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Supercritical CO_2

Supercritical Carbon Dioxide: A Promoter of Carbon–Halogen Bond Heterolysis**

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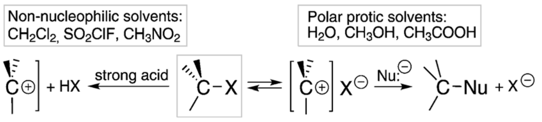
Supercritical carbon dioxide ($scCO_2$) is an alternative medium for sustainable chemistry[1] that is competitive in a variety of chemical processes of technological importance.[1,2] Carbon dioxide has zero dipole moment and very low polarizability,[3] and most polarity studies describe $scCO_2$ as a nonpolar medium with a very low dielectric constant and no hydrogen-bonding behavior, comparable to *n*-hexane or carbon tetrachloride.[3] These properties limit the applications of $scCO_2$ in chemical processes. However, carbon dioxide has a strong quadrupolar moment ($-14.3\times10^{-4}\,°\mathrm{C\,m^2}$)[4] arising from two opposed dipoles in the linear molecule, which allows for significant interactions with bond dipoles in solute molecules and justifies the ability of $scCO_2$ to dissolve solutes carrying structural motifs such as perfluorinated chains, sulfonate and phosphate groups, or carboxylic acid esters.[4] These peculiar properties prompted us to investigate strongly solvent-dependent reactions in $scCO_2$ as a method for probing intermolecular solute–solvent interactions,[5] which may contribute to expand the range of applications of this medium.

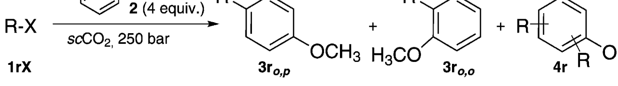
Unimolecular nucleophilic substitution (S_N1, Scheme 1) is a strongly solvent-sensitive reaction[3] as the leaving group departs from the carbon atom prior to the entrance of the nucleophile. Polar protic solvents with high dielectric constants promote polar bond heterolysis by providing effective H-bonding and electron-pair donation interactions to the leaving group and the incipient carbocation, respectively. Then, the solvent captures the carbocation intermediate to give the corresponding S_N1 products. Conversely, polar non-nucleophilic solvents, such as dichloromethane, nitromethane, SO_2ClF, or SO_2F_2, which are commonly used for the generation and observation of carbocations,[6] are unable to ionize polar covalent bonds and require the presence of strong Brønsted or Lewis acids to promote the departure of the leaving group.



Scheme 1. Reaction conditions for S_N1 reactions.

According to these features, $scCO_2$ is far from being an ideal solvent for S_N1 reactions in the absence of strong acids. Acid-catalyzed reactions, such as Friedel–Crafts alkylation with alcohols,[7] alkane isomerization,[8] glycosidation,[9] and etherification,[10] are known to proceed efficiently in $scCO_2$, although the involvement of carbocation intermediates has not been specifically ascertained. As these reports suggest that $scCO_2$ is able to sustain ionic processes, they prompted us to test the ability of $scCO_2$ to promote S_N1 reactions in the absence of acid catalysts.

1-Chloro-1-phenylethane (**1aCl**), a secondary benzylic substrate with well-known reactivity under conventional S_N1 conditions,[11] was first selected as the ionogen. 1,3-Dimethoxybenzene (**2**), a highly activated aromatic compound that is unable to assist polar σ-bond ionization through hydrogen bonding, was selected to trap any electrophilic species formed. Nucleophiles, such as azide or halide anions, which are commonly used to trap carbocationic intermediates in S_N1 reactions, are not appropriate in this case as their salts are insoluble in $scCO_2$. The reaction was performed at 60 °C and 250 bar by pressurizing with CO_2 a stainless-steel reactor containing 1-chloro-1-phenylethane (**1aCl**, 0.03 M) and 1,3-dimethoxybenzene (4 equiv). After 5 h under these conditions, the reactor was depressurized at 0 °C and the products were collected at −78 °C. The organic residues in the reactor and the trap were dissolved into diethyl ether and treated with sodium hydrogen carbonate. The GC and GC-MS analyses of the solution showed the complete conversion of **1aCl** into a mixture of the corresponding Friedel–Crafts adducts, 2,4-dimethoxy-1-(1-phenylethyl)benzene (**3a**$_{o,p}$) and 1,3-dimethoxy-2-(1-phenylethyl)benzene (**3a**$_{o,o}$) [Eq. (1)]. Substrate



(1)

a R= $PhCHCH_3$, **b** R= $PhCH_2$, **c** R= tert-butyl, **d** R= 1-adamantyl; X = Cl, Br

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Table 1: Reaction of ionogens **1** with 1,3-dimethoxybenzene (**2**) in *sc*CO_2.[a]

Run	**1** *r***X**	*T* [°C]	*t* [h]	**3**	**4**
1	$PhCH(CH_3)Cl$ (**1aCl**)	60	5	82	18
2	$PhCH(CH_3)Br$ (**1aBr**)	40	5	81	19
3	$PhCH_2Br$ (**1bBr**)	60	24	82	18
4	$PhCH_2Cl$ (**1bCl**)	70	8[b]	83	17
5	*t*BuBr (**1cBr**)	60	5	100	–
6	1-AdBr (**1dBr**)	70	5[c]	88	8
7	1-AdCl (**1dCl**)	70	5[d]	100	–

[a] Reactions were carried out at 250 bar with 4 equiv of **2**. *sc*CO_2 densities at 40, 60, and 70 °C are 887, 775, and 719 $Kg\,m^{-3}$, respectively. Substrate conversion were complete except where noted. [b] 9% substrate conversion. [c] 52% substrate conversion. Adamantane (4%) was obtained as a side product. [d] 23% substrate conversion.

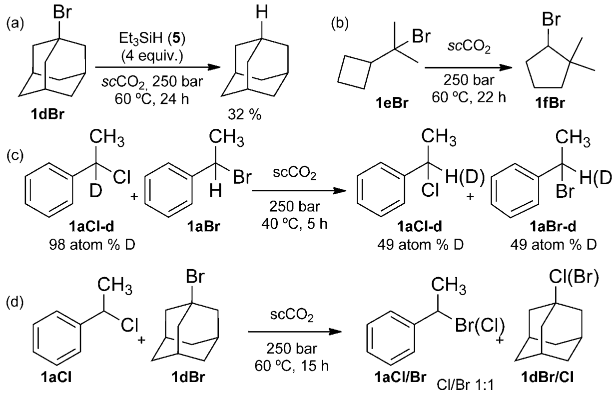
conversion was insensitive to pressure in the 75–250 bar range for a substrate concentration of 0.03 M and at 60 °C.

The reactions of a series of ionizable substrates **1** with **2** in *sc*CO_2 [Eq. (1), Table 1] illustrate the scope of this unconventional solvent-promoted Friedel–Crafts reaction. The reaction products were identified by comparison with independently prepared authentic samples. The mass balances determined in the presence of mesitylene (1 equiv) as an internal standard or with adamantane as external standard were correct (> 90%) in all cases.

Control experiments performed by introducing reagents **1** and **2** into the reactor separately, and collecting the reaction products by flowing *sc*CO_2 through the reactor for 3 h at the same reaction conditions and depressurizing the supercritical solution into a cold trap, led to the same results shown in Table 1. These results indicate that the reactions take place in a homogeneous supercritical solution and not in any condensed phase formed prior to the presence of *sc*CO_2 in the system or during the depressurization step. This fact was further ascertained by visual inspection of the reaction mixtures in a cell-view. Experimental details are provided in the Supporting Information.

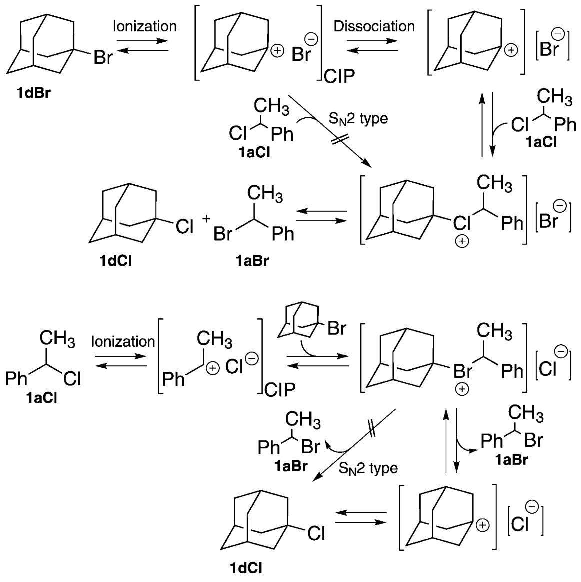
These results strongly support the proposal that *sc*CO_2 is able to ionize tertiary or benzylic carbon–halogen σ-bonds and to dissociate the resulting ion pairs in the absence of any acidic or polar protic solvent, catalyst, or additive. The relative stability of the carbocation intermediates, $PhCHCH_3$ > *tert*-Bu > $PhCH_2$, and the performance of halides as leaving groups, Br > Cl, determine the reaction conditions for ionogens **1**, which require different temperatures and reaction times in each case (Table 1). The reactions of 1-adamantyl halides **1dBr** and **1dCl** (Table 1, Runs 6,7) are noteworthy as the bicyclic structure prevents backside assistance by solvent or nucleophile molecules to the leaving group departure.

Further evidences of heterolytic processes promoted by *sc*CO_2 were found in the reactions of 1-adamantyl bromide (**1dBr**) with triethylsilane (**5**) (4 equiv) at 60 °C for 24 h to give adamantane, and 2-cyclobutyl-2-bromopropane (**1eBr**) at 60 °C for 22 h to give 1-bromo-2,2-dimethylcyclopentane (**1fBr**; Scheme 2a,b). These transformations are best interpreted respectively as the hydride abstraction[12] and rearrangement[13,14] reactions of the corresponding carbocations that would be generated in *sc*CO_2 from the corresponding alkyl halides in the absence of strong acids.



Scheme 2. Hydride abstraction (a), rearrangement (b), and halogen exchange (c,d) reactions in *sc*CO_2.

In a series of competitive experiments with two different ionogens **1** and 1,3-dimethoxybenzene (**2**) in *sc*CO_2, we noticed halogen exchange reactions[15] under our standard conditions. Thus, [1-D]-1-chloro-1-phenylethane ([D]-**1aCl**, 98 atom% D) and 1-bromo-1-phenylethane (**1aBr**) reacted in *sc*CO_2 at 250 bar and 40 °C for 5 h to give equimolar amounts of [D]-**1aCl** and [D]-**1aBr** (both 49 atom% D; Scheme 2c). The halogen exchange reaction also took place between 1-chloro-1-phenylethane (**1aCl**) and 1-bromoadamantane (**1dBr**) in *sc*CO_2 at 250 bar and 60 °C for 15 h to give equimolar amounts of **1aCl**, **1aBr**, **1dBr**, and **1dCl** (Scheme 2d). In this case, C–Cl bond formation at the bridgehead position through nucleophilic displacement of bromide by **1aCl** or chloride anion cannot take place on the undissociated ion pair formed from **1dBr** (Scheme 3). Therefore, this result evidences the formation of unpaired carbocations in *sc*CO_2 in the absence of strong acids.



Scheme 3. Reaction pathways proposed for the halogen exchange reaction of **1aCl** and **1dBr** observed in *sc*CO_2. Square brackets represent the solvation shells.

Products derived from the capture of CO_2 were not detected in these reactions, which is in agreement with the known inertness of carbon dioxide towards activation by Lewis acids.[16] Oxygen was present in the reaction system in all of the experiments reported in Table 1 and Schemes 2 and 3. Products characteristic of radical reactions, such as monomeric or dimeric alkanes or oxygenated products derived from peroxydic intermediates,[5,14,17] were not detected in any case. These results allow for disregarding the involvement of radical intermediates in these reactions. Water, ethanol, or organic solvents present in the supercritical medium strongly inhibited the reaction rates[18] and led to the recovery of the unchanged starting materials in all the cases. Control experiments performed in a stainless steel autoclave by heating solutions of ionogens **1** (0.03 M) in *n*-hexane, diethyl ether, carbon disulfide, acetonitrile, or dimethylformamide, led to the recovery of the unreacted starting materials in all of the cases, which permit us to rule out that the inner wall of the stainless steel reactor might catalyze the reactions.

Solvent-promoted heterolysis of σ-bonds initially forms solvated contact ion pairs, which then dissociate by the progressive penetration of the solvent molecules between the ions to eventually reach the unpaired solvated-ion stage.[19,20] To gain insight into the ion pair dynamics in *sc*CO_2, we determined the stereochemical course of the reaction and the secondary kinetic α-deuterium isotope effect. (*R*)-1-Chloro-1-phenylethane ((+)-**1aCl**) with 70–80 % *ee* completely racemized on standing in *sc*CO_2 at 60 °C and 250 bar for 5 h, and gave racemic Friedel–Crafts adducts $\mathbf{3a}_{o,p}$ in the reaction with 1,3-dimethoxybenzene (**2**) in *sc*CO_2 under the same conditions. Control experiments showed that Friedel–Crafts adducts **3a** do not undergo 1-phenylethyl group transfer reactions in *sc*CO_2 at 60 °C for 5 h in the presence of hydrogen chloride (2 equiv) and 1,4-dimethoxybenzene (4 equiv). This result allowed us to rule out that Friedel–Crafts adducts **3a** undergo acid catalyzed racemization under these reaction conditions. A secondary kinetic α-deuterium isotope effect was determined from the competitive reactions of equimolar amounts of **1aCl** and [1-D]-1-chloro-1-phenylethane ([D]-**1aCl**, 98 atom % D) with **2** (4 equiv) in *sc*CO_2 at 40 °C and 250 bar for 1 h to achieve alkyl halide conversions of about 20 %. An averaged k_H/k_D value of 1.168 ± 0.014 was obtained for both isomeric Friedel–Crafts adducts **3a** from 5 independent runs.

Racemization of (+)-**1aCl** in *sc*CO_2 indicates that the reaction medium dissociates the contact ion pair enough to allow carbocation rotation prior to collapse with the chloride anion. By way of comparison, the solvolysis of the optically active (+)-**1aCl** in absolute ethanol at 70 °C has been reported to proceed with about 5–15 % net inversion.[11] The kinetic α-deuterium isotope effect, $k_H/k_D = 1.168$, found for the reaction of **1aCl** with **2** in *sc*CO_2, suggests that the rate-determining step of the reaction is the dissociation of the ion pair.[21] Accordingly, the electrophilic species involved in this Friedel–Crafts reaction would be unpaired carbocations. Values of about 1.15 for the kinetic α-deuterium isotope effects in the solvolysis of organic chlorides have been considered indicative of limiting S_N1 reactions[11,21] in which the solvent does not provide nucleophilic assistance to the departure of the leaving group. These results are in agreement with the reactivity exhibited by 1-bromoadamantane (**1dBr**) in *sc*CO_2 (Table 1, Scheme 2a,c). Remarkably, the k_H/k_D value reported for the solvolysis of **1aCl** in 97 % aqueous 2,2,2-trifluoroethanol at 25 °C was 1.158.[11c]

The ability of *sc*CO_2 to ionize polar carbon–halogen bonds and to dissociate the resulting ion pairs can be related to the well-established clustering effect of *sc*CO_2 around polar solute molecules.[4,5,22] The spectroscopic and theoretical studies reported[23] for the ion-quadrupole complexes of halide anions with carbon dioxide in the gas phase have evidenced the transference of charge density from the halogen to the oxygen atoms with concomitant distortion of the CO_2 molecule from linearity. Solvent clustering around the polarized carbon dioxide molecules coordinated to the leaving group would further disperse the negative charge density and contribute to dissociate the ion pair. In this way, carbon dioxide would play the role of an H-bonding solvent by efficiently accepting electron density from leaving groups.[24] The negative charge densities localized at the oxygen atoms of the carbon dioxide molecule might stabilize the increasingly electron-deficient carbon atom of the ionogen. Nevertheless, these interactions fail to activate carbon dioxide to react with the highly activated nucleophiles present in the reaction medium.

In summary, we have found that *sc*CO_2 ionizes polar carbon–halogen bonds, dissociates the resulting ion pairs, and escapes from the capture by the carbocation intermediates at temperatures above 40 °C. This behavior allows carbocation reactions to be observed in *sc*CO_2 in the absence of any acidic or protic additive. The ionizing and dissociating abilities exhibited by *sc*CO_2 in these reactions are unprecedented for a reaction medium with a lower dielectric constant than pentane and non-hydrogen-bonding behavior. This information is valuable for designing efficient and competitive chemical processes in *sc*CO_2 and also for a better understanding of the reactivity of carbon dioxide.

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[1] a) *Handbook of Green Chemistry*, *Vol. 4 Supercritical Solvents* (Eds.: W. Leitner, P. G. Jessop), Wiley-VCH, New York, **2010**; b) *Green Chemistry Using Liquid and Supercritical Carbon Dioxide* (Eds.: J. M. DeSimone, W. Tumas), Oxford University Press, Oxford, **2003**; c) E. J. Beckman, *J. Supercrit. Fluids* **2004**, *28*, 121; d) C. M. Rayner, *Org. Process Res. Dev.* **2007**, *11*, 121; e) W. Leitner, *Acc. Chem. Res.* **2002**, *35*, 746.

[2] a) S. L. Wells, J. DeSimone, *Angew. Chem.* **2001**, *113*, 534; *Angew. Chem. Int. Ed.* **2001**, *40*, 518; b) R. A. Pai, R. H. Humayun, M. T. Schulberg, A. Sengupta, J. N. Sun, J. J. Watkins, *Science* **2004**, *303*, 507; c) J. M. Blackburn, D. P. Long, A. Cabañas, J. J. Watkins, *Science* **2001**, *294*, 141; d) J. D. Holmes, K. P. Johnston, R. Doty, B. A. Korgel, *Science* **2000**, *287*, 1471; e) A. H. Romang, J. J. Watkins, *Chem. Rev.* **2010**, *110*, 459; f) A. Caballero, E. Despagnet-Ayoub, M. M. Díaz-Requejo, A. Díaz-

Rodríguez, M. E. González-Núñez, R. Mello, B. K. Muñoz, W. Solo-Ojo, G. Asensio, M. Etienne, P. J. Pérez, *Science* **2011**, *332*, 835; g) R. A. Bourne, X. Hue, M. Poliakoff, M. W. George, *Angew. Chem.* **2009**, *121*, 5426; *Angew. Chem. Int. Ed.* **2009**, *48*, 5322; h) S. Wesselbaum, U. Hintermair, W. Leitner, *Angew. Chem.* **2012**, *124*, 8713; *Angew. Chem. Int. Ed.* **2012**, *51*, 8585.

[3] C. Reichardt, T. Welton, *Solvents and Solvent Effects in Organic Chemistry*, 4th ed., Wiley-VCH, Weinheim, **2011**.

[4] a) P. Raveendran, Y. Ikushima, S. L. Wallen, *Acc. Chem. Res.* **2005**, *38*, 478; b) S. Kazarian, M. F. Vincent, F. V. Bright, C. L. Liotta, C. A. Eckert, *J. Am. Chem. Soc.* **1996**, *118*, 1729.

[5] J. F. Brennecke, J. E. Chateauneuf, *Chem. Rev.* **1999**, *99*, 433.

[6] G. A. Olah, D. A. Klump, *Acc. Chem. Res.* **2004**, *37*, 211.

[7] a) J. E. Chateauneuf, K. Nie, *Adv. Environ. Res.* **2000**, *4*, 307; b) R. Amandi, K. Scovell, P. Licence, T. J. Lotz, M. Poliakoff, *Green Chem.* **2007**, *9*, 797.

[8] G. Olah, E. Marinez, B. Török, G. K. S. Prakash, *Catal. Lett.* **1999**, *61*, 105.

[9] X. B. Li, M. Ogawa, T. Monden, T. Maeda, E. Yamashita, M. Naka, M. Matsuda, H. Hinou, S. I. Nishimura, *Angew. Chem.* **2006**, *118*, 5780; *Angew. Chem. Int. Ed.* **2006**, *45*, 5652.

[10] W. K. Gray, F. R. Smail, M. G. Hitzler, S. K. Ross, M. Poliakoff, *J. Am. Chem. Soc.* **1999**, *121*, 10711.

[11] a) J. Steigman, L. P. Hammett, *J. Am. Chem. Soc.* **1937**, *59*, 2536; b) V. J. Shiner, Jr., W. E. Buddenbaum, B. L. Murr, G. Lamaty, *J. Am. Chem. Soc.* **1968**, *90*, 418; c) V. J. Shiner, Jr., W. Dowd, R. D. Fisher, S. R. Hartshorn, M. A. Kessick, L. Milakofsky, M. W. Rapp, *J. Am. Chem. Soc.* **1969**, *91*, 4838.

[12] H. W. Geluk, J. L. M. A. Schlatmann, *Tetrahedron* **1968**, *24*, 5369.

[13] G. K. S. Prakash, V. P. Reddy, G. Rasul, J. Casanova, G. A. Olah, *J. Am. Chem. Soc.* **1998**, *120*, 13362.

[14] Cyclobutylcarbinyl radical intermediates do not undergo ring-expansion reactions: A. L. J. Beckwith, G. Moad, *J. Chem. Soc. Perkin Trans. 2* **1980**, 1083.

[15] G. A. Olah, Y. K. Mo, *J. Am. Chem. Soc.* **1974**, *96*, 3560.

[16] G. A. Olah, B. Török, J. P. Joschek, I. Bucsi, P. M. Esteves, G. Rasul, G. K. S. Prakash, *J. Am. Chem. Soc.* **2002**, *124*, 11379.

[17] M. B. Smith, J. March, *March's Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*, 6th ed., Wiley, Hoboken, NJ, **2007**, p. 934.

[18] The counterintuitive inhibitory effect of water and ethanol on the solvolytic reactions in *sc*CO_2 (polar protic solvents promote S_N1 reactions under conventional conditions) can be attributed to the strong interactions of these additives with carbon dioxide and the carbocation intermediates involved in the reactions. These interactions and their impact on S_N1 reactions in *sc*CO_2 are presently under investigation and will be the subject of future reports.

[19] K. S. Peters, *Chem. Rev.* **2007**, *107*, 859.

[20] T. W. Bentley, P. v. R. Schleyer, *Adv. Phys. Org. Chem.* **1977**, *14*, 1.

[21] J. M. Harris, *Prog. Phys. Org. Chem.* **1974**, *11*, 89.

[22] a) M. Saharay, S. Balasubramanian, *J. Phys. Chem. B* **2007**, *111*, 387; b) J. F. Kauffman, *J. Phys. Chem. A* **2001**, *105*, 3433.

[23] D. W. Arnold, S. E. Bradford, E. H. Kim, D. M. Neumark, *J. Chem. Phys.* **1995**, *102*, 3493.

[24] Liquid sulfur dioxide exhibits also ionizing and dissociating behavior, although in this case the dipole moment is 1.62 D and dielectric constant 15.6 at 0°C. N. N. Lichtin, *Prog. Phys. Org. Chem.* **1963**, *1*, 75.