RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2014, **4**, 51016

On the ionizing properties of supercritical carbon dioxide: uncatalyzed electrophilic bromination of aromatics†‡

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Received 16th September 2014
Accepted 3rd October 2014

DOI: 10.1039/c4ra10557e

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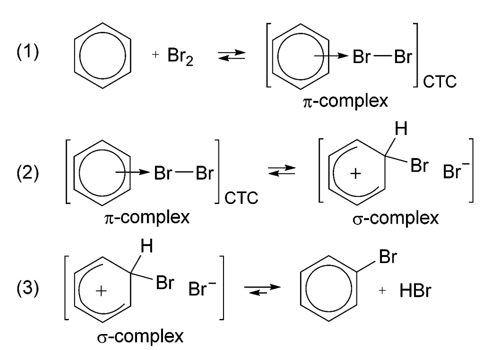
Supercritical carbon dioxide ($scCO_2$), a solvent with a zero dipole moment, low dielectric constant, and no hydrogen bonding behavior, is a suitable medium to perform the uncatalyzed electrophilic bromination of weakly activated aromatics with no interference of radical pathways. The ability of $scCO_2$ to promote these reactions matches those of strongly ionizing solvents such as aqueous acetic and trifluoroacetic acids. Conversely, carbon tetrachloride, with similar polarity parameters to $scCO_2$, leads exclusively to side chain functionalization. The strong quadrupole moment, and the acidic, but non basic, Lewis character of carbon dioxide, are proposed as key factors for the singular performance of $scCO_2$ in reactions involving highly polar and ionic intermediates.

Introduction

Supercritical carbon dioxide ($scCO_2$) is a unique solvent for chemical reactions[1] described as non polar, non nucleophilic and non basic, with low dielectric constant and no hydrogen-bonding behavior,[2,3] which nevertheless exhibits ionizing and dissociating properties.[4] This reveals the importance of the strong quadrupole moment and the acidic, but non basic, Lewis character of carbon dioxide for the specific solvation of polar and ionic solutes,[5] as well as its potential to influence the course of chemical reactions in ways that are unfeasible for conventional solvents.[6] Hence, understanding solvation in $scCO_2$ is crucial for devising competitive applications of this medium in green chemistry,[1] and the study of strongly solvent-dependent reactions in $scCO_2$ is a useful approach to this goal.[7]

The reaction of molecular bromine with alkyl aromatics[8] is a suitable probe for solvation in $scCO_2$ since it follows polar or radical pathways depending on the reaction conditions. In the presence of Lewis acid catalysts,[8,9] or in strongly ionizing solvents,[10] the reaction proceeds through the electrophilic aromatic substitution mechanism,[8–11] which involves the rapid formation of a charge transfer π-complex [$ArH \cdot Br_2$], followed by the rate-determining ionization of the Br–Br bond with σ-adduct formation [$ArHBr^+$, Br^-], and then loss of a proton to restore aromaticity (Scheme 1). Lewis acids facilitate the reaction[9] by coordinating bromine atoms, which enhances both the electrophilicity of the brominating species (Step 1, Scheme 1) and the ability of bromide as a leaving group (Step 2, Scheme 1). Strongly ionizing solvents promote the ionization of the polarized π-complex [$ArH \cdot Br_2$] by solvating the leaving bromide anion (Step 2, Scheme 1).[8,11] Conversely, reactions in apolar solvents under thermal conditions provide mainly side-chain functionalization at benzylic positions.[12]

Predicting the course of these reactions in $scCO_2$ is not obvious. Actually, $scCO_2$ is an excellent solvent for radical reactions[13] which has been found suitable for side-chain photobromination of alkyl aromatics[14] with minor interference of polar side processes. Therefore, the reaction of bromine with aromatics in $scCO_2$ represents an interesting test for solvation in this medium, as well as an alternative approach to a major



Scheme 1 Mechanism of the electrophilic bromination of aromatics.[10,11]

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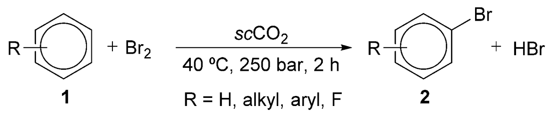
† This article is dedicated in memoriam to Professor Ruggero Curci.

‡ Electronic supplementary information (ESI) available: Detailed experimental procedures, gas chromatograms and mass spectra of the reaction products. See DOI: 10.1039/c4ra10557e

transformation in synthesis which continues to raise interest from mechanistic,[11] preparative, and environmental[15] points of view.

We herein report a comparative study of the reaction of bromine with weakly activated aromatics in different solvents under thermal conditions. The results show that $scCO_2$ is a suitable solvent to perform the selective electrophilic bromination of weakly activated aromatics in the absence of added catalysts (eqn (1)). The ability of $scCO_2$ to promote the uncatalyzed bromination of benzene is matched only by 85% aqueous trifluoroacetic acid, a strongly ionizing polar protic solvent. The results disclose the role of the Lewis acid character,[5] the quadrupole moment,[16] and the low basicity[17] of carbon dioxide in the solvation of the different species involved in the reaction.



(1)

Results

The experimental setup for the bromine reactions with aromatic substrates **1** in $scCO_2$ was designed to rigorously prevent catalysis by the stainless steel reactor walls. So reactions were run by placing a 2 mL amber glass ampule containing bromine capped with a pierced (1/32′) polypropylene top inside a 12 mL glass vial containing the aromatic substrate ([**1**] = 0.6 M, molar ratio **1** : bromine 3 : 1). Then the glass vial was fitted with a drilled (1/32′) polypropylene cap and inserted into a 33 mL stainless steel reactor. The system was carefully pressurized with CO_2 to 250 bar at 40 °C and was allowed to stand unstirred for 2 h at the same temperature.[18] Next the reactor was cooled to 0 °C and allowed to slowly depressurize into a trap at −78 °C.

Substrate conversion and product distribution were determined exclusively from the organic material collected from the internal walls of the glass vial and the ampule, which were washed with specific volumes of dichloromethane solutions of acetone or cyclohexene as quenchers for bromine, and adamantane as an external standard. The resulting solutions were treated with sodium bicarbonate and sodium sulphate, and then analyzed by gas chromatography and mass spectrometry (see the results in Table 1). The external walls of the glass vial, the stainless steel reactor, the outlet valve and the cold trap were washed separately and analyzed following the same procedure. Only trace amounts of starting materials or reaction products were found in these regions. Mass balances were >95% in all cases, indicating that the diffusion of reagents from the glass vial to the stainless steel external reactor walls was negligible in the experimental process. The control experiments performed by pressurizing the reactor to 250 bar at 40 °C, cooling the system to 0 °C and maintaining it at this temperature for 2 h, followed by depressurization and analysis of the reaction mixture as described above, showed no significant conversion of substrates. Comparative experiments in conventional solvents (neat and 85% v/v aqueous acetic and trifluoroacetic acids, and carbon tetrachloride) were done using the same concentrations, molar Br_2 : **1** ratios, temperature and reaction time, and protected from light (Table 1). The resulting mixtures were quenched and analyzed as described above. Detailed experimental procedures are described in the Experimental part and the ESI.‡

Bromine reacted with benzene (**1a**) in $scCO_2$ to give bromobenzene with 10% substrate conversion relative to bromine after 2 h under our reaction conditions (Entry 1, Table 1). Prolonging the reaction time up to 5 h did not improve the result. Conversely, bromine did not react with benzene in carbon tetrachloride, benzene, acetic acid or aqueous acetic acid, under similar reaction conditions. The reactions in neat and aqueous trifluoroacetic acid gave, respectively, 3% and 4% substrate conversions after 2 h at 40 °C.[19]

Toluene (**1b**) reacted with bromine in $scCO_2$ to give exclusively *ortho*- and *para*-monosubstituted products, with 38% substrate conversion *vs.* bromine (Entry 6, Table 1). *meta*-Bromotoluene was not found as a reaction product, which evidenced a high positional selectivity and absence of acid-catalyzed isomerization of the products.[20] Benzylic functionalization was never detected under our reaction conditions. The reactions of bromine with toluene in neat trifluoroacetic acid, aqueous acetic and trifluoroacetic acids gave, respectively, 68%, 20%, and 90% substrate conversions (Entries 7–9, Table 1).[21] The same results were obtained when the reactions were performed by slowly adding a bromine solution to the substrate solution under the same conditions.

The diffusion rate of bromine from the glass vial into the substrate solution had a significant impact on the reaction efficiency. Thus, increasing the contact area between the substrate and bromine solutions through the ampule cap generally improved the substrate conversion. However, no reaction took place when benzene (**1a**) and bromine were placed in the same glass vial at 250 bar and 40 °C for 2 h without stirring. This indicates that high bromine concentrations in the reaction mixture inhibits the reaction rate.[10] In the case of toluene (**1b**), the reactions performed by placing bromine in an open ampule inside the glass vial led to 29% substrate conversion. Control experiments performed by slowly adding (0.0196 mmol min^{-1}) a bromine solution in aqueous acetic and trifluoroacetic acid to a benzene solution (**1a**) in the same solvents at 40 °C showed no differences in relation to our standard conditions.

The relative reaction rates of benzene (**1a**) and toluene (**1b**) with bromine in $scCO_2$ were estimated in competitive experiments performed with initial molar ratios **1a** : **1b** : Br_2 1.5 : 1.5 : 1 for 15 min under our standard conditions. A gas chromatography analysis of the reaction products, performed as described above, showed an average relative conversion **1b** : **1a** of 5 : 1. The competitive reactions performed at 40 °C for 15 min in aqueous acetic or trifluoroacetic acids led to an exclusive reaction of **1b**, and relative conversions **1b** : **1a** of 350 : 1, respectively.[22] Therefore, the uncatalyzed bromination of aromatics in $scCO_2$ exhibited poorer substrate selectivity than the reactions in aqueous acetic or trifluoroacetic acids, but displayed similar positional selectivity.[23] By way of comparison, the substrate selectivity reported[9a] for the reaction of toluene

Table 1 Uncatalyzed bromination of aromatics **1** in $scCO_2$ and conventional solvents[a]

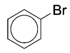
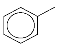
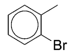
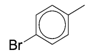
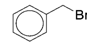
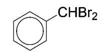
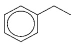
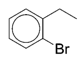
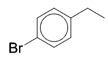
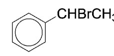
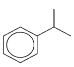
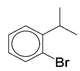
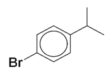
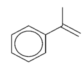
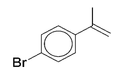
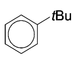
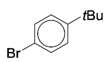
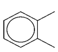
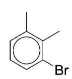
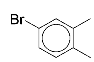
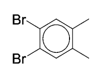
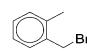
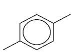
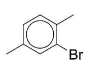
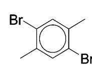
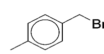
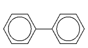
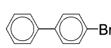
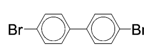
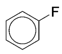
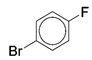
1/Run	Solvent[b]	Conv.[c] (%)	Product distribution (%)			
 **1a**			 **2a**			
1	$scCO_2$	10	100			
2	aq. AA	—	—			
3	TFA	3	100			
4	aq. TFA	4	100			
5	CCl_4	—	—			
 **1b**			 **2b$_o$**	 **2b$_p$**	 **2b$_\alpha$**	 **2b$_{\alpha\alpha}$**
6	$scCO_2$	38	38	62	—	—
7	aq. AA	20	39	61	—	—
8	TFA	68	36	64	—	—
9	aq. TFA	90	25	75	—	—
10	CCl_4	74	—	—	98	2
 **1c**			 **2c$_o$**	 **2c$_p$**	 **2c$_\alpha$**	
11	$scCO_2$	66	36	64	—	
12	AA	19	—	—	100	
13	CCl_4	100	—	—	100	
 **1d**			 **2d$_o$**	 **2d$_p$**	 **3d**	 **3d$_p$**
14	$scCO_2$	43	14	86	—	—
15	AA	33	10	32	23	35
16	TFA	100	17	83	—	—
17	CCl_4	91	—	—	98	2
 **1e**			 **2e$_p$**			
18	$scCO_2$	77	100			
19	AA	5	100			
20	CCl_4	—	—			
 **1f**			 **2f$_3$**	 **2f$_4$**	 **2f$_{4,5}$**	 **2f$_\alpha$**
21	$scCO_2$	>99	—	95	3[d]	—
22	AA	41	18	82	—	—
23	CCl_4	>99	—	—	—	98[e]
 **1g**			 **2g$_2$**	 **2g$_{2,5}$**	 **2g$_\alpha$**	
24	$scCO_2$	66	92	8	—	
25	AA	28	77	10	13	
26	CCl_4	83	—	—	100	
 **1h**			 **2h$_p$**	 **2h$_{p,p}$**		
27	$scCO_2$	32	88	12		
28	AA	—	—	—		
29	CCl_4	—	—	—		

Table 1 (*Contd.*)

1/Run	Solvent[b]	Conv.[c] (%)	Product distribution (%)
 **1i**			 **2i**$_p$
30	$scCO_2$	27	100
31	aq. AA	—	—
32	CCl_4	—	—

[a] Reactions in $scCO_2$ (250 bar) and conventional solvents performed at 40 °C for 2 h, with a molar ratio **1** : Br_2 3 : 1 and $[Br_2] = 0.2$ M. The results are the average of at least three independent runs. [b] AA: acetic acid, TFA: trifluoroacetic acid, aq. AA and aq. TFA: 85% v/v aqueous acids. [c] Substrate conversion relative to bromine. [d] 3,5-Dibromo-1,2-dimethylbenzene was obtained in a 2% yield. [e] *ortho*-α,α′-Dibromoxylene (**2f**$_{\alpha\alpha'}$) was obtained in a 2% yield.

(**1b**) and benzene (**1a**) with bromine in nitromethane at 25 °C in the presence of $FeCl_3$ was **1b** : **1a** 3.6 : 1. The *ortho*:*meta*:*para* regioselectivity of the bromination of **1b** under the same conditions was 68.7 : 1.8 : 29.5.

The bromine reactions with a series of aromatics **1** in $scCO_2$ exclusively gave the corresponding electrophilic substitution products in all cases (Table 1). Remarkably, the selectivity in the reaction of cumene (**1d**) (Entries 14–17, Table 1) was similar for $scCO_2$ and trifluoroacetic acid, while the reaction in acetic led mainly to the products derived from benzylic functionalization, followed by solvent-promoted ionization. Ethylbenzene (**1c**) also led to bromination at the benzylic position in acetic acid (Runs 11 and 13, Table 1). For ethylbenzene (**1c**), cumene (**1d**), *tert*-butylbenzene (**1e**), *ortho*-xylene (**1f**), biphenyl (**1h**), and fluorobenzene (**1i**), the electrophilic aromatic substitution reactions in $scCO_2$ took place preferentially at the less sterically hindered *para* positions (Table 1). *ortho*-Xylene (**1f**) reacted faster than *para*-xylene (**1g**), probably due to the less hindered reactive positions in the former. No acid-catalyzed rearrangement of the isomeric xylenes was observed under our reaction conditions.[20] The reactions of toluene (**1b**), ethylbenzene (**1c**), and *tert*-butylbenzene (**1e**) with bromine in $scCO_2$ at 100 bar and 40 °C led to the same results reported in Table 1, indicating that the electrophilic bromination or aromatics **1** is no pressure-sensitive.[4]

The reactions proved less efficient in glacial or aqueous acetic acid (Table 1). For instance, biphenyl (**1h**), and fluorobenzene (**1i**) failed to give any substitution product in acetic acid and aqueous acetic acid, respectively (Entries 28 and 31, Table 1), while they reacted with 32% and 27% substrate conversions in $scCO_2$ (Runs 27 and 30, Table 1). Remarkably, fluorobenzene (**1i**) reacted with bromine in $scCO_2$ to give *para*-bromofluorobenzene (**2i**$_p$) exclusively, while the regioselectivity reported[9b] for the reaction in nitromethane in the presence of $FeCl_3$ was *ortho*:*meta*:*para* 10.5 : <0.2 : 89.5. Chlorobenzene and bromobenzene were unreactive in both $scCO_2$ and conventional ionizing solvents.

Use of CCl_4 as a solvent for the reaction of alkyl-substituted aromatics with bromine always led to the exclusive functionalization of the benzylic position (Table 1). The dramatic change in the reaction course observed upon going from CCl_4 to $scCO_2$ contrasted with the similar standard polarity parameters tabulated for these solvents:[2] dipole moment (zero in both cases), relative permittivity (2.24 and 1.1–1.5), E_TN (0.052 and 0.068–0.116), and hydrogen-bond acceptor/donor indexes β/α (0.12/0 and 0/0).

Discussion

$scCO_2$ is a suitable solvent to perform uncatalyzed bromination of weakly activated aromatics without interference of radical pathways. Such performance is indicative of specific interactions of carbon dioxide with the different intermediate species involved in the reaction (Scheme 1), which can be summarized as follows:

(i) The lower toluene (**1b**)/benzene (**1a**) selectivity observed in $scCO_2$, if compared to that in aqueous acetic and trifluoroacetic acids, evidences a less substrate-selective $[ArH\cdot Br_2]$ π-complexation (Step 1, Scheme 1) and, therefore, a stronger electrophilic brominating species in $scCO_2$.[11,23] This suggests that the very low Lewis base character of carbon dioxide[17] prevents a strong interaction with bromine and preserves its electrophilic character. Accordingly, the actual brominating species in $scCO_2$ would be unsolvated bromine molecules.

(ii) At a low bromine concentration, the polarized $[ArH\cdot Br_2]$ π-complex evolves into the σ-adduct $[ArHBr^+, Br^-]$ through the solvent-promoted ionization of the Br–Br σ-bond (Step 2, Scheme 1).[10,11] The specific Lewis acid–base, dipole–quadrupole, and ion–quadrupole interactions of carbon dioxide with the leaving bromide anion[5d,24] appear strong enough to activate this process. The preference for the *para* position observed in the reactions of bromine with toluene (**1b**) in $scCO_2$ and conventional ionizing solvents (Table 1), if compared with the *ortho*-selectivity reported[9b] for the $FeCl_3$-catalyzed reaction, can be attributed to the greater steric hindrance of the solvation shells around the terminal bromine atom in the π-complex if compared to the complexed Lewis acid.[9,10d] In this context, the *para*-selectivity observed in the reaction of bromine with fluorobenzene (**1i**) in $scCO_2$ (Entry 30, Table 1) would be indicative of significant interactions of carbon dioxide with the fluorine atom, in agreement with the well-known CO_2-philic character of fluorinated hydrocarbons.[1]

(iii) The non basic character of carbon dioxide[17] further contributes to differentiate the reaction course in relation to conventional solvents as it enhances the role of bromide anion as a Bronsted base to remove the proton from the σ-complex in the rearomatization step (Step 3, Scheme 1), and prevents the ionization of HBr. In this way, $scCO_2$ should minimize the complexation of molecular bromine with bromide anion [$Br_2 + Br^- \leftrightarrows Br_3^-$],[10,11,25] a side process that actually depletes the electrophile from the solution. Although no data on this complex equilibrium in $scCO_2$ are presently available, this factor should not be disregarded as a significant contributor to the singular efficiency of this medium to promote the electrophilic aromatic bromination of benzene (**1a**).

(iv) At a high initial bromine concentration, the electrophile would compete with $scCO_2$ in the ionization of the polarized π-complex [$ArH \cdot Br_2$] to give the σ-complex and Br_3^- (Step 2, Scheme 1). Since the delocalized Br_3^- species is a weaker base than bromide anion, this process actually removes both the reactive electrophilic brominating species and the base required in the last rearomatization step (Step 3, Scheme 1) from the reaction medium. This side process accounts for the low reaction rates and the kinetic orders higher than two observed in conventional solvents,[10] and also the inhibitory effect by the high initial bromine concentrations observed in $scCO_2$. Indeed, these effects should be greater for reactions in $scCO_2$ as the solvent cannot participate as a base in the rearomatization step in this case.

The striking difference between the reaction courses observed in $scCO_2$ and carbon tetrachloride, both solvents with similar polarity parameters, evidences the ability of $scCO_2$ to solvate highly polar intermediates and transition states through intermolecular interactions which are silent to standard polarity probes.[2] These interactions strongly favor polar reaction pathways over alternative routes that lead to side-chain functionalization, such as the thermal homolysis of the Br–Br σ-bond, single electron transfer processes, or even molecule-induced homolysis, which are preferred in carbon tetrachloride.[11i,26] Notwithstanding, the solvent-promoted electrophilic aromatic substitution in $scCO_2$ is not fast enough to compete with the radical-mediated side-chain bromination of the alkyl aromatics performed under photochemical conditions,[14] and this fact makes $scCO_2$ a unique solvent to perform either polar or radical reactions of alkyl aromatics with bromine through the proper selection of reaction conditions.

Conclusions

Molecular bromine reacts with weakly activated aromatics in $scCO_2$ in the absence of Lewis acid catalysts to give electrophilic aromatic substitution products exclusively. The results reported herein evidence the singular ability of $scCO_2$ to promote strongly polar reaction pathways in spite of the non polar character, similar to pentane or carbon tetrachloride, attributed to this medium by standard polarity probes. The performance of $scCO_2$ in the electrophilic bromination of weakly activated aromatics, which matches that of aqueous acetic or trifluoroacetic acids, can be attributed to the high quadrupole moment, Lewis acid character and low basicity of carbon dioxide.

Acknowledgements

Financial support from the Spanish Ministerio de Economía y Competitividad (CTQ2013-47180-P), Fondos Feder, and Generalitat Valenciana (ACOMP/2012/217) is gratefully acknowledged. TDA and JRL thank 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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19 The rate constants reported[10d] for the reaction of benzene with bromine in neat and 87% aqueous trifluoroacetic acid at 25 °C were 7.62×10^{-7} and 144×10^{-7} M^{-1} s^{-1}, respectively. The rate constants for the uncatalyzed bromination of toluene in trifluoroacetic acid at 35 °C and in 87% aqueous trifluoroacetic acid were 3.81×10^{-3} and 1.97×10^{-3} M^{-1} s^{-1}, respectively.

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