

Role of an ionic liquid, 1-butyl-3-methylimidazolium 2-(2-methoxyethoxy)ethyl sulfate in extraction studies of gadolinium oxide

By Kamalika Sen^{1,*} and H. Th. Wolterbeek²

¹ Department of Chemistry, University of Calcutta, 92 APC Road, Kolkata 700009, India

² Department of Radiation, Radionuclides and Reactors, Section RIH (Radiation and Isotopes in Health), Faculty of Applied Sciences, Technical University Delft, Mekelweg 15, 2629 JB Delft, The Netherlands

(Received September 10, 2010; accepted in final form September 13, 2011)

(Published online February 27, 2012)

RTIL / Gd₂O₃ / Dextran / Biphasic extraction

Summary. The room temperature ionic liquid (RTIL), 1-butyl-3-methylimidazolium 2-(2-methoxyethoxy)ethyl sulfate was studied for its extraction behavior for ¹⁵⁹Gd in an environmentally benign liquid–liquid extraction system. The gadolinium oxide when dissolved in nitric acid and extracted in an RTIL/dextran biphasic system, was found to get completely extracted in the IL phase. The otherwise difficult to dissolve gadolinium oxide was found to have some solubility in the IL studied. Biphasic systems consisting of IL/dextran and certain IL/salt were studied for the extraction behavior of Gd₂O₃ dissolved in the above RTIL. A similar experiment was also done with acid-dissolved gadolinium oxide for comparison.

1. Introduction

Ionic liquids are emerging as green solvents for various chemical reactions. They are basically formed by a combination of large organic cations with a variety of anions and are intensively studied for potential applications as reaction media or for liquid–liquid extraction. Inherently they are non-aqueous, molten salts of organic type. Conventional molten salts exhibit a high melting point (*i.e.*, 801 °C for sodium chloride and 614 °C for lithium chloride), which greatly limits their use as solvents in most applications. RTILs, however, remain liquids at or below room temperature [1].

One of the primary driving forces behind research into ionic liquids is the perceived benefit of substituting traditional industrial solvents, most of which are volatile organic compounds (VOCs), with nonvolatile ionic liquids. Replacement of conventional solvents by ionic liquids would reduce the applications of VOCs, a major source of environmental pollution. Though ionic liquids are not intrinsically “green” they can be designed to be environmentally benign, with large potential benefits for sustainable chemistry. In recent years, people are increasingly interested in using ionic liquids (ILs) for analytical and separation processes due to their large liquid range and strong solubilising power and a number of

possible variations in cation and anion features which allow fine-tuning of the IL properties [2, 3]. As a pioneering work, aqueous two-phase extraction systems (ATPS) based on ionic liquids and water-structuring salts have been reported by Rogers and his co-workers for the first time in 2003 [4]. They also determined the phase diagrams for ATPSs based on different types of ionic liquids and the inorganic salts. Berthod and co-workers proposed a new aqueous two phase liquid system (ATPS) based on the ionic liquid 1-butyl-3-methylimidazolium chloride (BMIM Cl), potassium dibasic phosphate (K₂HPO₄) and water [5]. The full phase diagram of this ATPS was prepared and some tie lines were fully determined. Two countercurrent chromatography (CCC) columns were used to test the liquid phase retention of these ATPSs in all possible configurations. It was found that the BMIM Cl ATPS liquid phases were much easier to retain in the CCC columns. Using protein and alcohol solutes, it was established that the BMIM Cl ATPS has a polarity completely different from that of the polyethylene glycol (PEG) 1000 ATPS. A typical room temperature ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate [C₄mim][PF₆], was used as an alternative solvent to study liquid/liquid extraction of heavy metal ions. Dithizone was employed as a metal chelator to form neutral metal–dithizone complexes with heavy metal ions to extract metal ions from aqueous solution into [C₄mim][PF₆]. This extraction is strongly pH dependent, the extraction efficiencies of metal complexes were manipulated by tailoring the pH value of the extraction system [6]. To the best of our knowledge there has been no report with two phase systems consisting of IL/dextran.

Lanthanide extraction had been a subject of interest for many practical applications. Mixtures of chelating extractants and high molecular weight ammonium salts have been used for the synergistic extraction of lanthanides. Dukov *et al.*, studied the extraction of Pr, Gd and Yb with mixtures of 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone (HP) and several ammonium salts [7]. The effect of primary ammonium salts (tridecylammonium chloride, TDAHCl, and perchlorate, TDAHClO₄) on the extraction and separation of representative trivalent lanthanides (Pr, Gd and Yb) with HP (1-phenyl-3-methyl-4-benzoyl-5-pyrazolone) was also

* Author for correspondence (E-mail: kschem@caluniv.ac.in).

studied [8]. However, most extractions found in the literature involve organic solvents and reagents for extraction of lanthanides.

Rare earth oxides are also not very easy to dissolve. Very strong acids are required indeed to dissolve them properly for any chemical reaction to follow. The consequence that follows the dissolution in strong concentrated acids is that it is sometimes quite a problem to control the pH of the metal solution in different systems. Evaporation of the acid precipitates the required compound, neutralization with a base gives rise to a totally new compound. Literature review also indicates the emerging redox active drugs made of Moxetaxin Gadolinium (MGd) for cancer treatment. Gadolinium based contrast is popularly used in magnetic resonance imaging (MRI) [9]. The ^{159}Gd chosen for our study has important implications. Neutron Capture Therapy (NCT) for treatment has focused on using compounds containing Gd, which produces internal conversion and Auger cascade electrons upon absorbing thermal neutrons as ^{159}Gd is formed. Low energy Auger electrons are captured locally which significantly increase cell killing, when Gd binds to DNA. This isotope turns out to be favorable with an 18 h half life and low energy (580 ± 10 and 940 ± 15 keV) β emission. ^{159}Gd radionuclide therapy was found to produce more favorable dose distributions [10]. Dissolution of the lanthanide oxide and a subsequent drug development in a non acid media like the ILs might come out to be useful in handling and environmental concern.

Keeping in view the present days' need to design environmentally benign systems, the present article reports on the dissolution and extraction behavior of gadolinium oxide using an RTIL, 1-butyl-3-methylimidazolium 2-(2-methoxyethoxy)ethyl sulfate. Here we describe a nonconventional liquid–liquid biphasic system (none of the phases are organic solvents) for extraction of Gd using this RTIL. The IL in turn is water soluble or hydrophilic in nature. So if one has to design a biphasic system with this IL against another aqueous phase, the two phases should separate from one another. Only a few such conditions are possible, out of which certain salts with anions having high negative value of ΔG_{hyd} like sulphate, phosphate, carbonate, etc., are possible according to literature [11–13]. High molecular weight, water soluble organic compounds may also be used like dextrans. A close investigation of the chosen IL, 1-butyl-3-methylimidazolium 2-(2-methoxyethoxy)ethyl sulfate indicates that it has a good number of rotatable bonds (a bond is considered rotatable if it is single, not fixed by unsaturation, acyclic and not to a terminal atom) with a sulphate anionic part which is a hard Lewis base. This prompted us to find any interactions with a lanthanide which is hard Lewis acid keeping in mind a possible favorable hard–hard interaction. Biphasic systems consisting of IL/dextran and IL/salt were studied for the extraction behavior of Gd_2O_3 dissolved in the above RTIL. The similar experiment was also done with acid dissolved gadolinium oxide for comparison.

2. Experimental

2.5 mg of Gd_2O_3 was dissolved in 1 ml of the RTIL, 1-butyl-3-methylimidazolium 2-(2-methoxyethoxy)ethyl sulfate

(Sigma-Aldrich). The purity of the ILs was given to be $> 98\%$ with a water content of $< 1\%$. The solution was filtered through a Millipore filter paper of pore size $0.4 \mu\text{m}$. The filtrate was analyzed for dissolved Gd using ICPOES (Perkin Elmer, Optima 4300). 5 mg Gd_2O_3 was taken in a plastic capsule and irradiated for 2 h (at the BP3 facility) in the 2 MW research reactor of the Reactor Institute, Delft, The Netherlands, with a $4.26 \times 10^{16} \text{ nm}^{-2} \text{ s}^{-1}$ thermal neutron flux. 4 MBq of ^{159}Gd was produced. One such irradiated sample was cooled for 2 h and then dissolved in 2 mL concentrated nitric acid. 100 μL of this solution was added to the biphasic systems consisting of IL/dextran (11 000), IL/dextran (40 000), IL/ Na_2SO_4 , IL/ Na_2CO_3 and IL/ Na_3PO_4 . We have chosen dextran mainly because of two reasons. Firstly, as one of the phases is already ionic (IL), it would be interesting to see the behavior of the Gd in another ionic medium (salt) and in a neutral (dextran) phase. Dextran was chosen also because it is non toxic and biocompatible with potential medical applications. For example, dextran is used commonly by microsurgions to decrease vascular thrombosis. It is also used in some eye drops as a lubricant, and in certain intravenous fluids. Intravenous solutions with dextran function both as volume expanders and means of parenteral nutrition. If Gd is to be used for a medical purpose, dextran may be used as a potential medium directly after extraction in it.

The systems were allowed to equilibrate for 15 min in a rotator in closed vials and then allowed to settle for another 15 min. A 0.1 mL aliquot from each of the phases was collected and counted in a well type Ge Detector (Model no. GCW2022 having a resolution of 2.15 keV at FWHM and a relative efficiency of 13.6%).

Another Gd_2O_3 sample irradiated in the same way, was dissolved directly in 6.25 mL of the ionic liquid. This is done because our aim is to minimize the use of strong acids for dissolutions. Rare earths have the potential to get dissolved in certain ILs as oxides. Various biphasic systems for liquid–liquid extraction were made using IL/dextran and IL/salt combinations at different pH of the salt-rich phases and 0.1 mL IL solution containing ^{159}Gd . Extraction and measurement was done as before and compared with a standard prepared in the same way with only one phase. Measurement of γ -energy was done at the 363.5 keV peak with appropriate decay corrections.

3. Results and discussion

Two phase systems other than aqueous/organic type have been considered to form as a result of the combination of several factors *viz.*, unfavorable interaction of enthalpy arising from interaction of unlike structure of the compounds, differences in the hydrogen bond orientation in the two phases or simple salting out phenomenon [14–18]. The systems IL/dextran and dextran/salt chosen in our study respond well towards partitioning of ^{159}Gd depending on the speciation of Gd in the medium. The solubility of Gd_2O_3 in the IL as measured in ICPOES was found to be 1.25 mg/mL. Considering the fact that the lanthanides and specially lanthanide oxides have poor solubilities in many common media including certain ionic liquids and the kinet-

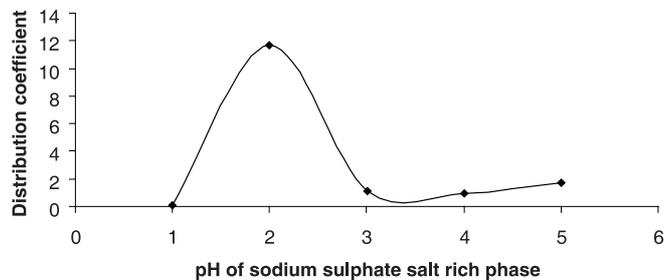
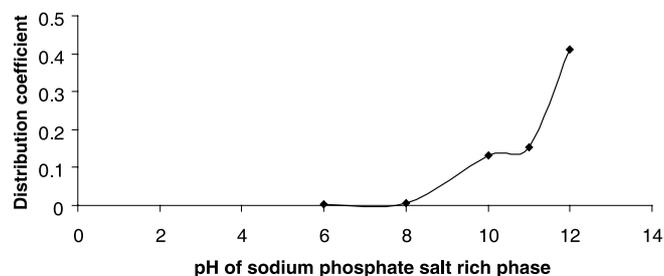
Table 1. Acid dissolved ^{159}Gd extraction using IL/dextran and IL/ salt biphasic systems.

System	Extraction in IL, %	Distribution coefficient, K_D	Final pH	Expected Gd species (from CHEAQS)
IL/Dextran (11 000)	100	25 000	0.5	$\text{Gd}(\text{NO}_3)^{+2}$
IL/Dextran (40 000)	100	28 500	1.4	$\text{Gd}(\text{NO}_3)^{+2}$
IL/ Na_2SO_4 (2M)	0.07	0.008	1.8	$\text{Gd}(\text{SO}_4)_2^-$
IL/ Na_2CO_3 (2M)	0	0.001	10	$\text{Gd}(\text{CO}_3)_2^-$
IL/ Na_3PO_4 (2M)	18.8	2.142	10	GdPO_4

ics are highly dependent on the chain length of the organic moiety containing the cation and also on the nature of the anion. To see the kinetics of solubility, the experiment was done after 5 min and 24 h of contact time. The solubility was found to be same after both the time intervals.

When the irradiated Gd_2O_3 was dissolved in concentrated HNO_3 gadolinium remains as $\text{Gd}(\text{NO}_3)^{+2}$ in solution and this was indicated by the theoretical calculations by ‘‘CHEAQS’’ [19]. The CHEAQS programme uses ‘‘NIST database 46 version 8.0’’ for calculating the equilibrium constant data for gadolinium. The extraction behavior of this Gd species in our biphasic systems shows that 100% of ^{159}Gd was extracted in the IL phase from dextran rich phase. Since ‘‘like favours like’’, the cationic form of $\text{Gd}(\text{NO}_3)^{+2}$ partitions in the IL phase of the IL/dextran system. Since dextran is a complex, branched glucan (polysaccharide made of many glucose molecules) the cationic species of gadolinium prefers the ionic liquid phase rather than the neutral dextran phase. When the nitric acid solution of gadolinium was taken in a biphasic system with IL/ Na_2SO_4 (2M), IL/ Na_2CO_3 (2M) and IL/ Na_3PO_4 (2M), most of the ^{159}Gd reports to the salt-rich phase excepting a little ($\sim 18\%$) in the IL when sodium phosphate was used as the salt rich phase (Table 1). It could be formulated from speciation program CHEAQS, that gadolinium remains as anionic $\text{Gd}(\text{SO}_4)_2^-$ in the sodium sulphate-salt-rich phase. The results of extraction indicate that this anionic form prefers the water structuring salt-rich phase and not in the molten salt IL system. Kosmotropic ions (e.g., PO_4^{-3} , CO_3^{-2} , SO_4^{-2}) have large negative Gibbs free energies of hydration (ΔG_{hyd}), indicating strong interactions with H_2O , and are thus water-structuring. Chaotropic ions have weak and unfavorable interactions with H_2O (slightly negative to positive ΔG_{hyd}) and are considered to be water-destructuring. The anionic species $\text{Gd}(\text{CO}_3)_2^-$ present in the sodium carbonate salt-rich phase also seems to prefer the kosmotropic phase. However, a small fraction of the neutral GdPO_4 species gets extracted in the IL phase from sodium phosphate salt-rich phase indicating a lower affinity for the water structuring phase.

When the irradiated Gd_2O_3 was dissolved directly in the ionic liquid, the extraction was found to follow a different trend. When the IL solution of Gd_2O_3 was extracted in the IL phase of the biphasic system, extraction was found to increase at certain pH of the salt rich phase (Figs. 1 and 2). For

**Fig. 1.** Extraction profile of IL dissolved Gd with pH of Na_2SO_4 .**Fig. 2.** Extraction profile of IL dissolved Gd with pH of Na_3PO_4 .**Table 2.** IL dissolved ^{159}Gd extraction using IL/dextran and IL/salt biphasic systems.

System	Extraction in IL, %	Distribution coefficient, K_D	Final pH	Possible Gd species
IL/Dextran (11 000)	10.5	3.5		
IL/Dextran (40 000)	11	4.1	4.5	$\text{Gd}_2(\text{SO}_4)_3$
IL/ Na_2SO_4 (2M)	1.5	0.9		
IL/ Na_2CO_3 (2M)	2	1.1		
IL/ Na_3PO_4 (2M)	32	9.5		

the Na_2CO_3 salt-rich phase, extraction studies with varied pH conditions could not be done because of absence of distinct phases with change of pH. However, variation of pH of the salt rich phases, Na_2SO_4 and Na_3PO_4 yields some better extraction of ^{159}Gd in the IL phase. With the IL/dextran systems it was found that only $\sim 11\%$ of ^{159}Gd could be extracted in the IL phase indicating some association between Gd and dextran molecules (Table 2). The pH of the IL phase after extraction experiments in this case was found to remain the same (4.5) as that of the original ionic liquid. This result also implies that the Gd_2O_3 on dissolution in the IL may not result in an ionic species and hence the major portion reports to the nonionic dextran rich phase. As the anionic part of the IL used is sulphate, the most probable form of Gd in the dextran-rich phase would be $\text{Gd}_2(\text{SO}_4)_3$. This conclusion is subject to further characterizations.

4. Conclusion

The present investigation reveals that the ionic liquid 1-butyl-3-methylimidazolium 2-(2-methoxyethoxy)ethyl sul-

fate can be used successfully for the dissolution as well as extraction of gadolinium oxide under varying conditions. Extraction patterns against some kosmotropic salts have been reported under different pH conditions along with that against a neutral organic compound dextran. The 100% extractability of ^{159}Gd in dextran from the RTIL suggests a potential clean separation media that can have direct medical applications in the future. Keeping in view the fact that the ionic liquids are emerging novel separation media, this study adds new evidences to the current literature and expand our understanding of the chemistry of lanthanides in RTILs.

Acknowledgment. The authors gratefully acknowledge the help of Mehmet Sarilar, RID, Delft University of Technology, for obtaining data in the Ge detector.

References

1. Visser, A. E., Swatloski, R. P., Reichert, W. M., Mayton, R., Sheff, S., Wierzbicki, A., Davis, J. H., Rogers, R. D.: Task-specific ionic liquids incorporating novel cations for the coordination and extraction of Hg^{2+} and Cd^{2+} : synthesis, characterization, and extraction studies. *Environ. Sci. Technol.* **36**, 2523 (2002).
2. Pandey, S.: Analytical applications of room-temperature ionic liquids: a review of recent efforts. *Anal. Chim. Acta* **556**, 38 (2006).
3. Pei, Y. C., Wang, J. J., Xuan, X. P., Fan, J., Fan, M. H.: Factors affecting ionic liquids based removal of anionic dyes from water. *Environ. Sci. Technol.* **41**, 5090 (2007).
4. Bridges, N. J., Gutowski, K. E., Rogers, R. D.: Investigation of aqueous biphasic systems formed from solutions of chaotropic salts with kosmotropic salts (salt–salt ABS). *Green Chem.* **9**, 177 (2007).
5. Ruiz-Angel, M. J., Pino, V., Carda-Broch, S., Berthod, A.: Solvent systems for countercurrent chromatography: an aqueous two phase liquid system based on a room temperature ionic liquid. *J. Chromatogr. A* **1151**, 65 (2007).
6. Wei, G. T., Yang, Z., Chen, C. J.: Room temperature ionic liquid as a novel medium for liquid/liquid extraction of metal ions. *Anal. Chim. Acta* **488**, 183 (2003).
7. Dukov, I., Genov, L.: Synergistic solvent extraction of lanthanides with mixtures of 1-phenyl-3-methyl-4-benzoyl pyrazol-5 one and tri-*n*-octylamine. *Solvent Extr. Ion Exch.* **6**, 447 (1989).
8. Dukov, I. L., Jordanov, V. M.: Synergistic solvent extraction of lanthanides with mixtures of 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone and primary ammonium salts. *Hydrometallurgy* **48**, 145 (1998).
9. Richards, G. M., Mehta, M. P.: Motexafin gadolinium in the treatment of brain metastases. *Expert Opin. Pharmacother.* **8**, 351 (2007).
10. Timothy, G. J.: A comparison of three gadolinium based approaches to cancer therapy. Thesis (Ph.D.), Massachusetts Institute of Technology, Dept. of Nuclear Engineering (2002), <http://hdl.handle.net/1721.1/30001>.
11. Rogers, R. D., Bond, A. H., Bauer, C. B.: Metal ion separations in polyethylene glycol-based aqueous biphasic systems. *Sep. Sci. Technol.* **28**, 1091 (1993).
12. Shibukawa, M., Nakayama, N., Hayashi, T., Shibuya, D., Endo, Y., Kawamura, S.: Extraction behaviour of metal ions in aqueous polyethylene glycol-sodium sulfate two-phase systems in the presence of iodide and thiocyanate ions. *Anal. Chim. Acta* **427**, 293 (2001).
13. Walter, H., Brooks, D. E., Fischer, D.: *Partitioning in Aqueous Two Phase Systems. Theory, Methods, Uses and Applications to Biotechnology.* Academic Press, Orlando, FL (1985), p. 185.
14. Abbott, N. L., Blankschein, D., Hatton, T. A.: On protein partitioning in two-phase aqueous polymer systems. *Bioseparation* **1**, 191 (1990).
15. Karlström, G. A.: New model for upper and lower critical solution temperatures in poly(ethylene oxide) solutions. *J. Phys. Chem.* **89**, 4962 (1985).
16. Albertsson, P. A.: *Partition of Cell Particles and Macromolecules.* 3rd Edn., Wiley, New York (1986), p. 22.
17. Rogers, R. D., Eiteman, M. A. (eds.): *Aqueous Biphasic Separations: Biomolecules to Metal Ions.* Plenum, New York (1995), p. 31.
18. Ananthapadmanabhan, K. P., Goddard, E. D.: A correlation between clouding and aqueous biphasic formation in polyethylene oxide/inorganic salt systems. *J. Colloid Interface Sci.* **113**, 294 (1986).
19. Verweij, W.: CHEAQS PRO: a program for calculating chemical equilibria in aquatic systems, see <http://home.tiscali.nl/cheaqs/> (2005).