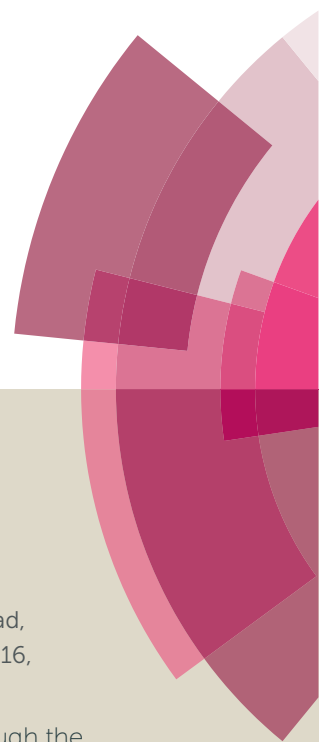
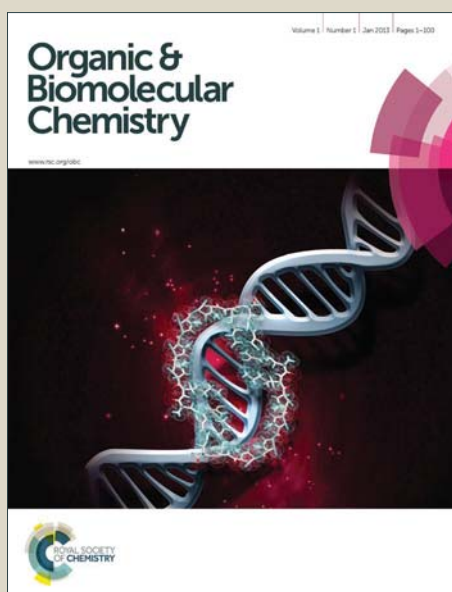


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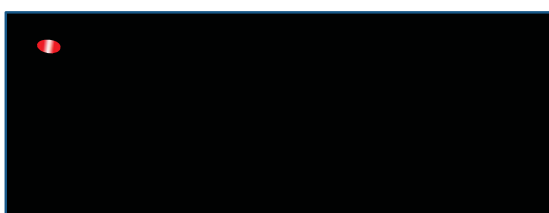
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Graphical abstract

No solvent, no reaction: ethanol inhibits S_N1 reactions of alkyl halides in $scCO_2$ 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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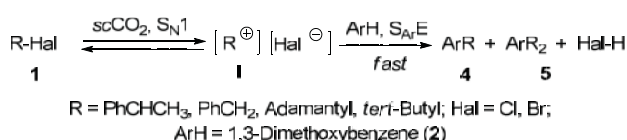
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Thais Delgado-Abad, Jaime Martínez-Ferrer, Rafael Acerete, Gregorio Asensio, Rossella Mello, María Elena González-Núñez*

Ethanol (**3b**) inhibits S_N1 reactions of alkyl halides **1** in supercritical carbon dioxide (scCO₂) 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 scCO₂ 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 scCO₂, which enhances the impact of preferential solvation on carbon dioxide availability for the solvent-demanding rate determining step.

Introduction

Supercritical carbon dioxide (scCO₂) is an alternative solvent for green chemistry¹ 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} account for the ability of scCO₂ to solvate ionic species and to avoid capture by acidic intermediates.



Scheme 1. Reaction of alkyl halides **1** with aromatic **2** in scCO₂.

In the course of our study^{3a} on the reaction of alkyl halides **1** with 1,3-dimethoxybenzene **2** in scCO₂, 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 behaviour⁵ for a polar, protic and nucleophilic additive prompted us to further explore S_N1 reactions as sensitive probes for solvation in scCO₂.⁶ Herein we report on reactions of alkyl halides **1**, 1,3-dimethoxybenzene (**2**), and alcohols **3** in

scCO₂ under different conditions, and disclose the reaction paths involved, as well as the impact of solvation on the product distribution and ionising ability of scCO₂. 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 scCO₂ when designing applications of this medium as a solvent for green chemistry.

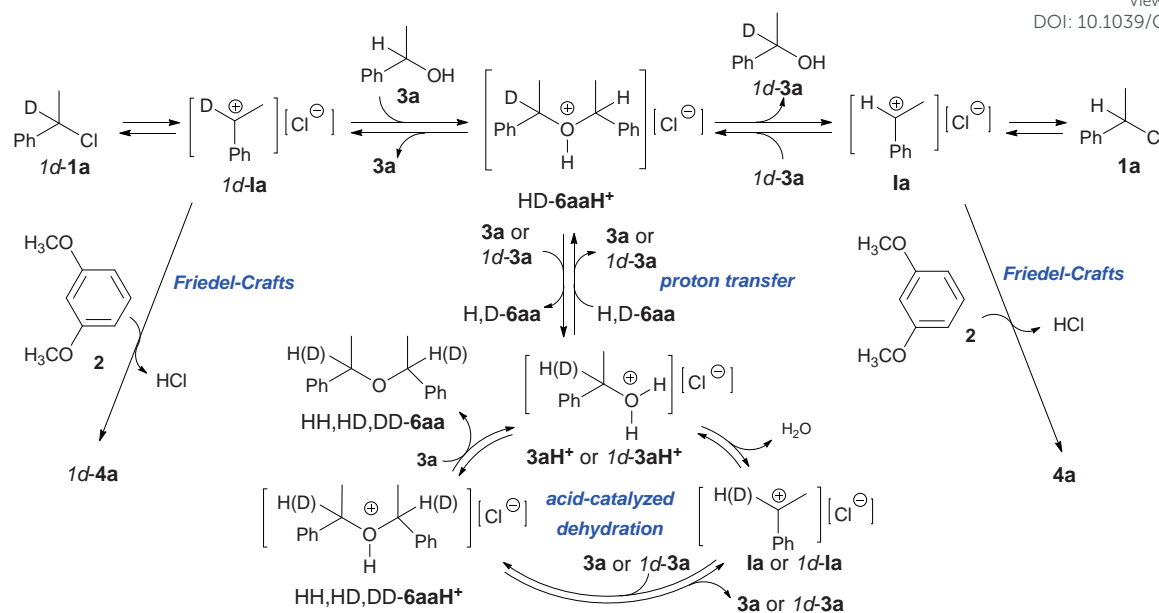
Results and discussion

The model systems selected for exploring S_N1 reactions in scCO₂ 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 CO₂-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 scCO₂: reaction pathways

The absence of ethers **6** as products from the reactions of alkyl halides **1** with aromatic **2** in scCO₂ in the presence of ethanol (**3b**) was firstly attributed to solvation by scCO₂, 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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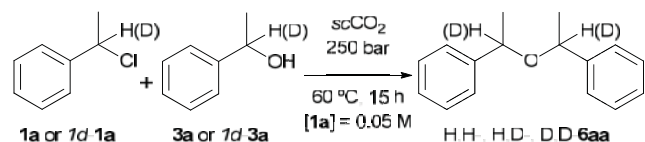
Scheme 2. Reaction paths proposed for 1-chloro-1-deutero-1-phenylethane (**1d-1a**), 1-phenylethanol (**3a**), and 1,3-dimethoxybenzene (**2**) in $sc\text{CO}_2$.

experiments with 1-chloro-1-phenylethane (**1a**) and 1-phenylethanol (**3a**) in $sc\text{CO}_2$ 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 $sc\text{CO}_2$ 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 $sc\text{CO}_2$ does not prevent alcohol **3a** from capturing carbocation intermediates **1d-1a** 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 **1a** or **1d-1a** (Scheme 2).

The reaction of 1-chloro-1-phenylethane (**1a**) with a twofold excess of 1-deutero-1-phenylethanol (**1d-3a**) in $sc\text{CO}_2$ under the same conditions (Entry 2, Figure 1) followed the



Run	Product distribution (%)					
	D-label distribution H,D or H,H:H,D:D,D (%)					
	1	3 (equiv)	1a	3a	<i>sin</i> -6aa	<i>anti</i> -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 $sc\text{CO}_2$ 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

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).

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 **1a** in $sc\text{CO}_2$.

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 $sc\text{CO}_2$ 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'**),

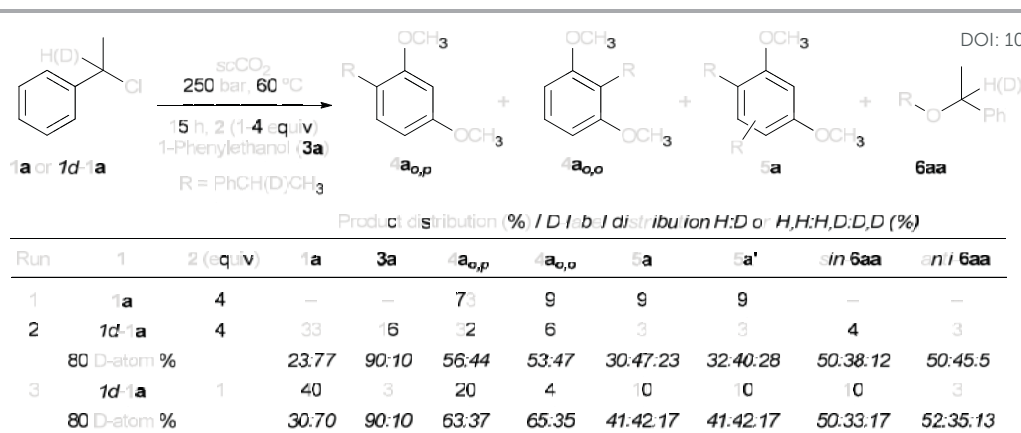


Figure 2. Reactions of 1-chloro-1-phenylethane (**1a**) (0.05) M, 1,3-dimethoxybenzene (**2**), and 1-phenylethanol (**3a**) in $scCO_2$ for 5 h (run 1)^{3a} and 15 h (runs 2 and 3). Isotopic labels were obtained from the relative intensities of the ions $[M^+]$ for **1d-1a**, **3a**, **4a**, and **5a**, and $[M-15^+]$ for **6aa**. The figures are the average of at least three independent experiments within standard deviation of $\pm 15\%$.

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-1a** and **1a**, and indicate that protonated ether H,D-**6aaH**⁺ is the major source of electrophilic intermediates for this reaction. Therefore, carbocations **1d-1a**, 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 **1a** and **1d-1a** to trap alcohol **3a**, and that the H-bonding interactions⁸ 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.

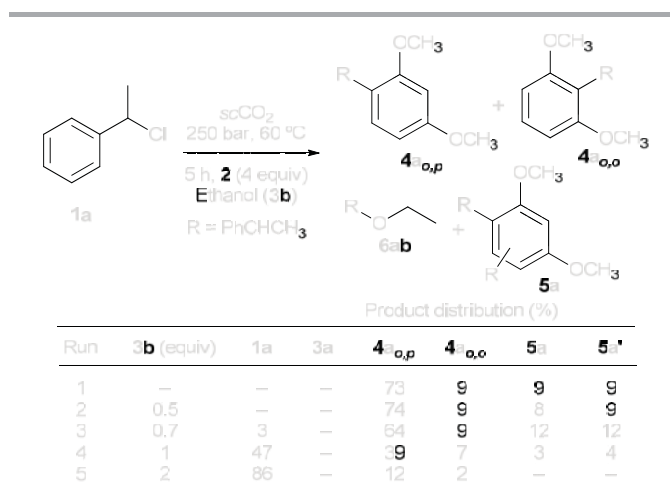
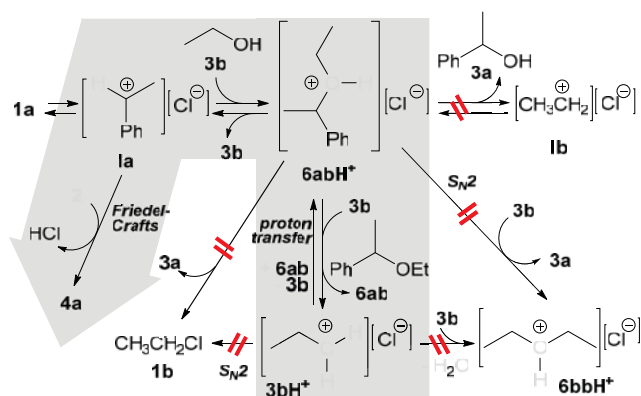


Figure 3. Reactions of 1-chloro-1-phenylethane (**1a**) (0.05) M and ethanol (**3b**) with 1,3-dimethoxybenzene (**2**) (4 equiv) in $scCO_2$. The figures are the average of at least three independent experiments within standard deviation of $\pm 15\%$.

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-1a** and **1a** 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 $scCO_2$.

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 **1a** 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 **1a** (Scheme 2).

S_N1 reactions of alkyl halides **1** and alcohols in $scCO_2$: preferential solvation

The results reported in Figures 1-3 have shown that alcohols **3** react with carbocation intermediates **1a** formed by the $scCO_2$ -promoted ionisation of **1a** faster than 1,3-dimethoxybenzene (**2**), and that the irreversible Friedel-Crafts reaction with 1,3-dimethoxybenzene (**2**) involves carbocations **1a** 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,

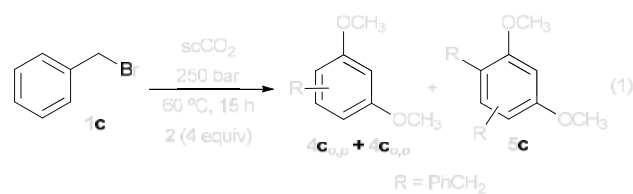
for the low isotopic dilution found for unreacted substrates **1a** and **3a** (Table S1), the low conversions of alkyl halide **1a** (Figures 1 and 2; Table S1), nor for the progressive reaction inhibition promoted by increasing amounts of ethanol (**3b**) (Figure 3). These results rather suggest that 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 $scCO_2$, 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 $scCO_2$ 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, **1c** < **1a**.

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 equilibria¹⁵ 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-

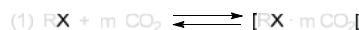
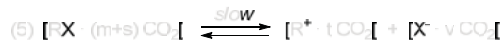
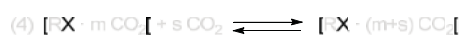
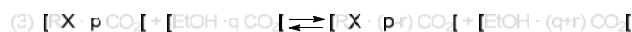
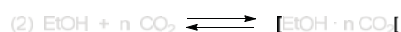
Table 1. Reaction of benzyl bromide (**1c**) with 1,3-dimethoxybenzene (**2**) in *scCO*₂, in the presence of ethanol (**3b**).^a

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 $\pm 15\%$. ^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 *scCO*₂ would then depend on its basicity. Accordingly, reactions would be insensitive to phenol¹⁷ or increasing concentrations of aromatic **2** (Entries 1-3, Table 1), while readily inhibited by

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$$v = K_1 K_4 K_5 [\text{X}] [\text{CO}_2]^{m+s} = K_1 K_4 K_5 [\text{X}] \{[\text{CO}_2]_0 - n[\text{EtOH}] \}^{m+s}$$

Scheme 4. Mechanistic scheme with solvation equilibria for the reaction of alkyl halide **1** (X = Cl, Br) with 1,3-dimethoxybenzene (**2**) in *scCO*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**).

tertiary amines or water.^{3a} It is noteworthy that solvation in *scCO*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.

The reaction of benzyl bromide (**1c**) with 1,3-dimethoxybenzene (**2**) at 60°C in *scCO*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 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 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 $scCO_2$ 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 $scCO_2$ 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 $scCO_2$ 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 $scCO_2$ is a remarkably structured solvent² 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 $scCO_2$ 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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