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Does Thermosalient Effect Have to Concur with a Polymorphic Phase Transition? The Case of Methscopolamine Bromide

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Abstract: In this paper, we report for the first time an observed thermosalient effect that is not accompanied with a phase transition. Our experiments found that methscolopamine bromide—a compound chemically very similar to another thermosalient material, oxitropium bromide—exhibited crystal jumps during heating in the temperature range of 323–340 K. The same behavior was observed during cooling at a slightly lower temperature range of 313–303 K. Unlike other thermosalient solids reported so far, no phase transition was observed in this system. However, similar to other thermosalient materials, methscolopamine showed unusually large and anisotropic thermal expansion coefficients. This indicates that the thermosalient effect in this compound is caused by a different mechanism compared to all other reported materials, where it is governed by sharp and rapid phase transition. By contrast, thermosalient effect seems to be a continuous process in methscolopamine bromide.

Keywords: thermosalient materials; jumping crystals; scopolamine bromide; negative thermal expansion; HT-XRPD

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1. Introduction

Materials that exhibit mechanical response to external stimuli (heat or light) in the form of jumping, bursting, curling, bending, etc. are at the frontier of research into potential actuators at the nanoscale. Molecular crystals that exhibit such behavior are extremely interesting from not only a scientific aspect, but also from a technological point of view due to the rapidness of their actuation. The rapidness, controllability, and high efficiency rate of energy transduction make such materials excellent candidates for production of smart medical devices or implants, artificial muscles, biomimetic kinetic devices, electromechanical devices, actuators, materials for electronics, and heat sensitive sensors [1,2]. Among mechanically responsive single crystals, thermosalient (TS) materials are a class that stand out in particular [3–11]. Thermosalient materials, colloquially known as "jumping crystals", are materials that exhibit mechanical motion during heating/cooling, thus transforming thermal energy into mechanical work. Although thermosalient compounds are known to belong to different classes of materials—from simple organic molecules to organometallic compounds, from metal complexes all the way to inorganic solid—all thermosalient compounds exhibit three common features: 1) crystallinity, 2) negative thermal expansion for at least of one of the cell parameters, and 3) a phase transition concomitant with a sudden change of cell parameters. Even though the liberation of crystal stress during the phase transition is the most probable explanation for this, a full elucidation that would be valid for all thermosalient systems is still not established. Recent studies have shown that negative compressibility might be the driving force for thermosalient effect [12]. Additionally, our own theoretical calculations—performed for the first time on thermosalient materials—showed that thermosalient effect is caused by the softening of the low-energy phonon [12]. Despite the fact that the mechanism beyond the thermosalient phenomena is not yet completely resolved, practical applications are slowly emerging. For example, the movement or breakage of a crystal of 1,2,4,5-tetrabromobenzene coated with silver has been used for the preparation of a fuse that is activated by increasing temperature [13].

In the light of all the new cognitions on thermosalient behavior and several years after we first published a comprehensive study on TS materials, we again return to the anticholinergic agent oxitropium bromide, which sparked our initial interest in this field [14]. This compound has two polymorphs (A and B), both belonging to the space group $P2_12_12_1$, with subtle differences in the molecular conformations. The thermally induced single-crystal-to-single-crystal polymorphic transition from phase A to phase B occurs at $T = 331$ K. Phase transition is characterized by anisotropic changes in the cell parameters (Δa: +1%, Δb: +11%; Δc: −7%; ΔV: +4%) accompanied by jumping of crystals up to 2 cm in height while maintaining the crystal integrity. Considering all the accumulated knowledge about TS materials, this paper endeavors to answer a new question: What would happen if we introduce a small, subtle change in the chemical composition of oxitropium bromide? We do this by examining methscopolamine bromide, a compound chemically very similar to oxitropium bromide. The only difference between oxitropium and scopolamine bromide is the aza-tricyclic part of the molecules; in oxitropium bromide, the quaterny nitrogen atom has both methyl and ethyl group as substituents, whereas in methscopolamine bromide, the nitrogen atom bears two methyl groups (Figure 1).

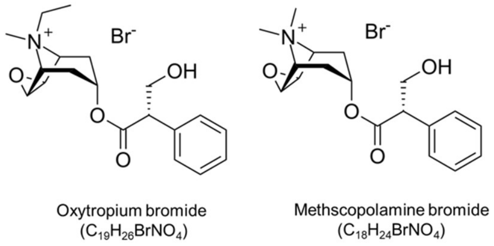

Figure 1. Chemical structures of oxitropium bromide and methscopolamine bromide.

The crystal structure of scopolamine bromide has been thoroughly described by Glaser et al. (orthorhombic space group $P2_12_12_1$ at 293(2) K: a = 7.0403(8), b = 10.926(2), c = 23.364(5) Å, V = 1797.2(6) Å^3, Z = 4) [15]. In the present paper, we use variation temperature study to show that methscopolamine bromide exhibits thermosalient behavior without any associated phase transition. This is contrary to all previously reported thermosalient materials. Indeed, methscopolamine bromide is the only known compound in which TS behavior is not concomitant with a phase transition. Results presented in this work show that thermosalient effect is possible even without phase transition and that despite all the knowledge we have already acquired in this field, there is still a long way before the mystery of thermosalient effect is resolved.

2. Materials and Methods

Methscopolamine bromide used for the experiments was purchased from Sigma Aldrich (Sigma Aldrich, Steinheim, Germany) (>99%, HPLC). It was used as received.

2.1. X-Ray Powder Diffraction (XRPD)

Temperature-induced structural changes were tracked by in situ HT variable temperature (VT) XRPD using a Philips PW 1710 diffractometer (Philips, Almelo, The Netherlands) equipped with high temperature chamber. Diffraction patterns were collected in 2θ range 5–50° using monochromatized CuKα radiation (monochromator: graphite). Data were collected in temperature range of 300 K–458 K. Crystal structures were refined by the Rietveld method using HighScore Xpert Plus (Version 4.5, March 2016). Thermal expansion coefficients were calculated from the refined unit cell parameters obtained from variable temperature diffraction data. Linear axial thermal expansion coefficients along the principal axes were calculated using the PASCal software [16].

2.2. Thermal Analysis

Differential Scanning Calorimetry (DSC) was carried out on Mettler Toledo DSC 822e instrument (Mettler Toledo, Columbus, OH, USA) in dynamic helium atmosphere (flow rate 50 mL/min) on the pristine samples in the temperature range between 298 K and 573 K.

2.3. Hot-Stage Microscopy

Mechanical behavior during heating/cooling was recorded using Nikon Eclipse LV150NL (Nikon, Tokyo, Japan) optical microscope equipped with a Linkam THMS600 hot-stage and OPTOCAM-II color camera with a resolution of 1600 × 1200 pixels. Crystal behavior was monitored in the temperature interval from room temperature to the melting point (503 K).

3. Results and Discussion

3.1. Hot-Stage Microscopy and Thermal Analysis

Hot-stage experiments were conducted on methscopolamine bromide crystals in air. During the first heating run, crystals started jumping at ~323 K. Jumping of crystals continued up to ~340 K. Not all the crystals jumped in the course of heating, with approximately 50% doing so. Interestingly, during the cooling run, crystals jumped again, starting at the temperature of ~313 K and finishing at around 303 K. During the second heating run, several crystals jumped again at the same temperature, but the number of crystals jumping was much smaller compared to the first heating. Hot-stage experiments were performed many times with different parameters. This included heating/cooling rate (10 to 50 K/min), number of cooling runs (up to five), crystals monitored for jumping when heating/cooling was stopped at selected temperatures (323 K, 333 K, and 343 K), number of crystals, different crystal sizes, and crystal orientation.

Several features were observed:

- Jumping (in terms of number of crystal that jumped, their frequency, or strength of the jumps) did not depend on the heating/cooling rate.
- Jumping did not depend on the size, shape, or orientation of the crystals. As expected, jumps of the smaller crystals were more forceful, whereas the more massive crystals would only slightly move or turn over to another facet.
- The number of crystals that jumped decreased drastically with consecutive heating/cooling runs. For example, if 10 crystals jumped during the first heating run, only 2–3 would jump in the second heating run.
- Crystals continued to jump sporadically when temperature was maintained for some time within the jumping temperature interval between 323 K and 333 K. Time period of jumping depended on the temperature. At 323 K, crystals continued to jump for 10 minutes, whereas the jumps ceased after 1–2 minutes at 343 K.
- No breaking or cracking of the crystals were observed during the jumping.
- Overall, the jumps of scopolamine bromide crystals were less energetic compared to the crystals of oxitropium bromide.

Figure 2 shows crystals of scopolamine bromide before jumping (left panel, taken during heating at the temperature of 315 K) and after jumping (right panel, taken during heating at the temperature of 345 K). Crystals that exhibited mechanical motion are marked with blue, green, orange, red, and purple rectangles. Blue, orange and red rectangles mark crystals that jumped off the hot-stage and left the recorded area. The green rectangle marks a large crystal that flipped to the other side but remained in more or less the same position. The purple rectangle marks a crystal that rotated around its axis but was held at the same place by the larger crystal on top of it.

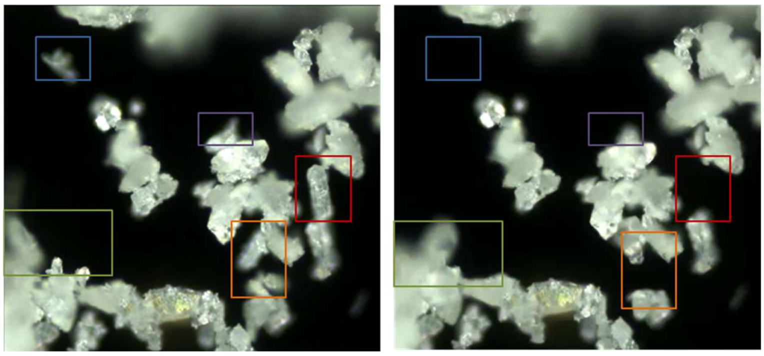

Figure 2. Crystals of scopolamine bromide before jumping (**left panel**) and after jumping (**right panel**).

Videos of crystals of methscopolamine bromide jumping during heating and cooling are provided in the supporting information (Video S1 and Video S2). DSC measurements were performed on the pristine crystals in order to reveal the phase transitions of methscopolamine bromide. In addition, thermal behavior of methscopolamine bromide was examined in the temperature interval between 298 K and 573 K. Much to our surprise, as can be seen from Figure S1, no maxima corresponding to phase transitions were observed before the melting point (around 503 K).

3.2. *In Situ Variable Temperature X-ray Powder Diffraction (VT XRPD)*

In situ XRPD measurements on methscopolamine bromide were performed in the temperature range of 300 K to 458 K, as shown in Figure 3.

Careful examination of powder diffraction data collected as a function of temperature (prior to any calculations) revealed quite pronounced shift in diffraction lines. Depending on the *hkl* index, diffraction lines shifted towards a lower or a higher 2θ angle; this was the first indication that scopolamine bromide is characterized by anisotropic thermal expansion. This is best illustrated in the narrow 2θ range between 16° and 17° shown in Figure 3; the diffraction line 020 shifted to higher values of 2θ angle with the increase in temperature, while the diffraction line 112 shifted towards lower angles, indicating that the unit cell of methscopolamine bromide decreased in *b*-direction and expanded in *c*-direction during heating. The shift of the 112 peak was greater compared to the 002, suggesting that the absolute value of the thermal expansion coefficient along the *c* axis was larger than along the *b* axis.

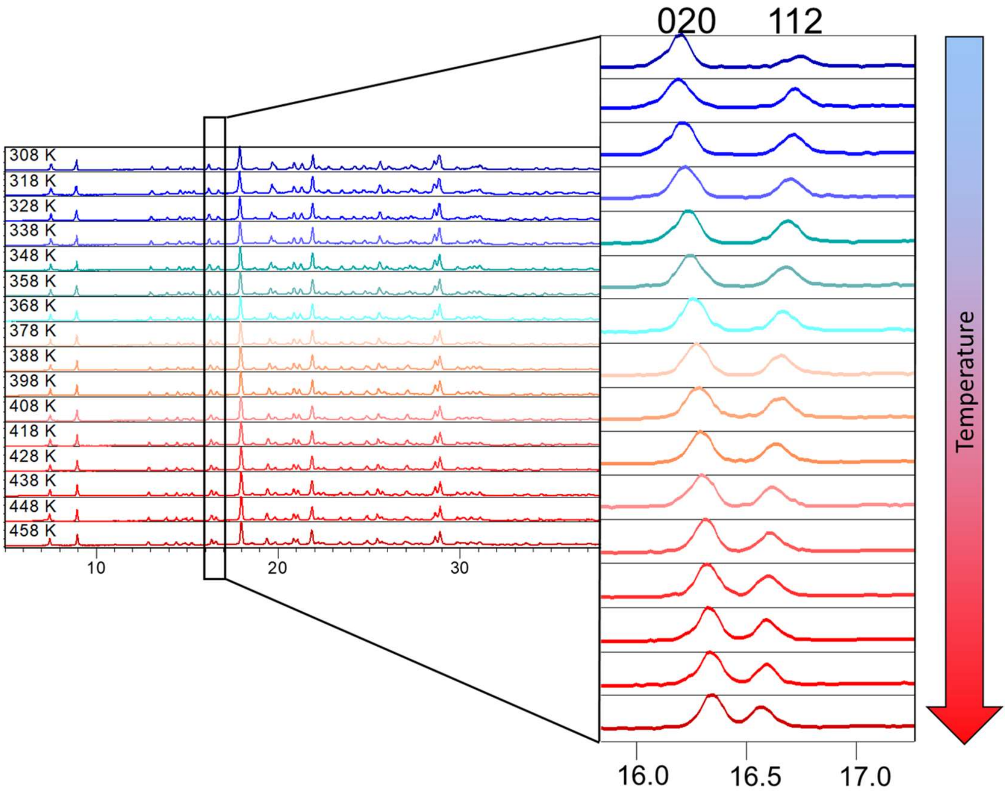

Figure 3. In situ variable temperature X-ray diffraction patterns of methscopolamine bromide in the temperature range of 308 K to 458 K. The 2θ range from 16° to 17° is enlarged and clearly shows the thermally induced shifts of the diffraction lines 020 and 112.

In order to get an insight into the temperature-induced structural changes of scopolamine bromide, Rietveld refinements were carried out on datasets collected in the temperature range of 308–458 K. Refinements were carried out starting from the structural model of Glaser [15]. Figure 4 shows the Rietveld refinements of scopolamine bromide at 308 K and 458 K; refined crystal packings at 308 K and 458 K are showed in overlap manner. Figure 4c,d shows that besides the anisotropic expansion of cell, there were no significant changes in the crystal packing. An in situ single-crystal X-ray diffraction study is also underway to get a better understanding of the molecular motion of SMB with changing temperature. Preliminary data seems to confirm the results of the Rietveld refinements. Contrary to methscopolamine bromide, quite pronounced differences in molecular structures and crystal packings have been noted in the case of oxitropium bromide between low-temperature phase A and high-temperature phase B. In fact, the proposed mechanisms beyond the thermosalient effect—not only for oxitropium bromide but for most thermosalient materials—was based on the following scenario: Heating of low-temperature polymorph is accompanied by various conformational changes of the molecule itself and consequently causes continuous changes of the packing. The shear strain caused by the distortion of the unit cell, which is almost always very anisotropic, is accrued to the point where it overweighs the cohesive interactions. At this point, accumulated stress is released and low-temperature polymorph abruptly switches to high-temperature phase. However, this premise gives rise to a new question about the rationale behind the thermosalient effect in scopolamine bromide, a material that exhibits no conformational changes during heating. A somewhat similar situation has been noted by researchers for 1,2,4,5-tetrabromobenzene. This compound does have a phase transition, but the difference in the crystal structures and intermolecular interaction energies of the low- and high-temperature phases is too small to be able to account for the large stress that arises over the course of the transformation [17].

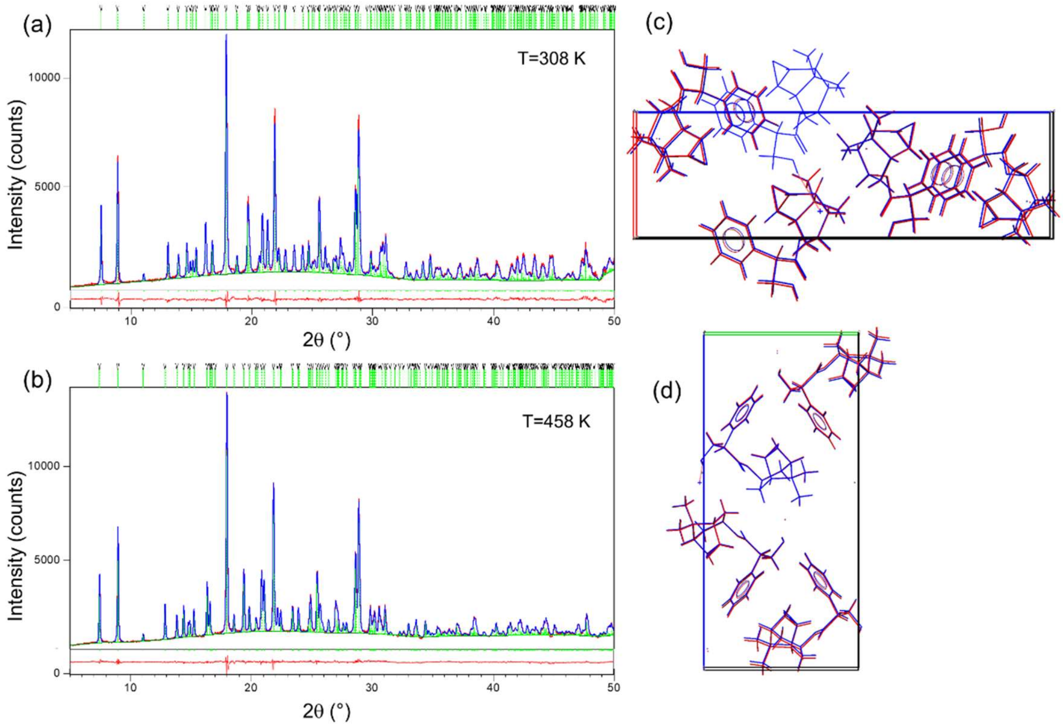

Figure 4. (**a**) Rietveld refinement fit for data collected at 308 K. (**b**) Rietveld refinement fit for data collected at 458 K. Experimental data are given as red line, calculated diffraction pattern as blue line, and the difference curves are given in red underneath the patterns. The green vertical lines represent positions of Bragg reflections of scopolamine bromide. (**c**) Overlap of crystal packings of scopolamine bromide at 308 K (blue) and 458 K (red) viewed along *b*-direction. (**d**) Overlap of crystal packings of scopolamine bromide at 308 K (blue) and 458 K (red) viewed along *a*-direction.

In the course of Rietveld refinement, unit cell parameters were determined and refined. Thermally induced changes of the unit cell parameters of methscopolamine bromide are shown in Figure 5 together with thermal expansivity indicatrix. As evident from the Figure 5, cell parameters *a* and *c* showed positive and linear thermal expansion in the investigated temperature range, while negative expansion occurred along *b*. A linear model was used to calculate the axial thermal expansion coefficients, although a slight deviation from linearity was observed along *b*. Negative thermal expansion was observed in several inorganic compounds, but it was very rare for organic compounds [18]. Also, the values of the thermal expansion coefficients were larger than is usual for molecular solids. Typical values for molecular solids are in the range of 0–20 $\times 10^{-6}$ K^{-1} [19], and our values were six times higher for the positive expansion than the maximum typical values (along *a* and *c* axis) and two times higher for the negative expansion (along *b* axis).

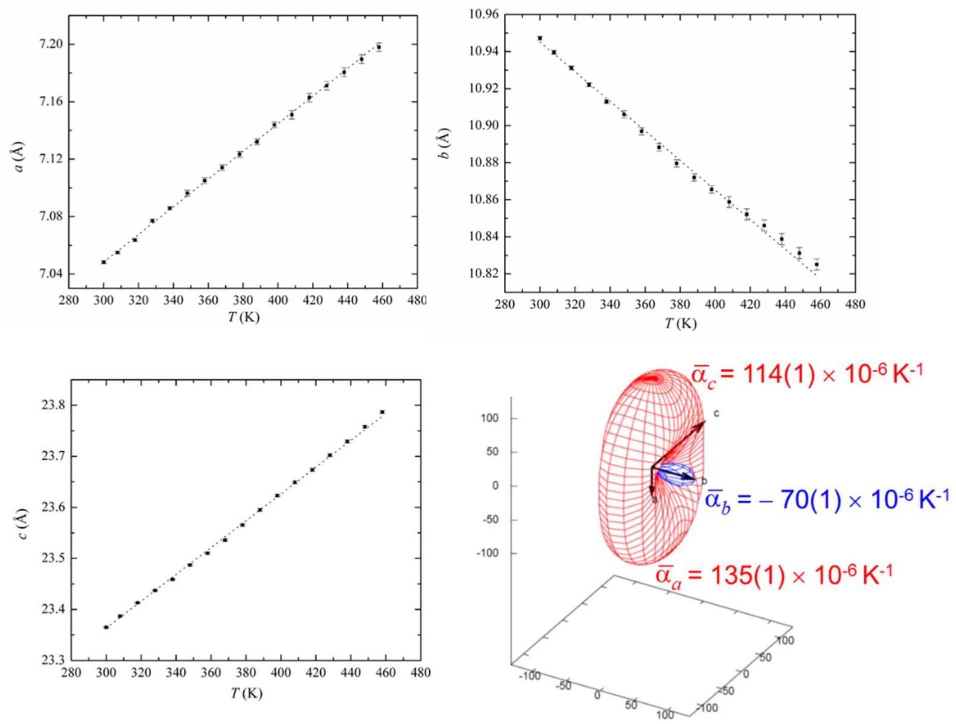

Figure 5. Temperature dependence of the unit cell parameters *a*, *b* and *c* of methscopolamine bromide. Thermal expansivity indicatrix is showing large anisotropic thermal expansion.

Since phase transition can be ruled out as a governing force for thermosalient effect in scopolamine bromide, the only plausible explanation can be that it is caused by the extremely large and anisotropic thermal expansion. Large anisotropic thermal expansion is characteristic of all reported thermosalient materials, and this extraordinary feature is shared with methscopolamine bromide as well. At the same time, this is also what differentiates them from non-thermosalient materials. All thermosalient materials exhibit uniaxial, or even biaxial, negative thermal expansion, which accommodates extremely large positive expansion. This preserves the integrity of the crystal lattice and the crystal as a whole during heating/cooling (during which stress is accumulating in the lattice). More importantly, this probably allows absorption of large elastic energy, which is released at some point in the form of mechanical motion of the crystals. The thermosalient mechanism in methscopolamine bromide is a continuous process unlike other thermosalient materials, which are characterized by sharp phase transition during which thermosalient effect abruptly takes places. This is evidenced by the quite broad temperature interval during which the crystals were jumping (more than 10 K), by the lower intensity of jumps compared to, for example, oxitropium bromide, and by the retained integrity of the crystals.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4352/8/7/301/s1, Figure S1: Differential scanning calorimetry of scopolamine bromide; Table S1: Summary of Rietveld structure refinement for methscopolamine at T= 308 K and T = 458 K; Table S2: Atomic coordinates and isotropic displacement parameters of methscopolamine at 308 K. Hydrogen atoms were not refined; Table S3: Atomic coordinates and isotropic displacement parameters of methscopolamine at 458 K. Hydrogen atoms were not refined. Video S1: heating of methscopolamine bromide (heating rate 10 K/min). Video S2: heating of methscopolamine bromide (heating rate 20 K/min). Video S3: cooling of methscopolamine bromide (cooling rate 10 K/min). Video S4: cooling of methscopolamine bromide (cooling rate 20 K/min).

Author Contributions: The study was designed by Ž.S.; Manuscript was written by J.P and Ž.S.; Experimental work was conducted by T.K.; Data were interpreted by Ž.S., J.P., J.F., M.Z., S.C.T., and T.K.

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Conflicts of Interest: The authors declare no conflict of interest.

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