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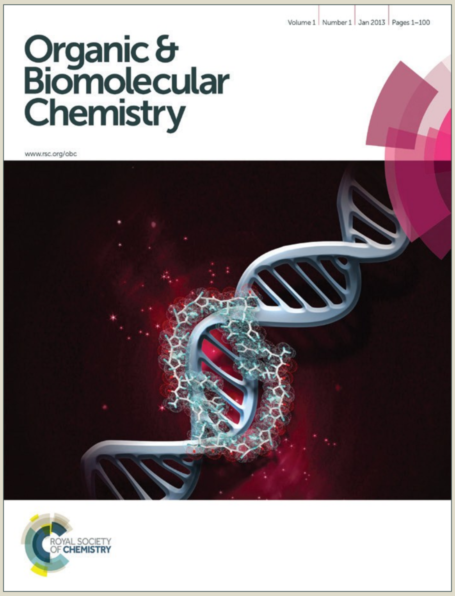

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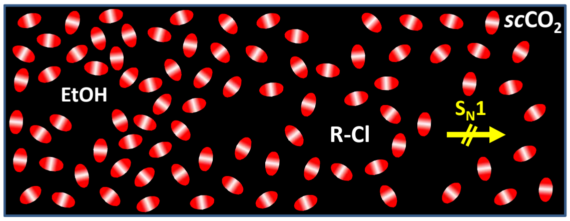
Graphical abstract

No solvent, no reaction: ethanol inhibits S_N1 reactions of alkyl halides in *sc*CO_2 by competing with the substrate for solvation.



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ARTICLE

S_N1 Reactions in Supercritical Carbon Dioxide in the Presence of Alcohols: the Role of Preferential Solvation

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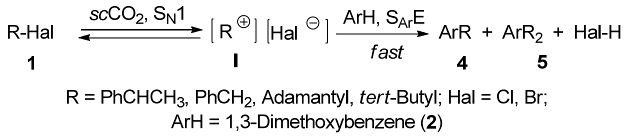
Ethanol (**3b**) inhibits S_N1 reactions of alkyl halides **1** in supercritical carbon dioxide (*sc*CO_2) and gives no ethers as products. The unexpected behaviour of alcohols **3** in the reaction of alkyl halides **1** with 1,3-dimethoxybenzene (**2**) in *sc*CO_2 under different conditions is rationalised in terms of Bronsted 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 uncatalised 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] account for the ability of *sc*CO_2 to solvate ionic species and to avoid capture by acidic intermediates.



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

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.

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 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 homogenous 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 Supplementary Material provides a detailed description of the experimental procedure and the balance of products for the isotopic tracer experiments (Table S1).

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

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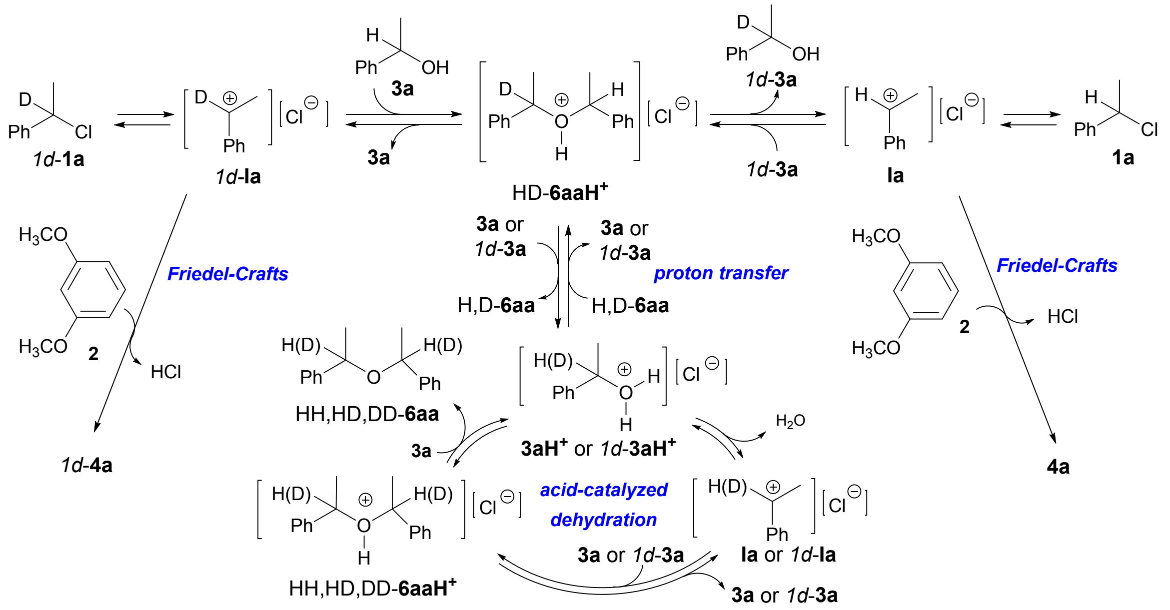


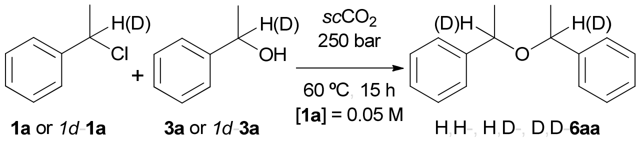
Scheme 2. Reaction paths proposed for 1-chloro-1-*deutero*-1-phenylethane (*1d*-**1a**), 1-phenylethanol (**3a**), and 1,3-dimethoxybenzene (**2**) in *sc*CO_2.

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 (*1d*-**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 *sin*- and *anti*-diastereomers (Run 1, Figure 1). This result shows that *solvation by scCO$_2$ does not prevent alcohol **3a** from capturing carbocation intermediates 1d-**Ia** formed by the solvent-promoted ionisation of alkyl halide 1d-***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, Figure 1), and the higher conversion rate of alcohol **3a** (81%) compared to alkyl halide *1d*-**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, Figure 1) suggests that protonated ether H,D-**6aaH$^+$** ionises in the reaction medium to release alcohols **3a** or *1d*-**3a** and carbocation intermediates **Ia** or *1d*-**Ia** (Scheme 2).

The reaction of 1-chloro-1-phenylethane (**1a**) with a twofold excess of 1-deutero-1-phenylethanol (*1d*-**3a**) in *sc*CO_2 under the same conditions (Entry 2, Figure 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 *1d*-**3a** of 8% and 48%, respectively (Table S1).

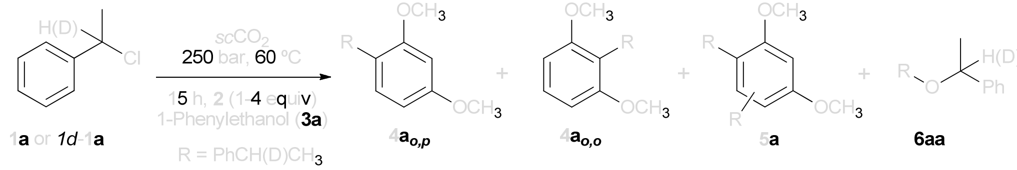


			Product distribution (%) *D-label distribution H:D or H,H:H,D:D,D (%)*			
Run	**1**	**3** (equiv)	**1a**	**3a**	*sin*-**6aa**	*anti*-**6aa**
1	*1d*-**1a**	**3a** (1)	51	13	20	16
	80 D-atom %		*43:77*	*84:16*	*50:33:17*	*41:38:41*
2	**1a**	*1d*-**3a** (2)	37	42	11	10
		88 D-atom %	*79:41*	*14:88*	3:40:57	*<1:39:61*

Figure 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 *1d*-**1a**, **3a**, and [M-15$^+$] for **6aa**. The figures are the average of at least three independent experiments within standard deviation of ±15 %.Figure 1

Finally, the low isotopic dilution observed for unreacted alkyl halide *1d*-**1a** and alcohol *1d*-**3a** (4-13% and 7-0%, respectively, Table S1) compared to the relatively high extent of ethers **6aa** formed (Entries 1 and 2, Figure 1), indicates that *chloride anion does not compete efficiently with alcohols **3a** to trap carbocation intermediates **Ia** in scCO$_2$*.

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'**),



Product distribution (%) / D-label distribution H:D or H,H:H,D:D,D (%)

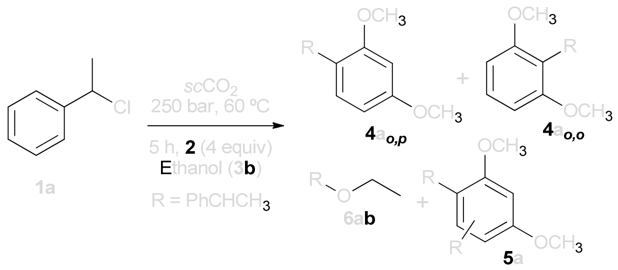
Run	**1**	**2** (equiv)	**1a**	**3a**	**4a**$_{o,p}$	**4a**$_{o,o}$	**5a**	**5a'**	*sin* **6aa**	*anti* **6aa**
1	**1a**	4	--	--	73	9	9	9	--	--
2	*1d*-**1a**	4	33	16	32	6	3	3	4	3
	80 D-atom %		*23:77*	*90:10*	*56:44*	*53:47*	*30:47:23*	*32:40:28*	*50:38:12*	*50:45:5*
3	*1d*-**1a**	1	40	3	20	4	10	10	10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

Figure 2. Reactions of 1-chloro-1-phenylethane (**1a**) (0.05) M, 1,3-dimethoxybenzene (**2**), and 1-phenylethanol (**3a**) in scCO$_2$ 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 *1d*-**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 %.

respectively (Entry 1, Figure 2).[3a] Conversely, the reaction of equimolar 1-chloro-1-deutero-1-phenylethane (*1d*-**1a**) 80 D-atom % and 1-phenylethanol (**3a**), with 4-fold excess of 1,3-dimethoxybenzene (**2**) in scCO$_2$ for 15 h under the same conditions (Entry 2, Figure 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, Figure 1). Substrate conversions were 42% and 72% for *1d*-**1a** and **3a**, respectively (Table S1).

These data evidence that the Friedel-Crafts reaction involves nearly equivalent amounts of carbocations *1d*-**Ia** and **Ia**, and indicate that protonated ether H,D-**6aaH**$^+$ is the major source of electrophilic intermediates for this reaction. Therefore, *carbocations 1d-**Ia**, formed by the ionisation of alkyl halide 1d-**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 scCO$_2$. Thus the preferential formation of symmetrical H,H-ethers **6aa** (Entries 2 and 3, Figure 2), and the conversions of alkyl halide *1d*-**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, Figure 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 1d-**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.*



Product distribution (%)

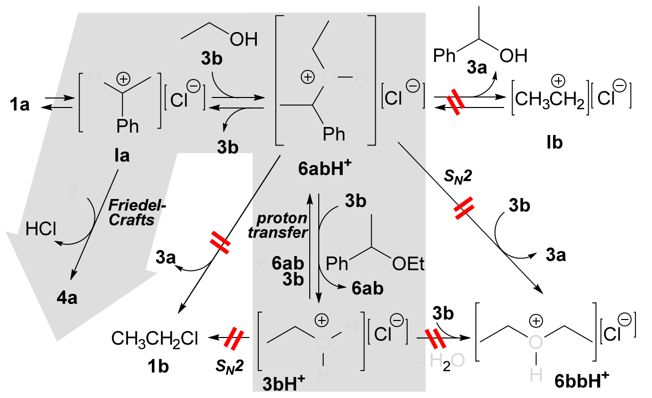
Run	**3b** (equiv)	1a	3a	**4a**$_{o,p}$	**4a**$_{o,o}$	**5a**	**5a'**
1	--	--	--	73	9	9	9
2	0.5	--	--	74	9	8	9
3	0.7	3	--	64	9	12	12
4	1	47	--	39	7	3	4
5	2	86	--	12	2	--	--

Figure 3. Reactions of 1-chloro-1-phenylethane (**1a**) (0.05) M and ethanol (**3b**) with 1,3-dimethoxybenzene (**2**) (4 equiv) in scCO$_2$. The figures are the average of at least three independent experiments within standard deviation of ±15 %.

The reactions performed with equimolar amounts of ionogen *1d*-**1a**, alcohol **3a** and 1,3-dimethoxybenzene (**2**) (Entry 3, Figure 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 *1d*-**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 *1d*-**Ia** and **Ia** compared to the reactions performed with a 4-fold excess of **2** (Entry 2, Figure 2).

The isotopic dilutions found for the unreacted substrates in these reactions (Entries 2 and 3, Figure 2) were 4-13% for alkyl halide *1d*-**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 scCO$_2$ in the presence of ethanol (**3b**) followed a different course (Figure 3). Thus increasing



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

amounts of ethanol (**3b**) above 0.5 equiv progressively inhibited the conversion of alkyl halide **1a** (Entries 2-5, Figure 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). Absence of 1-phenylethanol (**3a**) 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 chloride anion do not compete with unimolecular pathways under these conditions* (Scheme 3). Solvation by carbon dioxide probably hinders nucleophiles to approach electrophilic sp^3 carbon atoms in a 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 funnels 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 (Figure 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 Figures 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 *1d*-**1a** and **3a** (Table S1), the low conversions of alkyl halide **1a** (Figures 1 and 2; Table S1), nor for the progressive reaction inhibition promoted by increasing amounts of ethanol (**3b**) (Figure 3). These results rather suggest that *alcohols **3** inhibit the ionisation of alkyl halide **1a** in scCO_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 non-protic solvents,[5d] 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]

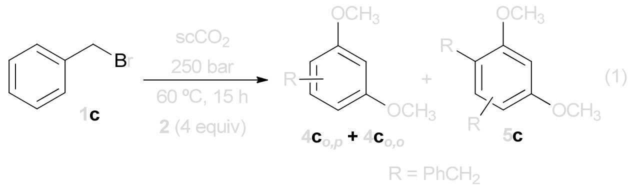
The changes in the reaction rates and equilibria promoted by additives or cosolvents are generally attributed to competitive substrate-solvent, substrate-cosolute, and cosolute-solvent interactions.[12] This concept suggests that *alcohols **3** may hinder the highly solvent-demanding rate-determining step of S_N1 reactions in scCO_2 by competing with alkyl halides **1** for solvation*. Properties of *sc*CO_2, such as compressibility, densities lower than 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 (Equation 1, Table 1).

Friedel-Crafts reactions of alkyl halide 1c in the presence of ethanol (3b). Benzyl bromide (**1c**) 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, Figure 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 depended on both ethanol (**3b**) and benzyl bromide (**1c**) concentrations (Table 1). Thus reactions with molar ratio **1c**:**3b** 1:0.5 proceeded for [**3b**] = 0.025 M, but not for [**3b**] = 0.05 M (Entries 6 and 11, Table 1), while the reactions with **1c**:**3b** molar ratio 1:1 did not proceed at all, not even for [**3b**] = 0.025 M (Entries 5,8,13, Table 1). These trends strongly suggest that ethanol (**3b**) competes with alkyl halide **1c** for solvation.[15]

Scheme 4 illustrates the solvation equilibriums[15] for alkyl halide **1** and ethanol (**3b**) (Steps 1, 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-

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

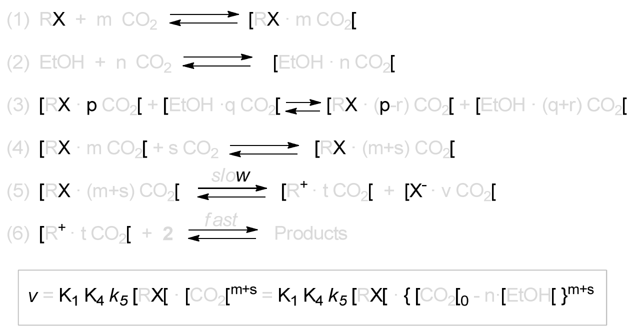


Run	Molar ratio **1c**:**3b**	[**1c**] (M)	[**3b**] (M)	Conv. (%)
1[b]	--	0.1	--	98
2[b]	--	0.05	--	98
3[b]	--	0.025	--	99
4[b,c]	--	0.05	--	99
5	1:1	0.1	0.1	--
6	1:0.5	0.1	0.05	--
7	1:0.25	0.1	0.025	76
8	1:1	0.05	0.05	--
9	1:0.7	0.05	0.035	--
10	1:0.6	0.05	0.03	76
11	1:0.5	0.05	0.025	77
12	1:0.25	0.05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

[a] Reactions performed with molar ratio **1c**:**2** 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.

determining step (Step 5). Steps 4 and 5 are expected to be strongly sensitive to the cosolutes that compete with the 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 equations 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**) (Figure 3, Table 1).

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 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" for 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.



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 equations 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**).

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 relates 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** (Figure 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 equilibriums 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 scCO₂ 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 (Figures 1, 2 and 3, Table 1).

These results showed that the *S_N1 reactions of alkyl halides **1** in scCO₂ 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 Supplementary Material 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.

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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 non-protic solvents through hydrogen bonding (see reference 5d).

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