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Chiral Nucleation

O. Vogl[1], **M. Qin**[1], **J. Bartus**[1], and **G. D. Jaycox**[2]

[1] Polytechnic University, Six MetroTech Center, Brooklyn NY, 11201-2990, U.S.A.
[2] DuPont Central Research and Development, Experimental Station, Wilmington DE, 19880-0328, U.S.A.

Summary. The crystallization of agitated aqueous solutions of sodium chlorate and sodium bromate was nucleated with levo- or dextrorotatory crystal powders of sodium chlorate and sodium bromate to furnish new crystals with a high degree of chiroptical purity.

Keywords. Chiral crystallization, Nucleation, Chiral inorganic salts, Sodium chlorate, Sodium bromate, Optical activity.

Chirale Nukleierung

Zusammenfassung. Die Kristallisation aus agitierten wässrigen Lösungen von Natriumchlorat und -bromat wurde mittels levo- und dextrorotatorischem pulverförmigem Natriumchlorat und -bromat nukleiert. Es entstanden Kristalle mit einem hohen Grad an optischer Reinheit.

Introduction

Crystallization involves the agglomeration of molecules from solution or the melt into solids having highly organized structures. This process can often be initiated by the addition of "seed-crystals" or other nucleating agents. Crystallization has been employed for centuries for the isolation and purification of both organic and inorganic compounds [1]. Some of the most elegant crystals are produced by nature as "minerals"; a number of these are valued as "precious stones".

A number of the most common minerals, such as quartz, have an asymmetric, *i.e.* helical, lattice that is not superimposable upon its mirror image and can rotate the plane of polarized light. The origins of optical activity in crystalline solids have been extensively studied [2–7].

The crystallization behavior of sodium chlorate and sodium bromate has fascinated workers for over 100 years [8]. These salts are achiral in solution and crystallize from aqueous media into large dextrorotatory or levorotatory crystals that can reach several centimeters in size [9]. An accurate X-ray analysis of levorotatory sodium chlorate has been carried out [10, 11] and shows clearly the existence of a helical arrangement of atoms in the crystal.

Several years ago we embarked upon the development of a technique to measure the optical activity of solid powders in suspension. We chose to test our ideas on sodium chlorate and sodium bromate which obviated the need for large crystalline specimens and to compare measurements of the optical rotations in the crystal and in powder suspension. In our laboratory, large crystals were obtained when saturated aqueous solutions of sodium chlorate or sodium bromate were slowly allowed to evaporate under conditions where dust and other particulates were carefully excluded. We have confirmed that the chiroptical properties of these crystals are isotropic [12, 13]. For example, sodium chlorate possesses a specific rotation magnitude of 122° (sodium d-line) in all three crystallographic directions. It is interesting to note that nearly a century ago, *Landolt* [14] attempted to measure the optical activity of sodium chlorate powders and, on finding significant discrepancies between his crystal and powder values, concluded that his efforts were without merit.

The development of chirality during the crystallization of inorganic salts like sodium chlorate has been studied extensively. In a typical crystallization, more or less statistically equivalent, *i.e.* racemic, populations of large dextrorotatory and levorotatory crystals are usually obtained if experiments are carried out with highly purified salts that are devoid of chiral impurities and other chiral influences [12]. The questions of stirring and secondary nucleation in sodium chlorate crystallization were addressed some years ago [15, 16].

Recently, in a startling report [17], spontaneous chiral symmetry breaking during sodium chlorate crystallization was observed in one laboratory, which was very recently followed up by some theoretical considerations [18, 19]. On stirring saturated solutions of this salt, excess populations of *D*- or *L*-crystals were reportedly deposited *in the absence of any added chiral nucleating agent*. The authors of this study speculated that their stirring process somehow provided an autocatalytic seeding event which was followed by a successful competition between growing *D*- and *L*-crystals to furnish an excess of one chiral crystal population. In about half of their trials, *D*- crystals predominated while in the other half, *L*-crystals were favored. Optical rotation data for the individual crystals isolated during this investigation were not published, although it is often possible to identify the handedness of macroscopic crystals even without rotation measurements [20].

Results and Discussion

With our experience of measuring accurately the optical rotation of sodium chlorate and sodium bromate in powder suspension, we realized that we had in hand a powerful technique to check the crystallization experiments of sodium chlorate and sodium bromate, now with the objective of creating small crystals during the crystallization. Our basic experiment was as follows: Into a clean 7 ml test tube were placed highly purified sodium chlorate (3.0 g) and water (1.8 ml). After capping the tube with a silicone rubber septum, the solution was heated to 85 °C in an apparatus that was specially designed to allow the tubes to slowly rotate around a horizontal axis at various rotation speeds. After some experimentation, we chose as the optimal speed of rotation 70 rotations per minute. The apparatus containing the tube was then cooled at 1.2 °C per minute while rotation was continued. In most cases, small crystals began to appear at or below 58 °C, sometimes as low as 35 °C and sometimes not even at 35 °C.

Table 1. Crystallization of $NaClO_3$ from aqueous solution; statistical (spontaneous) nucleation (no nucleating agent added); amounts: 3.0 g $NaClO_3$ in 1.8 ml H_2O; rate of tumbling: 70 ± 10 rotations per minute; rate of temperature decrease from temperature of dissolution (85 °C): 1.2 °C/min; number of experiments: 41; (+)-crystals: 21, (−)-crystals: 20

I. Number of experiments to produce	
chirally pure crystals (+) or (−):	32 (78%)
more than 80% chirally pure crystals:	6 (15%)
nearly "racemic" crystals:	3 (7%)
II. Crystallization temperature to produce	
chirally pure crystals:	>40 °C
more than 80% pure crystals:	<40 °C
nearly "racemic" crystals:	35 °C

The results of 41 separate experiments are as follows (Table 1). The accuracy of all our measurements of the optical rotations is ±3%. 21 experiments provided samples that contained all (or mostly all) dextrorotatory crystals while 20 furnished samples that were either all or mostly all levorotatory crystals. Moreover, a total of 78% of the experiments furnished optically pure crystalline powders with rotation magnitudes (sodium d-line) of 122° whereas 15% of the experiments provided sodium chlorate solids that were more than 80% optically pure. The remaining 3 experiments afforded solids that were nearly racemic, possessing some but little optical rotation. Interestingly, we observed that solids of the highest optical purity resulted when the crystallizations began within the higher temperature range, generally above 50 °C. In those experiments where crystal formation begin near 40 °C, chiroptical purities of the resulting samples were sometimes substantially lower. Finally, nearly racemic compositions resulted from the few experiments where crystalline solids had not formed by the time 35 °C was reached. In these cases, the tubes were manually shaken to rapidly induce crystallization which apparently proceeded by essentially random nucleation. In some cases, vigorous shaking produced sodium chlorate crystals that were chirally pure, apparently by chiral secondary nucleation. Similar experimental results of spontaneous nucleation were obtained when our tubes were rotated in clockwise or counterclockwise fashion about the horizontal axis (Table 2). Similar results were obtained from crystallization experiments for sodium bromate (Table 3).

We interpret our preliminary findings in the following way: The agitation or tumbling action within our tubes generates a chiral "seed" of sodium chlorate having one handedness or the other. The actual mechanism by which this seed is generated is still unknown. However, our data do suggest that there exists an equal chance that a given seed will be "right-handed" or "left-handed". No chiral bias seems to be apparent. Further agitation seems to break this seed (either as aggregates still in solution or when first precipitation occurs) into a large number of secondary chiral seeds which then go on to rapidly nucleate the solution in chirally specific fashion. When the sodium chlorate solutions are above 50 °C, this process has little

Table 2. Crystallization of $NaClO_3$; statistical (spontaneous) nucleation (no nucleating agent added); amounts: 3.0 g $NaClO_3$ in 1.8 ml H_2O

Tumbling direction	Runs	Percent of max. optical rotation in each sample
clockwise	4	(+) 100, (+) 83, (−) 100, (−) 100
counterclockwise	4	(+) 100, (+) 100, (−) 100, (−) 100
Tumbling speed (rpm)	Runs	Percent of max. optical rotation in each sample
50	2	(+) 97, (−) 94
60	2	(+) 94, (−) 98
72	2	(+) 98, (−) 99
90	2	(−) 99, (−) 89

Table 3. Crystallization of $NaBrO_3$ from aqueous solution; statistical (spontaneous) nucleation (no nucleating agent added); amounts: 2.8 g $NaBrO_3$ in 4.0 ml H_2O; rate of tumbling: 70 ± 10 rotations per minute; rate of temperature decrease from temperature of dissolution (85 °C): 1.2 °C/min.

1. Deionized water as a solvent:		
Starting material $NaBrO_3$ ($[\alpha]_d$)	Number of experiments	Percent of max. optical rotation (range)
+ 57.0°	8	8 exps (+) 95–97
0°	4	3 exps (+) 94–98, 1 exp (+) 58
− 48.7°	8	6 exps (+) 80–95, 2 exps (−) 98
2. Tap water as a solvent:		
Starting material $NaBrO_3$ ($[\alpha]_d$)	Number of experiments	Percent of max. optical rotation (range)
−48.7°	8	6 exps (−) 99–100, 2 exps (+) 92–97
3. Freshly distilled deionized water as a solvent:		
Starting material $NaBrO_3$ ($[\alpha]_d$)	Number of experiments	Percent of max. optical rotation (range)
−48.7°	8	4 exps (−) 99–100, 1 exp (−) 61 3 exps (+) 92–98

competition and crystalline solids having high chiroptical purities are ultimately produced as the solutions slowly cool. For those experiments where the initiation of crystallization is delayed until lower temperatures are reached, the solutions become increasingly supersaturated. Now, there is a greater tendency for "normal" crystallization to occur and competition with the original seeding process ensues. Depending on the exact dynamics of each system, solids having lower chiroptical purities will generally result. Finally, if the sodium chlorate solutions cool to a point where they are completely supersaturated, a simple agitation event will result in the rapid formation of an essentially racemic mixture of seeds. Here, the normally observed crystallization process without chiral preference will dominate and optically inactive samples will be obtained. Chiral preference but not chiral specificity is observed when both processes occur simultaneously.

Molecular recognition at crystal interfaces has been recognized as the central theme in many crystallization processes [21]. Proper manipulation of these principles can bring about enantioselective crystallization of solutions of racemates, however, resulting in a substantial excess of either the *D*- or the *L*-crystal population as was demonstrated in the development of the technical process for the preparation of *D*-Methyl-DOPA and described in greater detail for enantioselective seeding [22]. These crystallizations were carried out on actual racemates where the solution from which the crystallization is carried out consisted of 50:50 mixtures of the *D*- and *L*-compounds. In this case of enantiomeric nucleation, the maximum yield of chiral specific nucleation is 50%, a 100% yield of one of the enantiomers [23].

We chose to study the chiral nucleation of sodium chlorate and sodium bromate solutions. Since the solutions of either salt are achiral, proper nucleation and successful enantiospecific crystallization could lead to a 100% yield of a 100% optically pure substance in powder form. We nucleated supersaturated solutions of sodium chlorate with *D*- and *L*- sodium chlorate powders and demonstrated this phenomenon. In 10 separate experiments using the crystalline *D*-powder as a "chiral seed", dextrorotatory crystals were always obtained–each with a specific rotation magnitude near 122° at the sodium d-line. In 10 further trials with nucleation using the *L*-powder of sodium chlorate, levorotatory crystals were isolated having the same rotation magnitude (Table 4). Similar results were obtained for sodium bromate (Table 5).

We then attempted to nucleate sodium chlorate solutions with the isomorphous sodium bromate salt. Interestingly, the *D*-sodium bromate powder furnished levorotatory sodium chlorate crystals while the *L*-sodium bromate seed afforded dextrorotatory sodium chlorate crystals. This same "reverse" pattern was observed when sodium chlorate was used to nucleate sodium bromate crystals. *Abrahams*

Table 4. Chiral nucleation of sodium chlorate (3.0 g $NaClO_3$ in 1.8 ml H_2O); temperature of nucleation: 61 °C; amount of nucleating agent: 10 mg

Type of nucleating agent	Number of experiments	Percent of max. optical rotation (range)
(+) $NaClO_3$	10	(+) 98–100
(−) $NaClO_3$	10	(−) 98–100
(+) $NaBrO_3$	10	(−) 98–100
(−) $NaBrO_3$	10	(+) 98–100

Table 5. Chiral nucleation of sodium bromate (3.0 g $NaBrO_3$ in 4.0 ml H_2O); temperature of nucleation: 61 °C; amount of nucleating agent: 10 mg

Type of nucleating agent	Number of experiments	Percent of max. optical rotation (range)
(+) $NaBrO_3$	10	(+) 98–100
(−) $NaBrO_3$	10	(−) 98–100
(+) $NaClO_3$	10	(−) 98–100
(−) $NaClO_3$	10	(+) 98–100

Table 6. $NaClO_3$ recrystallized by the addition of non-solvent; saturated $NaClO_3$ solution; amount of nucleating agent: 50 mg

Type of nucleating agent	Non-solvent	Percent of max. optical rotation
(+) $NaClO_3$	Acetone	(+) 91
(+) $NaClO_3$	Ethanol	(+) 99
(+) $NaClO_3$	Methanol	(+) 98
(−) $NaClO_3$	Acetone	(−) 86
(−) $NaClO_3$	Ethanol	(−) 97
(−) $NaClO_3$	Methanol	(−) 96
None	Acetone	(−) 90
None	Ethanol	(−) 92
None	Methanol	(−) 100
(±) $NaClO_3$	Acetone	(+) 50
(±) $NaClO_3$	Ethanol	(−) 55
(±) $NaClO_3$	Methanol	(−) 52

[10, 11] earlier determined by X-ray crystallography the structures of sodium chlorate and sodium bromate crystals and found that corresponding configurations have opposite optical rotations.

Instead of lowering the temperature to create saturated solutions, water miscible non-solvents, such as methanol, ethanol, and acetone were used for the chiral crystallization of sodium chlorate. Single experiments were carried out in each case to demonstrate the feasibility of chiral nucleation as seen in Table 6.

The use of non-solvents could, of course, guarantee a nearly quantitative recovery of the salts rather that the 30% recovery for the chirally pure salts obtained by chiral crystallization from aqueous solutions. We have found that crystallization from aqueous methanol gives similar results to that performed in pure water with essentially 100% optical purity of the salts. In our preliminary experiments, the use of acetone, a more effective non-solvent, gives results that are more similar to those obtained by crystallizing at 35 °C, with crystals of sodium chlorate having substantially lower optical rotations than those for optically pure sodium chlorate.

It is important to note that spontaneous macroscopic resolutions of the kind demonstrated in our experiments with sodium chlorate and sodium bromate salts could provide considerable insight into the origins of biomolecular chirality on earth. The origins of biomolecular handedness, including such problems as chiral synthesis, chiral fields, parity-nonconservation, and chiral symmetry breaking have all been considered by *Mason* [24].

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