

Effect of Surface Scraping on Chiral Symmetry in Seeded Cooling Crystallization of Sodium Chlorate

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Abstract

We report, for the first time, that the number of nuclei with opposite handedness to seed is directly related to the amount of scraping generated between baffle edge and wall surface in an oscillatory baffled crystalliser (OBC) and reaches an asymptotical maximum of 43.4 %, when primary nucleation events due to scraping dominate over secondary nucleation by seeding in a daylong operation. The 6.6 % shortfall to the theoretical symmetry of 50 %:50 % of dextrorotatory to laevorotatory crystals could be a quantitative indication of the remaining effect of secondary nucleation. We examine the effect of scraping durations at a fixed seeding time and the effect of seeding times at a fixed oscillation period on chiral symmetry. Based on our experimental data, the rate of primary nucleation events due to scraping and the rate of secondary nucleation due to seeding are evaluated. We show that the relative importance of primary to secondary nucleation in seeded cooling crystallisation of sodium chlorate can be varied by the amount of scraping in the OBC.

Introduction

Mirror symmetry exists extensively in nature from elementary particles to large biological molecules and understanding how biological molecules exist only as one of the two mirror enantiomers (e.g. left-handed amino acids, right-handed sugars) has attracted intense interest since the 19th Century. In 1898, Kipping and Pope¹ measured the handedness of 3,137 sodium chlorate crystals from 46 separate crystallisation tests and showed 50.08 %:49.92 % of dextrorotatory (R) to laevorotatory (L) crystals. This was well within the statistical error of the unbiased 50 %:50 % distribution they anticipated.

Kondepudi et al.² repeated the work of Kipping and Pope and obtained equal numbers of left- and right-handed crystals in evaporation crystallisation of sodium chlorate through a non-stirred spontaneous nucleation. On the introduction of stirring at 100 rpm, however, >99 % of crystals displayed a single enantiomorphism. They explained that this chiral symmetry breaking on stirring was due to secondary nucleation in which a “mother crystal” was struck by the stirrer to clone secondary nuclei that have the same chirality as their “mother”. Total symmetry breaking achieved in massive instantaneous primary nucleation was revealed by Viedma,³ broadened the mechanism proposed by Kondepudi et al.^{2, 4, 5} in that the real chiral symmetry breaking occurs in the first steps of the primary nucleation, whereas secondary nucleation only amplifies the symmetry breaking, known as Viedma ripening. This effect has also been observed for molten crystallisation.⁶ Further studies have demonstrated that chiral symmetry breaking can be achieved by grinding and abrasive motions between glass balls and nuclei⁷, ultrasonic fields^{8, 9}, lasers^{10, 11}, cavitation¹², temperature gradients under boiling¹³, the presence of a co-solute or other additives¹⁴⁻¹⁷ and heating-cooling cycles.^{18, 19}

Callahan and Ni (2012)^{20, 21} repeated the work of Denk and Botsaris (1972)²² in seeded cooling crystallisation of sodium chlorate at a fixed supercooling of 1 °C in both a stirred tank crystalliser (STC) and an oscillatory baffled crystalliser (OBC); mixing in the latter is generated by moving a set of orifice baffles up and down the column.²³ They obtained the same results in the STC where 100 % of crystals displayed a single enantiomorphism when seeded with either a L or R crystal, however, 10 - 20 % of crystals with the opposite handedness were identified when the same tests were repeated in the OBC. Callahan and Ni credited this finding to primary nucleation that took place during scraping between the outer edges of the baffles and the inner surface of the column wall; local hot spots were generated, leading to local higher supersaturation and the birth of R nuclei when seeded with L crystal and vice versa.^{20, 21} By removing the scraping in the OBC and by adding the scraping in the STC, their results verified that scraping was the sole source for the primary nucleation of the opposite handedness. However, they did not explore how the number of nuclei could be related to the number scratches: this is the objective of this work. Any correlation between the number of nuclei and the amount of scraping would add significant scientific insight into this matter, allowing either prevention (if it is to be avoided, e.g. where chirality is an issue²⁴) or utilization (when scraping could be the means of generating regular and quantifiable nuclei). From an operational viewpoint, encouraging or discouraging baffle scraping

against the wall of the crystalliser is an easy parameter to manipulate and requires no additional equipment or compounds.

Experimental and Analytical Methods

Reagents

Laboratory-grade sodium chlorate (99+ % purity) was sourced from Fischer Scientific UK; distilled water from in-house. Seed crystals were prepared in the same way as that described in other work.^{20, 21}

Apparatus

The OBC (shown in Figure 1) was made up of a jacketed-glass column of an internal diameter of 52 mm and a height of 280 mm, supported on a metal frame. The working volume was 250 mL. The baffle string consisted of 3 PTFE baffles (outer diameter 52 mm, orifice diameter 24 mm, orifice thickness 3 mm and baffle spacing 70 mm), of which only 2 baffles were submerged during operation. Heating and cooling to the OBC were controlled by a water bath (Neslab RTE 100). A polarimeter (details of which are described elsewhere^{20, 21}) was used to distinguish between the two handedness of crystals, as they interact with polarised light differently.

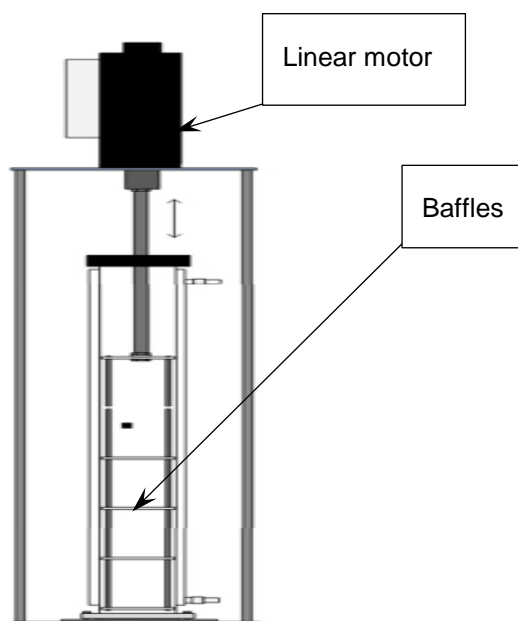


Figure 1: Schematic of the OBC

Experimental Procedure

Using published solubility data,²⁵ Table 1 lists the mass of sodium chlorate and the volume of water needed to prepare a saturated solution at 31 °C. The required materials were added to the OBC and held at 40 °C for 30 minutes under agitation (0.4 Hz, 35 mm) until full dissolution had been achieved. The solution was then hot-filtered (Whatman glass fibre filters Grade GF/C) at 40 °C in a control box to remove any foreign particles. The filtrate was returned to the OBC at 40 °C and then cooled to 30 °C at a rate of about 1 °C min⁻¹. Once a temperature of 30 °C had been attained, it was maintained throughout the experiment, ensuring 1 °C supercooling for all experiments. A single washed seed crystal (2 – 4 mm) of known-handedness was suspended in the OBC by a thread. At the same time, oscillatory mixing was applied. In the work of Callahan and Ni, the duration of 3 minutes was used for both seed and mixing. In order to explore any relationship between scraping and the number of nuclei, we tested various durations as given in Table 2 while keeping the same oscillation condition (0.4 Hz, 35 mm). Each test was carried out 3 times to ensure good reproducibility.

Table 1: Amounts of reagents required to prepare a saturated solution at 31 °C

T _{Sat} (°C)	Concentration (g NaClO ₃ / 100 mL saturated solution)	Density (kg/m ³)	Mass of NaClO ₃ (g)	Volume of water (mL)
31	73.79	1435	192	184

Table 2: Summary of experimental conditions

Run	Seeding time (min)	Mixing time (min)
1	3	3
2	12	12
3	30	30
4*	720	720

*Only one run was done at this condition

After the allotted time, the seed crystal was removed and the mixing was stopped at the same time. The contents in the OBC were then left overnight to grow, before being vacuum filtered (Whatman Grade 1) and washed twice with distilled water. The recovered crystals were dried overnight at 60 °C. Table 3 provides the information on the product crystals with a yield of about 10 % for 1 °C supercooling. After experiments, the OBC was washed at 60 °C with detergent and rinsed 3 times with hot water to remove any dust or residual sodium chlorate; was then ready for the next run. The selected dry crystals were manually analysed for handedness using the polarimeter. Because of its time-consuming nature, only a 5 % sample was analysed.

Table 3: Information on product crystals

Product Crystal Yield	Number of Product Crystals	Mass of Product Crystals	Number of Product Crystals Analysed	Mass of Product Crystals Analysed
~ 10 %	~ 4,000	~ 18 g	~ 200	~ 0.9 g

Results and Discussions

Equal durations of seeding and scraping

The benchmark experiments by Callahan and Ni (2012) showed that 100 % of the product crystals were of the same handedness as the seed in the absence of mixing (scraping) in the OBC; deviations from 100 % handedness to the seed crystal were noted when the durations of 3 mins were used for both seeding and mixing in the OBC, outlining the clear influence of scraping. A comparison of our work with the benchmarking data is given in Table 4. We see that the number of crystals of the opposite handedness to the seed increases as the durations of both seeding and mixing are lengthened for both L and R seeds, indicating more primary nucleation events were generated by scraping and a minimum value of 56.6 % similarity to seed was reached over 12 hrs. Noted that there was a slight difference in data between the benchmarking and ours, which is likely due to a larger diameter OBC used in our work.

Table 4: Product crystals similar to either R- or L-handed seed ($x_0 = 35 \text{ mm}$, $f = 0.4 \text{ Hz}$)

Test	3 mins of seeding and mixing [16]	3 mins of seeding and mixing	12 mins of seeding and mixing	30 mins of seeding and mixing	720 mins of seeding and mixing
Similarity to seed with a R seed (%)	94.2 ± 1.8	92.5 ± 5.3	70.3 ± 0.7	61.1 ± 2.1	
Rate of primary nucleation event for L crystal (/min)		2.50	2.48	1.30	
Similarity to seed with a L seed (%)	94.3 ± 0.6	85.7 ± 1.9	73.7 ± 2.4	65.2 ± 1.5	56.6
Rate of primary nucleation event for R crystal (/min)		4.77	2.19	1.16	

The number of scratches the baffles make against the OBC wall can be quantified using

$$N_{\text{Scratches}} = f * N_b * t \quad (1)$$

Where f is the oscillation frequency (Hz), N_b is the number of submerged baffles (= 2 for this work) and t (s) is the mixing time. Figure 2 plots the percentage of products crystals of the same handedness as the seed as a function of $N_{\text{Scratches}}$. We see that product crystals of seed-similarity decreases exponentially with the number of scratches, approaching 56.6 % asymptotically, where primary nucleation is dominating over secondary nucleation; the 6.6 % above the theoretical symmetrical value of 50 % could be the remains of the secondary nucleation effect.

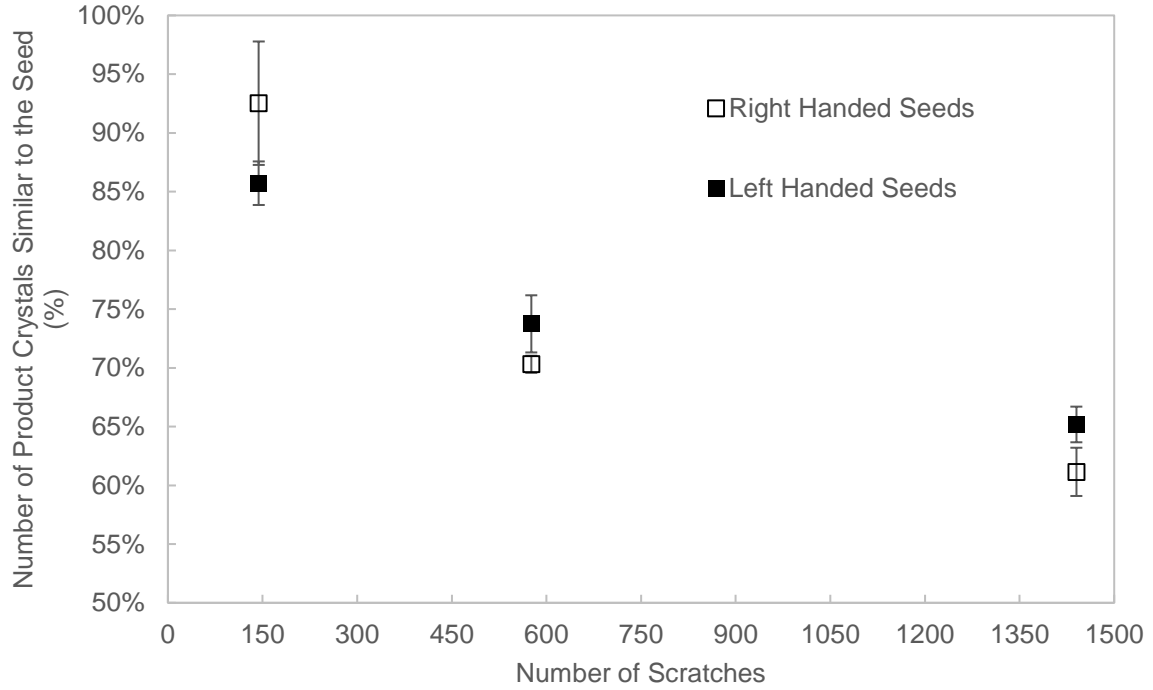


Figure 2: Comparison of product crystal handedness to the seed crystal varies with the number of scratches

The general form can be represented by:

$$\%Similarity = Min_T + (1 - Min_T) * \exp(-\beta * N_{Scratches}) \quad (2)$$

Where Min_T is the theoretical minimum seed-similarity (= 0.5), β is a constant (≈ 0.002 here) whose value depends on the specific conditions and $N_{Scratches}$ is the number of scratches.

In cooling crystallisation of sodium chlorate in the absence of baffle-scraping, we have a pot containing X g of solids in Y ml of liquid, where the solid is assumed to have a 50:50 split of R and L forms. When a L seed crystal is introduced, this not only encourages L crystals to form and grow, but also suppresses the generation of R crystals, and vice versa, due to various autocatalytic and amplification mechanisms aforementioned.^{2-4, 26}

With the presence of baffle scraping against the vessel wall, local high temperatures, in turn, local high supersaturation generated nuclei of opposite handedness to seed. There are likely two

autocatalytic processes present: one with the seed (secondary) and one with scraping (primary). When the seed crystal was first introduced to the batch, secondary nucleation dominated; the rate of primary nucleation was low with no or few scratches, leading to majority of product crystals of seed-similarity. This agrees with previous work.^{2, 27} As the number of scratches increases, primary nucleation and its autocatalytic effect was now amplified by scraping.^{3, 28, 29} Normally, the secondary mechanism suppresses the primary one, because the energy barrier for the former is much lower.³⁰ However, in the presence of regular isolated regions of high supersaturation, as in the case of baffle-scraping, primary nucleation occurred earlier at higher local temperatures (hence at higher rates) than that of secondary nucleation, and gradually outcompeted the secondary, as the rate of primary nucleation is proportional to the exponential of the supersaturation squared.³¹ While the energy barrier (i.e. the solubility) is the same for both R and L crystals, scraping should in theory generate equal amounts of R and L-nuclei in the seeded environment. If this was the case, the opposite nuclei would have been suppressed due to the increased total number of nuclei similar to seed (= seed + nuclei of seed-similarity). As there are no other sources, mechanisms or driving forces in the crystalliser, our data imply that nuclei of rebellion to seed could only be generated by scraping. While the reason for this is still unclear, our work on non-chiral compounds (urea, adipic acid, salicylic acid, glutamic acid and acetaminophen) bear the same essential phenomena, i.e. the higher nucleation temperatures with scraping; local high supersaturation seems favouring for nuclei of opposite handedness for this compound.

At a fixed 1 °C supercooling and the same experimental conditions, the overall number of crystals produced did not vary significantly, nor did the yield, because of the low degree of supersaturation. Although it is difficult to determine the exact number of primary nucleation events which had occurred, we assume that the scraping efficiency was constant and each scrape had an equal likelihood of contributing to a nucleation event (a similar concept to that used for bubble-induced nucleation^{32, 33}). For simplicity, we relate the percentage of product crystals of opposite handedness to seed directly to the number of primary nucleation events occurred, in this way, the maximum potential rate of primary nucleation events due to scraping can be evaluated (see Table 4), which provides the purpose of indication and proportionality. We see that the rates are higher for shorter than longer durations; there is a big difference in the rates between L and R nuclei initially, which diminishes with the increase of

scraping. This resembles the statistics of tossing a coin, the differences between heads and tails are high initially, and gradually approaches equal probability when the number of tosses increases.

Effect of scraping duration

Further data reported in Table-5 show the effect of scraping duration on chiral symmetry when the seed was removed after 3 minutes in each case. Once again we see that the role of secondary nucleation was initially dominant^{28, 34} and was then suppressed once the primary nucleation had become a regular event; product crystals of a lower seed similarity were obtained when scraping was continued for further 9 and 27 minutes after the seed had removed. Based on the previous assumptions, the relative importance of primary nucleation rate by scratches (r_P) over secondary nucleation rate by seed (r_S) can directly be captured by the number of scratches as:

$$r_P/r_S = m * N_{Scratches} \quad (4)$$

Where m is the proportionality constant. The relative importance between the rate of primary and secondary events is given in Table 5 together with the rate of primary nucleation events per scratch (or equally the number of scratches required to generate one primary nucleation event). The relative importance increases with the duration of scraping, indicating even more dominate effect of primary nucleation events by scraping. During the first 3 mins, the efficiency of generating primary nucleation by scraping is much higher, i.e. requiring fewer scratches to generate one primary nucleation; decreases when the number of scratches increases and the local high temperature areas become consistent.

Table-5: The effect of scraping duration on chirality of product crystal (left handed seed)

Number of scratches	Product crystals of seed-similarity (%)	Rate of primary nucleation event (/scratch)	Scratches required for one primary nucleation event	Relative importance of primary to secondary r_P/r_S
3 mins seeding and 3 mins mixing (144 scratches)	85.7	0.099	10.1	0.17
3 mins seeding and 12 mins mixing (576 scratches)	66.7	0.058	17.2	0.50

3 mins seeding and 30 mins mixing (1,440 scratches)	52.8	0.033	30.3	0.89
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Effect of seeding duration

Table 6 compares the effect of seeding duration on the chiral symmetry. The extra 9 and 27 minutes of seeding increases, on one hand, the product crystals of seed-similarity by about 10% and 24% respectively. On the other hand, the rate of secondary nucleation event decreases from 0.78 to 0.47 /min, suggesting that increasing the duration of seeding under scraping is less efficient in promoting secondary nucleation, or in other words, primary nucleation by scarping soon prevails.

Table-6: The effect of duration of scraping on chirality of product crystal (left-handed seed)

($x_0 = 35 \text{ mm}$, $f = 0.4 \text{ Hz}$)

Investigated Parameter	Product crystals of seed-similarity (%)	Increased rate of secondary nucleation event due to longer seeding duration (/min)
3 mins seeding and 12 mins mixing (576 scratches)	66.7	0.78
12 mins seeding and 12 mins mixing (576 scratches)	73.7	
3 mins seeding and 30 mins mixing (1,440 scratches)	52.8	0.47
30 mins seeding and 30 mins mixing (1,440 scratches)	65.5	

Conclusions

We have reported, for the first time, that the number of seed-similar nuclei in cooling crystallisation of sodium chlorate is affected by the number of scraping in the OBC and decays to a minimum when the number of scratches increases. For equal durations of seeding and mixing, the asymptotical minimum of 56.6 % product crystal similar to seed after a daylong operation indicates the dominance of primary nucleation events due to scraping over secondary nucleation by seeding and provides a quantitative measure for the remaining effect of secondary nucleation over and above the theoretical symmetry of 50 %:50 %. Increasing the duration of scraping at a fixed seeding time promotes further primary

nucleation, however, the number of scratches required to generate one nucleation event also increases. Increasing the duration of seeding at a fixed time of scraping improves secondary nucleation, but not as much as that by primary nucleation. Although the reason why scraping only generates nuclei of opposite handedness is unclear, we are able, based on the experimental data, to postulate the rates of primary and secondary nucleation events; and demonstrate that the relative importance of primary to secondary nucleation in the cooling crystallisation of sodium chlorate can be varied by the amount of scraping in the OBC.

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References

1. F. S. Kipping and W. J. Pope, *Nature*, 1898, **59**, 53.
2. D. K. Kondepudi, R. J. Kaufman and N. Singh, *Science*, 1990, **250**, 975-976.
3. C. Viedma, *Journal of Crystal Growth*, 2004, **261**, 118-121.
4. D. K. Kondepudi, K. L. Bullock, J. A. Digits, J. K. Hall and J. M. Miller, *J. Am. Chem. Soc.*, 1993, **115**, 10211-10216.
5. D. K. Kondepudi, K. L. Bullock, J. A. Digits and P. D. Yarborough, *Journal of the American Chemical Society*, 1995, **117**, 401-404.
6. C. I. Sainz-Díaz, A. P. Martín-Islan and J. H. E. Cartwright, *The journal of physical chemistry. B*, 2005, **109**, 18758.
7. C. Viedma, *Physical Review Letters*, 2005, **94**, 1-4.
8. Y. Song, Chen. W. and Chen. X., *Crystal Growth and Design*, 2008, **8**, 1448-1450.
9. Y. Song, Chen. W. and Chen. X., *Crystal Growth and Design*, 2012, **12**, 8-11.
10. M. R. Ward, G. W. Copeland and A. J. Alexander, *The Journal of Chemical Physics*, 2011, **135**.
11. M. Ward, G. Copeland and A. Alexander, *Chemical Communications*, 2010, **46**, 7634-7636.
12. P. Cintas, *Crystal Growth and Design*, 2008, **8**, 2626-2627.
13. C. a. C. Viedma, P., *Chemical Communications*, 2011, **47**, 12786-12788.
14. A. J. Alexander, *Crystal Growth & Design*, 2008, **8**, 2630-2632.
15. C. Roth, D. Passerone and K.-h. Ernst, *Chem. Commun.*, 2010, **46**, 8645-8647.
16. I. Sato, K. Kadowaki, Y. Ohgo and K. Soai, *Journal of Molecular Catalysis. A, Chemical*, 2004, **216**, 209-214.

17. N. Jiang, Y. Wang, Q. Liu, Y. Zhang, Z. Deng, K.-h. Ernst and H.-j. Gao, *Physical Chemistry Chemical Physics*, 2010, **12**, 1318-1322.
18. Z. Wu, Yang, S. and Wu. W., *Crystal Engineering Communications*, 2016, **18**, 2222-2238.
19. K. Suwannasang, Flood, A.E., Rougeot, C. and Coquerel, G., *Crystal Growth and Design*, 2013, **13**, 3498-3504.
20. C. J. Callahan and X. W. Ni, *Crystal Growth and Design*, 2012, **12**, 2525-2532.
21. C. J. Callahan and X.-w. Ni, *CrystEngComm*, 2013, **16**, 690-697.
22. E. G. Denk and G. D. Botsaris, *Journal of Crystal Growth*, 1972, **13-14**, 493 - 499.
23. R. I. Ristic, *Chemical Engineering Research and Design*, 2007, **85**, 937-944.
24. D. Zhang, S. Xu, S. Du, J. Wang and J. Gong, *Engineering*, 2017, **3**, 354-364.
25. S. C. Lind, *The Journal of Physical Chemistry*, 1942, **46**, 608-608.
26. L.-C. Sgtoğlu, R. R. E. Steendam, H. Meekes, E. Vlieg and F. P. J. T. Rutjes, *Journal*, 2015, **44**, 6723-6732.
27. P. Cruz, F. Rocha and A. Ferreira, *CrystEngComm*, 2016, **18**, 9113-9121.
28. P. Cruz, F. Rocha and A. Ferreira, *CrystEngComm*, 2018, **20**, 829-836.
29. S. S. Kadam, S. A. Kulkarni, R. Coloma Ribera, A. I. Stankiewicz, J. H. Ter Horst and H. J. M. Kramer, *Chemical Engineering Science*, 2012, **72**, 10-19.
30. S. G. Agrawal and A. H. J. Paterson, *Chemical Engineering Communications*, 2014, **202**, 698-706.
31. P. G. Vekilov and J. J. de Yoreo, *Reviews in Mineralogy and Geochemistry*, 2003, **54**, 57 - 93.
32. K. Wohlgemuth, A. Kordylla, F. Ruether and G. Schembecker, *Chemical Engineering Science*, 2009, **64**, 4155-4163.
33. K. Wohlgemuth, F. Ruether and G. Schembecker, *Chemical Engineering Science*, 2010, **65**, 1016-1027.
34. M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez and J. C. Palacios, *Chemical Communications*, 2000, 887-892.