on the solvation requirement of alkyl halide **1** in the rate-determining step (Scheme 4). Therefore, the impact of alcohol **3b** on the reaction depends on carbocation stability, the leaving group ability of the halide anion, and the solvation demand of the ion pairs. Accordingly, 1-chloro-1-phenylethane (**1a**) was found to be less sensitive to ethanol (**3b**) than benzyl bromide (**1c**) (Fig. 3 and Table 1).

$$
\begin{array}{ll}
(1) & RX + m\ CO_2 \rightleftharpoons [RX \cdot m\ CO_2] \\
(2) & EtOH + n\ CO_2 \rightleftharpoons [EtOH \cdot n\ CO_2] \\
(3) & [RX \cdot p\ CO_2] + [EtOH \cdot q\ CO_2] \rightleftharpoons [RX \cdot (p\text{-}r)\ CO_2] + [EtOH \cdot (q\text{+}r)\ CO_2] \\
(4) & [RX \cdot m\ CO_2] + s\ CO_2 \rightleftharpoons [RX \cdot (m\text{+}s)\ CO_2] \\
(5) & [RX \cdot (m\text{+}s)\ CO_2] \xrightleftharpoons{slow} [R^+ \cdot t\ CO_2] + [X^- \cdot v\ CO_2] \\
(6) & [R^+ \cdot t\ CO_2] + \mathbf{2} \xrightarrow{fast} \text{Products}
\end{array}
$$

$$\boxed{v = K_1\, K_4\, k_5\, [RX] \cdot [CO_2]^{m+s} = K_1\, K_4\, k_5\, [RX] \cdot \{\, [CO_2]_0 - n \cdot [EtOH]\, \}^{m+s}}$$

Scheme 4 Mechanistic scheme with solvation equilibria for the reaction of alkyl halide **1** (X = Cl, Br) with 1,3-dimethoxybenzene (**2**) in *sc*CO_2 in the presence of ethanol (**3b**). The rate law applies to eqn (1), (2), (4) and (5), by considering the actual concentration of CO_2 available for solvation of alkyl halide **1** as that remaining after solvation of ethanol (**3b**).

Ethanol (**3b**) exerts stronger interactions with carbon dioxide than alkyl halides **1** and 1,3-dimethoxybenzene (**2**) given its stronger basic and H-bond donor character.[8] Hence the solvation shell for **3b** would be larger than that for **1** ($n > m$), and the solvent exchange equilibrium would favour the solvation of **3b** (step 3, Scheme 4). In this way, ethanol (**3b**) rarefies the reaction medium and renders it less efficient to perform the solvent-demanding ionisation of **1** and the dissociation of the resulting ion pair (Scheme 4).[16] The ability of a cosolute to perturb S_N1 reactions in *sc*CO_2 would then depend on its basicity. Accordingly, reactions would be insensitive to phenol[17] or increasing concentrations of aromatic **2** (entries 1–3, Table 1) while readily inhibited by tertiary amines or water.[3a] It is noteworthy that solvation in *sc*CO_2 could involve solute–solvent interactions that are not directly related to basicity. For instance, fluorinated solutes are commonly called "CO_2-philic" owing to the ability of fluorine atoms to interact with carbon dioxide.[18] Actually, we found that 2,2,2-trifluoroethanol inhibits the ionisation of alkyl halides **1** as efficiently as ethanol (**3b**) or water.

The reaction of benzyl bromide (**1c**) with 1,3-dimethoxybenzene (**2**) at 60 °C in *sc*CO_2 in the presence of ethanol (**3b**) was found to be pressure-insensitive within the 100–250 bar range for [**1c**] = 0.05 M and ratios **1c** : **3b** 1 : 0.5, 1 : 0.6 and 1 : 0.7. This result is related to the dependence of the size of the solvation shells on pressure, which follows the same pace as the bulk density within this range.[14] Thus raising pressure does not provide larger amounts of uncoordinated carbon dioxide molecules available for solvation of **1c** since the size of the clusters around the solutes also increases.[14]

If alcohol **3** does not fully prevent the ionisation of alkyl halide **1** (Fig. 3), the subsequent reactions generate hydrogen halides, which readily ionise in the reaction medium (Schemes 2 and 3). Since these ionic species introduce further solvation equilibria and displace the alkyl halide ionisation equilibrium to the left-hand side (step 5, Scheme 4), the S_N1 reactions of alkyl halides **1** in *sc*CO_2 in the presence of alcohols **3** are expected to autoinhibit to an extent that depends on the solvation requirements of alkyl halide **1**, alcohol **3**, halide anions X^-, protonated intermediates, and side products (ethers, water), in agreement with the experimental observations (Fig. 1–3 and Table 1).

These results show that the S_N1 reactions of alkyl halides **1** in *sc*CO_2 are extremely sensitive to cosolutes that are able to exert strong interactions with carbon dioxide. Therefore, alcohols **3**, water, amines, phosphines, ketones, esters or fluorinated compounds, among others, must be rigorously excluded from the reaction medium in order to obtain reproducible results. In the ESI† we provide detailed experimental procedures that address avoiding reaction medium contamination while performing these reactions.

Conclusions

In summary, the unexpected behaviour of ethanol (**3b**) in the S_N1 reactions of alkyl halides **1** with 1,3-dimethoxybenzene (**2**) in *sc*CO_2 namely, reluctance to form ethers and reaction rate inhibition, is the result of the Brønsted and Lewis acid–base equilibria that take place in a peculiar reaction medium in which: (i) the strong quadrupole and Lewis acid character of carbon dioxide hinders S_N2 paths by strongly solvating basic and nucleophilic solutes; (ii) the weak Lewis base character of carbon dioxide prevents it from behaving as a proton sink; (iii) the compressible nature of *sc*CO_2 enhances the impact of preferential solvation on carbon dioxide availability for the solvent-demanding rate-determining step. Thus the S_N1 reactions of alkyl halides **1** in *sc*CO_2 are inhibited in the presence of cosolutes that are able to exert stronger interactions with the solvent than substrates **1**. The same behaviour is known for the S_N1 reactions of alkyl halides **1** in an aqueous medium in the presence of additives. The results reported herein reveal that *sc*CO_2 is a remarkably structured solvent[2] capable of promoting and sustaining ionic reactions and is, therefore, not at all similar to *n*-hexane or carbon tetrachloride as commonly regarded.

Acknowledgements

Financial support from the Spanish Ministerio de Economía y Competitividad (CTQ2013-47180-P), and Fondos FEDER is gratefully acknowledged. TDA thanks the Spanish Ministerio de Educación, Cultura y Deporte for fellowships. We thank the SCSIE (Universidad de Valencia) for access to its instrumental facilities.

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16 This process is analogous to the salting-out effect, *i.e.* the diminished solubility of non-electrolytes in the presence of ionic solutes with highly structured solvation shells.[2]

17 S_N1 reactions in *sc*CO_2 in the presence of phenol proceed efficiently to give Friedel–Crafts products derived from 1,3-dimethoxybenzene (**2**) and phenol. These results have not been included in the present study since phenol catalyzes S_N1 reactions in non-polar and non-protic solvents through hydrogen bonding (see ref. 5*c*).

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