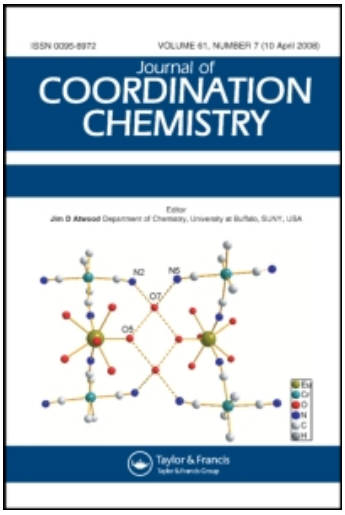

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Synthesis and characterisation of strontium carboxylates formed at room temperature and under hydrothermal conditions

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Synthesis and characterisation of strontium carboxylates formed at room temperature and under hydrothermal conditions

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A novel method was developed for the synthesis of highly pure strontium complexes in high yield. Syntheses proceeded along three pathways with optimum conditions being at $T = 120$–140°C, a base : acid ratio of 1.2 and 15 min reaction-time in an autoclave vessel. Large crystals were readily obtained within hours. The crystal structures of strontium *R*-glutamate hexahydrate (I) and strontium di(hydrogen *S*-glutamate) pentahydrate (II) were determined by X-ray powder diffraction methods at 295 K with Rietveld refinement (I: Space group $P2_12_12_1$, $Z = 4$, $a = 7.3519(2)$, $b = 8.7616(2)$, $c = 20.2627(5)$ Å; II: Space group $P2_1$, $Z = 2$, $a = 8.7243(1)$, $b = 7.2635(1)$, $c = 14.6840(2)$ Å, $\beta = 100.5414(7)^{\circ}$). Synthesis at room temperature provided four additional new strontium compounds that may be applicable as constituents of pharmaceutical products for the treatment of bone conditions.

Keywords: Strontium; Caboxylates; Amino acids; Anions; X-ray diffraction

1. Introduction

In Group II of the Periodic Table, chemical properties of the elements change systematically from Mg to Ba. The lightest elements Mg and Ca occur ubiquitously and are essential minerals in all biological systems, playing important roles in numerous enzyme and cellular mechanisms. The heavier elements, Sr and Ba are rarer, and they do not appear to have any significant role in biological systems. High levels of Ba are considered to be harmful for human health with a WHO health limit of 0.7 ppm for drinking water [1]. The physiological properties of Sr are not yet fully understood, and the metal is generally considered to be benign with respect to human health. In the environment Sr typically occurs in conjunction with Ca. Accordingly, Sr is a significant constituent of drinking water of appreciable hardness, or in calcium-rich foods such as dairy products. Since strontium is a natural component of the diet, it will be taken up in the body. Several studies have revealed that ionic strontium is taken up in the

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gastrointestinal tract and excreted in the kidneys by the same transport mechanisms as calcium [2]. As with calcium, the major part (up to 99%) of strontium retained in the mammalian body is localized in the skeleton. This has led to speculation, from the beginning of the 20th century, that strontium may have some beneficial effects, especially in mineralized tissues such as dentine and bone [3, 4]. Subsequently, *in vitro* and *in vivo* studies have been performed to assess the potential of strontium in promoting bone strength and as a potential prophylactic or therapeutic agent in metabolic bone diseases such as osteoporosis. These investigations have yielded an overwhelming body of evidence in support of a positive role for strontium in promoting an increase in bone strength and quality. However, the physiological mechanisms of action of strontium have not been fully established. These investigations have also led to a growing interest in the synthesis of new strontium salts, such as strontium ranelate [5], applicable for pharmaceutical use. In turn this also means that methods of synthesis of coordination compounds of strontium that provide products of high yield and of high purity may be of commercial interest.

In nature, strontium exists as a divalent cation and consequently is found as a salt, or complexed with either inorganic or organic anions. Generally, the strontium salts studied show properties very similar to the corresponding salts of other alkaline earth metals. Several studies of coordination compounds containing strontium have been reported in the literature [6]. According to the Cambridge Crystallographic Database, the number of structures of strontium compounds is rather limited, while corresponding compounds of magnesium and calcium are more abundant. Strontium salts containing small organic anions are frequently obtained by mixing strontium hydroxide with the appropriate organic acid and allowing solutions to evaporate at room temperature [5, 7–9]. However, the yields obtained by this method are low, being approximately 20% for strontium *S*-glutamate [5] or strontium malonate [7], for example. A slightly higher yield (46%) could be obtained by high temperature synthesis of strontium oxalate in an autoclave [10]. Only in rare cases has a yield of more than 60% been reported, as in the synthesis of strontium citrate [8]. Synthesis of strontium coordination compounds with larger ligands is facilitated by using non-aqueous solvents that may give yields of around 50% [11]. A yield of this magnitude is generally not satisfactory for large-scale production of salts, owing to expenses involved in purification. For contemplated pharmaceutical use, it is of paramount importance that reaction products be obtained in high and consistent purity. For such use, organic acid salts of strontium may be particularly desirable, and thus there is a need for an improved synthetic methods and understanding of the chemical properties of carboxylic acid salts of strontium.

In principle, the synthesis of strontium salts is uncomplicated and can be performed along one of the three straightforward pathways. Reaction of strontium hydroxide with an acid or strontium chloride with the sodium salt of the corresponding base has been used [12]. Salts may also be obtained by the reaction of the acid and strontium carbonate. Such routes have been applied to give large crystals that could be used for structure determination by X-ray crystallography [13–15]. However, the apparent ease of preparation and obtained yields and purities were not previously documented and no methods are available for production of the salts with high yield on a commercial scale. The aim of the present work is to investigate the possibility of optimising synthetic routes and to elucidate mechanisms of reaction. Salts obtained were characterised by X-ray powder diffraction.

2. Experimental

The chemicals used for the syntheses, $Sr(OH)_2 \cdot H_2O$, $SrCO_3$, *S*-glutamic acid, *R*-glutamic acid, $SrCl_2 \cdot 6H_2O$, disodium *S*-glutamate, malonic acid, *S*-ascorbic acid, salicylic acid and sodium ibuprofenate were obtained from commercial sources and used as received. Solutions were prepared by dissolution in Millipore water (>18 MΩ resistance). Optimised syntheses were performed using an autoclave vessel (CertoClav, Austria) at temperatures up to 140°C and pressures of 2 hPa.

In order to monitor structure and purity, all salts were subjected to X-ray powder diffraction analysis. Powder diffraction data were collected on a Huber G670 imaging plate Guinier camera using Cu-Kα1 radiation ($\lambda = 1.54051$ Å) and data were recorded between $3 < 2\theta < 100°$ in 2θ with an exposure time of one hour. Raw data was subjected to background subtraction prior to Rietveld refinement, while original diffraction patterns were used for weighting. Refinements were started with parameters from single-crystal data collected at 120 K, employing split *pseudo*-Voigt peak and Chebyshev background functions. For both structures isotropic thermal parameters (one for Sr, one for each glutamate and one for the water molecules) were refined. For strontium bis-(hydrogen-*S*-glutamate) pentahydrate, the coordinates of Sr and water molecules were refined. Further crystallographic and refinement details are given in table 1.

A Perkin-Elmer M2100 instrument equipped with a deuterium lamp for background correction was used to measure strontium contents of the products. Strontium was measured at 460.7 nm using a lamp current of 20 mA; the ethylene flow rate was 8 L min^{-1} and air was supplied at a flow rate of 2.9 L min^{-1}.

Table 1. Crystallographic and Rietveld refinement data for strontium *R*-glutamate hexahydrate (**1**) and strontium di(hydrogen-*S*-glutamate) pentahydrate (**2**).

	1	**2**
Temperature (K)	295	295
Crystallographic data		
Space group	$P2_12_12_1$	$P2_1$
Z	4	2
Unit cell (Å, °)		
a	7.3519(2)	8.7242(1)
b	8.7616(2)	7.2635(1)
c	20.2627(5)	14.6840(2)
β		100.5415(7)
V (Å^3)	1305.2(1)	914.80(4)
Powder diffraction data		
2θ interval (°)	7–100	4–100
No. of observations	9300	9600
Bragg reflections	813	1114
Refined parameters	25	46
R_p (%)	11.5	11.9
R_{wp} (%)	11.6	12.6
GoF	1.4	6.5
R_{Bragg} (%)	7.3	7.7

3. Results and discussion

In initial experiments, we investigated the influence of key parameters in the synthesis. Reaction products consisting of chloride or hydroxide salts of strontium, and the desired anion in free acid or sodium salt form were dissolved and mixed in aqueous media. Precipitation at room and at high temperature generally resulted in incomplete reaction and low yields. It was found that high temperatures and alkaline conditions resulted in improvements in both yield and purity.

$$CO_2(g) + H_2O(l) \rightarrow HCO_3^-(aq) + H^+(aq) \quad (1)$$

$$Sr^{2+}(aq) + HCO_3^-(aq) \rightarrow SrCO_3(s) + H^+(aq) \quad (2)$$

$$Sr^{2+}(aq) + C_5H_9NO_4^-(aq) + 5H_2O(l) \rightarrow Sr(C_5H_8NO_4)_2 \cdot 5H_2O(s) + H^+(aq) \quad (3)$$

According to equations (1)–(3) alkaline conditions drive the equilibria to the right, favouring formation of the desired product as well as strontium carbonate impurity. Crystals of the carbonate salt gradually sink to the bottom of the beaker, consuming substantial amounts of strontium from solution. Accordingly, recrystallisation of strontium salts under normal atmospheric conditions followed by filtering increases the risk of formation of strontium carbonate. This may be circumvented by performing the synthesis in closed vessels without carbon dioxide in the surrounding atmosphere.

As outlined in table 2, temperature, time of reaction, concentration ratios and total volume were varied in the indicated ranges with the aim of optimizing synthesis conditions. As a representative example, reaction conditions were evaluated using strontium glutamate as a model compound. In order to obtain a successful synthesis, the salt was prepared by using three different sets of reagents and it was found that a number of conditions should be controlled in the process. In the first series of experiments, 0.12 mol of strontium hydroxide octahydrate was added to a glass bottle (100 cm^3) containing 0.1 mol of *R*-glutamic acid and 75 cm^3 L of Millipore water. After mixing, the lid was mounted on the bottle without tightening it too much, to allow liberation of steam in the autoclave. At this stage of the synthesis, concentrations exceeded the aqueous solubility of the material, and the reaction mixture was a white suspension. The bottles were heated in an autoclave at 140°C for 15 min. Steam was vented and the product of strontium was filtered hot. Results were obtained through

Table 2. Optimised conditions for the synthesis of strontium coordination compounds by three comparable methods, (a) reaction of strontium hydroxide octahydrate with the appropriate acid; (b) reaction of strontium carbonate with the appropriate acid; (c) reaction of strontium chloride hexahydrate with the sodium salt of the appropriate anion.

Strontium salt	*T* (°C)	Method
R-glutamate hexahydrate	140*	a
Bis-(hydrogen-*S*-glutamate) pentahydrate	120*	c
Salicylate monohydrate	25–40	b
Malonate sesquihydrate**	25–75	b
Diascorbate dihydrate	25–40	b
Diibuprofenate dihydrate	25–40	c

* Autoclavate. ** Transforms irreversibly in solution to the anhydrous form.

nine experiments where strontium dihydroxide octahydrate and *S*-glutamic acid were used as reactants, as shown in table 3. Optimum conditions thus obtained were applied to the synthesis of other strontium compounds and yields obtained fell in the range of 85–100%. Thus, in order to increase the yield of other salts, individual optimisations may be required.

In a second series of experiments, 0.1 mol of strontium chloride hexahydrate and 0.1 mol of disodium *S*-glutamate were mixed as described for the synthesis of strontium *R*-glutamate but the temperature did not exceed 120°C during one 15 min autoclave run. At temperatures up to 130°C mixed forms of hydrogen glutamates were obtained while higher temperatures yielded predominantly the pure strontium *S*-glutamate hexahydrate [5]. It was found that the synthesis was not limited to strontium glutamate but gave high yields of a number of similar coordination compounds including strontium malonate [7], strontium tartrate [12], strontium oxalate [10], strontium maleate [9], strontium citrate [8] and strontium *S*-aspartate [16]. The short reaction time and high yield are of the advantages of the autoclave method, but another advantage is the possibility of adding reactants in an undissolved state; this may be convenient for production on an industrial scale. Some salts decomposed upon further heating (the melting points of strontium *R*-glutamate and of strontium bis-(hydrogen-*S*-glutamate) were determined as 81 and 112°C, respectively).

All the compounds listed above could also be synthesised by slowly adding powdered strontium carbonate to a solution of the appropriate acid dissolved in water at 40°C. These conditions produced the novel salts strontium malonate sesquihydrate, strontium ibuprofenate and strontium salicylate, which could be crystallised from solution at room temperature. Structures were resolved by single-crystal X-ray methods [13]. Strontium malonate sesquihydrate irreversibly loses its crystal water by heating to 75°C and anhydrous strontium malonate similar to the product obtained by autoclaving precipitates upon cooling. Thus, anhydrous strontium malonate could be produced by boiling the solution after controlled reaction of strontium carbonate and the acid at room temperature. The synthesis of strontium (+)-ascorbate was not possible to perform by autoclaving, due to the instability of ascorbic acid. Distrontium di-(+)-ascorbate tetrahydrate was also obtained by reaction of strontium carbonate with (+)-ascorbic acid in solution but the product was highly soluble, resulting in formation of a thick syrups after addition of large amounts of reactants to water at 40°C. Drying the yellow-coloured syrup in a desiccator initiated crystallisation after

Table 3. Yield of strontium *S*-glutamate as a function of conditions applied during the optimisation of autoclave synthesis using *S*-glutamic acid and strontium hydroxide octahydrate. These results were obtained in nine experiments and the optimum conditions were identified as $T = 133$°C, time = 15 min, base/acid ratio = 1.2 and $V = 50\,cm^3$. The conditions were confirmed as optimal, providing a yield of close to 100%.

T (°C)	Yield/T (%)	Time (min)	Yield/time (%)
124	69	15	106
130	57	30	103
133	89	60	84
Base/acid ratio	Yield/base/acid ratio (%)	Volume (cm^3)	Yield/volume (%)
0.8	84	50	99
1	103	75	84
1.2	107	100	105

24 h to give a white crystalline powder. The yellowing observed in reaction mixtures above 50°C is due to decomposition; mixtures containing mainly strontium oxalate were obtained.

After each synthesis, the strontium content of the salts was quantified by FAAS to establish the purity of the products. Before weighing, the salts were dried at 110°C for one hour. The purity and the homogeneity of the products were determined by powder X-ray crystallography during the optimisation steps. Total yield measured after drying and strontium contents were used as quality parameters during process optimisation. Total yield was close to 100% in most experiments. Figure 1 shows powder diffractograms of strontium *R*-glutamate hexahydrate and strontium di(hydrogen-*S*-glutamate) pentahydrate. The diffractograms show no evidence of other crystalline compounds. Additional salts synthesised by the optimised method were also characterised by X-ray powder diffraction and are readily identified as pure compounds [4, 6, 9–11] in yields close to 100%.

Other reactions, such as decarboxylation, may occur, and this can result in reduced yield and purity of the desired salts. The extent of decarboxylation notoriously depends on the pH of the solution, temperature and pressure. Hence, these parameters must be carefully controlled during reaction. The process may be illustrated by the decarboxylation of glutamic acid, according to equation (4).

$$\begin{aligned} &HOOC(CH_2)_2CHNH_2COO^-(aq) + H^+(aq) \longrightarrow \\ &CO_2(g) + HOOC(CH_2)_2CH_2NH_2(aq) \end{aligned} \tag{4}$$

Temperatures above 100°C favour the yield of the strontium compound but at temperatures of 240°C or above, as previously applied to the synthesis of strontium oxalate [10], yield decreased to less than 50%. This may also explain the relatively low yields reported with syntheses in organic solvents at lower temperatures [6, 11]. When glutamic acid and strontium chloride were the reactants, the pH of the reaction mixture was relatively low; enhancing the risk of decarboxylation. However, short synthesis times, high pH (glutamate rather than glutamic acid) and elevated pressures counteract decarboxylation and ensure a high yield.

Carboxylates of divalent earth metals such as strontium, and dicarboxylic acids in particular, have unique properties and form complexes in solution [17]. Such complexation may be important in biological systems, where the alkaline earth metals, especially calcium and magnesium, play vital physiological roles. A majority of the divalent metal ions may exist in complex-bound forms in aqueous biological systems. However, formation constants with the alkaline earth metals in aqueous solution are higher for amino acids than for hydroxycarboxylic acids and related non-carboxylic acids, suggesting that the amino group plays a role in complex formation. Generally, differences in association constants and hydration enthalpies for the various ligands become smaller as the radius of the metal ion increases. The difference in experimental conditions of synthesis of the product compounds from either strontium carbonate or strontium hydroxide most likely is related to the difference in enthalpy of hydration of the anions. This would explain the observed low yield that was obtained when the synthesis was performed at room temperature using strontium hydroxide. Thus, the stability of strontium complexes with a dicarboxylic acid is lower than the stability of the comparable complexes with calcium and magnesium ions. This means that in aqueous solution the chelating dicarboxylic acids

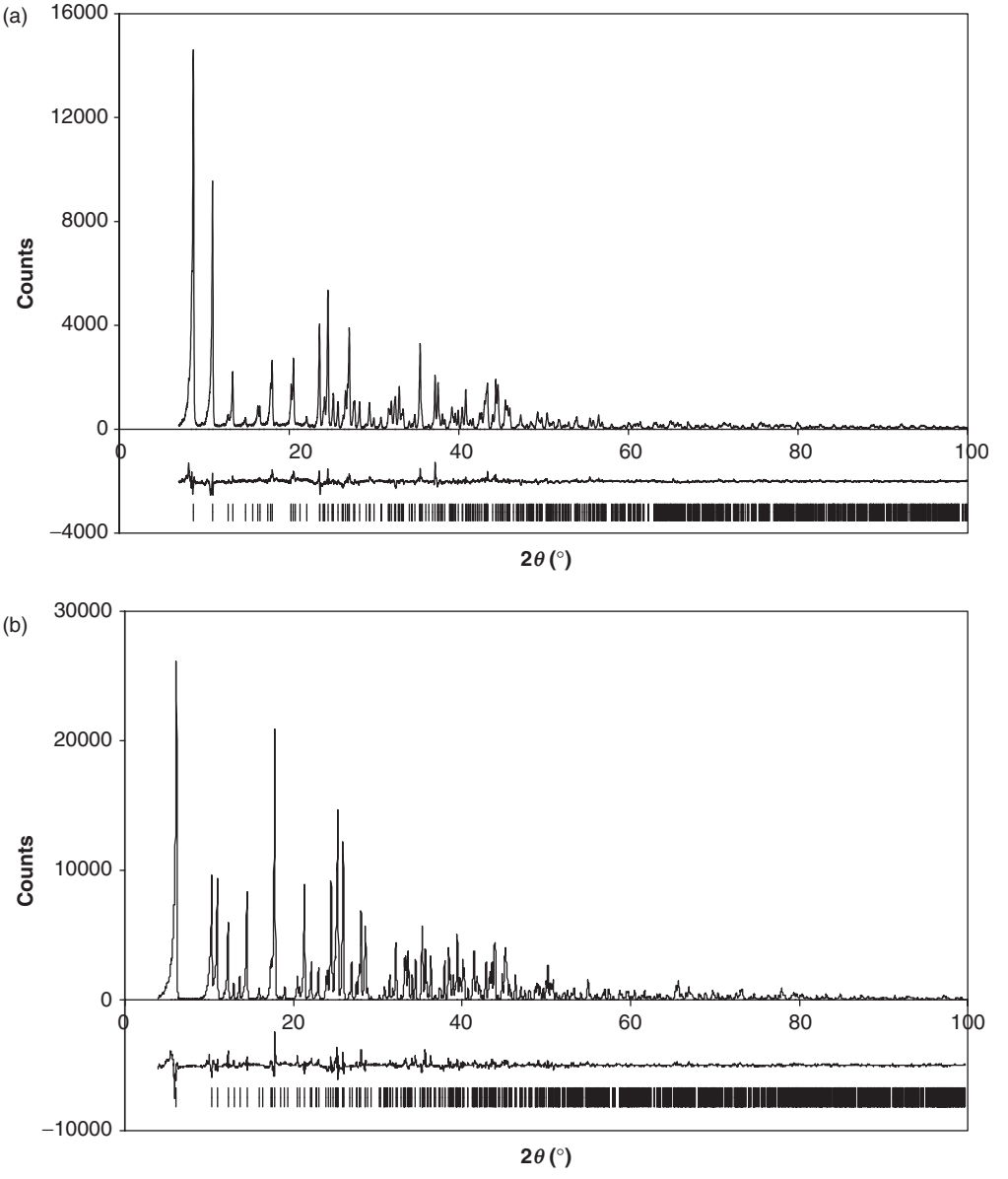

Figure 1. (a) X-ray powder diffraction pattern of strontium *R*-glutamate hexahydrate; top: background subtracted pattern; centre: final difference pattern; bottom: Bragg peak positions. (b) X-ray powder diffraction pattern of strontium di(hydrogen-*S*-glutamate) pentahydrate; top: background subtracted pattern; centre: final difference pattern; bottom: Bragg peak positions.

will have a propensity to preferentially bind calcium and magnesium rather than strontium (or barium). Accordingly, the new short time and high yield and purity method described in this report may have particular relevance for larger metal ions such as Sr(II).

4. Conclusions

An optimised synthesis for generation of organic strontium salts in high yield and purity is outlined. Furthermore, a new route is disclosed for the synthesis of strontium coordination compounds of particular relevance for production of strontium salts of temperature-sensitive organic anions. High yield was promoted by slowly adding solid powdered strontium carbonate to a solution of the appropriate acid at room temperature. However, following this pathway of synthesis by applying strontium hydroxide octahydrate instead of the carbonate reduced considerably the yield. Application of strontium hydroxide to the synthesis was optimised and it was determined that the products could also be obtained in high yield when reactants in alkaline solution were treated by autoclaving at temperatures between 120 and 140°C at pressures of 1–2 bars. By applying these conditions, the reactants could be mixed in water without prior dissolution. The time of reaction could be reduced to 15 min. Temperature was found to be the key parameter for the synthesis and strontium bis-(hydrogen-*S*-glutamate) pentahydrate was obtained at temperatures below 120°C from strontium chloride while strontium *S*-glutamate hexahydrate was obtained at higher temperatures. Strontium malonate sesquihydrate was obtained by reaction of strontium carbonate with malonic acid at temperatures below 75°C. At 75°C, the sequihydrate transforms into the anhydrous malonate. Strontium salicylate and strontium ascorbate were obtained at lower temperatures but degraded on heating above 50°C. In contrast to most of the salts, the solubility of strontium ascorbate is extremely high in water, and crystals were only obtained after carefully drying the highly concentrated syrup-like solutions obtained.

Acknowledgements

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References

[1] http://www.who.int/water_sanitation_health/dwq/chemicals/en/barium.pdf
[2] S.C. Verberckmoes, M.E. De Broe, P.C. D'Haese. *Kidney Intl*., **64**, 534 (2003).
[3] R. Barto, A.J.A.M. Sips, W.J.F. van der Vijgh, J.C. Netelenbos. *Clin. Chem*., **41**, 1159 (1995).
[4] I. Schrooten, G.J.S. Behets, W.E. Cabrera, S.R. Vercauteren, L.V. Lamberts, S.C. Verberckmoes, A.J. Bervoets, G. Dams, W.G. Goodman, M.E. De Broe, P.C. D'Haese. *Kidney Intl*., **63**, 927 (2003).
[5] H. Schmidbaur, I. Bach, D.L. Wilkinson, G. Müller. *Chem. Ber*., **122**, 1433 (1989).
[6] N. Miyoshi. *Science of Synth*., **7**, 685 (2004).
[7] B. Briggman, A. Oskarsson. *Acta Cryst*., **B33**, 1900 (1977).
[8] D.E. Zacharias, J.P. Glusker. *Acta Cryst*., **C49**, 1732 (1993).
[9] G.D. de Delgado, P.P. Parra, A. Briceño, J.M. Delgado. *J. Chem. Cryst*., **25**, 241 (1995).
[10] D.J. Price, A.K. Powell, P.T. Wood. *Polyhedron*, **18**, 2499 (1999).
[11] B.-J. Bae, J.T. Park, I.-H. Suh. *J. Organomet. Chem*., **648**, 214 (2002).
[12] A.R. Patel, S.K. Arora. *J. Mat. Sci*., **11**, 843 (1976).
[13] S. Christgau, J. Oddershede, K. Ståhl, J.E.T. Andersen. *Acta Cryst*., **C61**, 259 (2005).
[14] B. Paluchowska, J.K. Maurin, J. Leciejewicz. *Acta Cryst*., **C52**, 342 (1996).
[15] B. Paluchowska, J.K. Maurin, J. Leciejewicz. *Acta Cryst*., **C53**, 287 (1997).
[16] H. Schmidbaur, P. Mikulcik, G. Müller. *Chem. Ber*., **123**, 1599 (1990).
[17] Z.F. Fei, T.J. Geldbach, D.B. Zhao, R. Scopelliti, P.J. Dyson. *Inorg. Chem*., **44**, 5200 (2005).