Temperature Switch: Why a Solution Reversely Changes Between Transparent @ 25 °C and Cloudy @ 45 °C

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Abstract. The solubility of a substance determines how much of it will dissolve in a particular solvent at a given temperature. For most of the organic/inorganic compounds such as glucose and sodium chloride, their solubility in water increases with temperature. However, for polymers such as poly N-isopropylacrylamide and polyethylene oxide, they show lower critical solution temperature (LCST) behaviors and their solubility decreases when temperature increases. A small molecule, 1,8-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)anthracene-9,10-dione) (AQ-1,8-3E-OCH3), shows an LCST behavior that its water solution is transparent at a temperature less than 45 °C, and cloudy at a temperature above 45 °C. More importantly, the whole process is reversible.[19] The aim of this study is to explain the LCST behavior of AQ-1,8-3E-OCH3 so that further application can be developed. After reviewing inorganic compounds, organic molecules, and polymers, The essay concluded that the hydrophilic tails (3E-OCH3) and the hydrophobic core (AQ) of AQ-1,8-3E-OCH3 endow its amphiphilic property to form micelles, thus being phase separated from water when it is heated. In the future, it is expected that AQ-1,8-3E-OCH3 can be applied for drug release. For example, drug molecules can be first surrounded in the AQ-1,8-3E-OCH3 micelles at a higher temperature, then get released to targeted cells at a lower temperature.

1. Introduction
In the kitchen, sugar and salt are two prevalent flavoring agents. However, it is observed that cooks add salt at all the time but seldom add sugar to the dishes when the pot is cooled. Are there any reasons behind the differences? The phenomenon is related to the effect of temperature on the solubility. It is a common sense that with the rise of temperature, the solubility of a substance will increase and that the sugar and salt can be more soluble in hot water rather than in cold water. Such cases are not rare and can be observed in many circumstances. For example, Starbucks increases the temperature at which it brews coffee. In that way, caffeine can be dissolved in water to have better taste and fragrance.

In this study, we investigated the solubility of sodium chloride, a typical salt, and glucose, a common sugar, at varying temperature. Lower critical solution temperature (LCST) behaviors of polymers and relevant explanations are also explored. Then an explanation and a conclusion about the LCST behavior about a typical small molecule, AQ-1,8-3E-OCH3, is achieved to apply the molecule. One of the possible applications of small molecules with LCST behaviors is to control drug releasing and to become temperature switch. Currently such works are done by polymers as they have pedants and cores and therefore LCST behaviors, even though they are hard and complex to be synthesized. The investigation will provide references for possible LCST behaviors of small molecules. They can be synthesized in the light of micelle form of AQ-1,8-3E-OCH3. As small molecules are quicker and
easier to be synthesized, they can be a replacement of polymers for medical use and temperature switch.

2. Experimental Results and Discussions

2.1. How temperature influences solubility of inorganic compounds and small organic molecules

The solubility of sugar and salt is different in varying temperatures and the influence of temperature on their solubility is divergent. As shown in Figure 1, the solubility of salt looks almost independent of temperature while the solubility of sugar is highly dependent on temperature within the given temperature region. The solubility of salt (NaCl) increases from 0.357 g/mL\[^{1}\] at 0 °C to 0.391 g/mL\[^{1}\] at 100 °C, increasing by 9.52% when temperature rises from 0 °C to 100 °C. The increase of solubility for salt is minimal compared to the solubility of sugar, which increases from 1.79 g/mL\[^{2}\] at 0 °C to 4.87 g/mL\[^{2}\] at 100 °C, increasing by 172% when temperature increases from 0 °C to 100 °C.

\[ \text{NaCl(s)} + (x+y)\text{H}_2\text{O(l)} \rightarrow \text{Na}^+(\text{H}_2\text{O})_x\text{(l)} + \text{Cl}^-(\text{H}_2\text{O})_y\text{(l)} \quad (\text{Equation 1}) \]

For sodium chloride, when the temperature is rising, water molecules, which are solvent molecules, have higher kinetic energy, leading to more frequent collisions of molecules, thus increasing the possibility of water molecules to meet solid sodium chloride (NaCl). Once NaCl collides with a moving H\(_2\)O molecule which has huge kinetic energy, the water molecule will pass the energy to NaCl and enable it to move, making the following dissolution reaction moving forward. Water molecules thus hydrate both cation and anion to form hydrated Na\(^+\)(H\(_2\)O\(_x\))\(_{(l)}\) and Cl\(^-\)(H\(_2\)O\(_y\))\(_{(l)}\), as shown in Equation 1. Therefore, NaCl becomes more soluble at elevated temperatures.

As illustrated in Figure 2, with the increase of temperature, the solubility of sodium chloride increases to some extent. In a given solution, with the increase of solubility of sodium chloride, the number of Na\(^+\) and Cl\(^-\) increases and the number of water molecules surrounding Na\(^+\) and Cl\(^-\) decreases. In other words, the hydration number decreases.
Figure 2. Schematic of dissolving NaCl solid and forming saturated NaCl solution at 0 °C, 50 °C, and 100 °C. With the increase of temperature, the solubility of NaCl increases, corresponding hydration numbers of both Na⁺ and Cl⁻ decrease on average.

The decrease in hydration number restricts dissolution of NaCl. As we know, the density of water is 1.00 g/mL and molar mass of water is 18.0 g/mol; sodium chloride has a molar mass of 59.0 g/mol. The solubility of sodium chloride at 0 °C is 0.357 g/mL. [1] 1 mL saturated NaCl solution at 0 °C contains 55.6 mmol water molecules and 6.05 mmol Na⁺ and Cl⁻ respectively. On average, each ion is surrounded by about 4.59 water molecules. When it is 100 °C, the solubility of sodium chloride is 0.391 g/mL. [1] After the calculation with the same process above, each ion in 100 °C is surrounded by about 4.19 water molecules on average, forming ion pairs between hydrated cation and hydrated anion (Figure 3). The distance between hydrated ions decreases with the increase of solubility, preventing themselves from being separated and soluble when extra NaCl is added. Consequently, the stronger attraction between ions led by the increment of temperature prevents sodium chloride from dissolving more in higher temperatures.

Figure 3. Ion pairs of hydrated Na⁺ and Cl⁻ at 0, 50, and 100 °C with different shield effects between Na⁺ cation and Cl⁻ anion. The ion pairs were categorized as fully solvated ion pair (left), solvent-shared ion pair (middle), and contact ion pair (right) with different ionic distancing.

In addition to the decrease in hydration number, the strength of the ionic bond, a type of bond caused by the attraction of anion and cation in ionic compounds prohibits further dissolution too. Ionic bond strength seems to be independent of temperature and is a dominant factor limiting the solubility of salt. As a result, the solubility of salt in Figure 1 appears relatively steady as temperature rises.
Except for the parameters mentioned above influencing the solubility of sodium chloride in water, there are some other parameters. For example, as in Figure 2, the lattice energy of unit cells disfavors the dissolution of salt in water. Whereas, the hydration energy of sodium cation and chloride anion, as shown in Equation 1, favors the dissolution of salt in water. As enthalpy of the equation is positive (3.87 kJ/mol at 25 °C),\[4\], the reaction in Equation 1 is endothermic. When the temperature rises, the forward dissolution reaction is favored, causing the substance to dissolve more. Generally, considering all the limiting and driving factors, the solubility of sodium chloride keeps relatively stable as temperature rises.

Glucose is a typical sugar whose hydration energy and lattice energy are not influenced by temperature; therefore, hydration number and ionic bonds have limited influence on the solubility of glucose at varying temperatures. Because each glucose molecule has five hydroxyl(-OH) groups, one glucose molecule is easy to form inter-molecular hydrogen bonds with another glucose. When glucose is added into water, these inter-molecular hydrogen bonds among glucose molecules are damaged by water molecules. New hydrogen bonds are formed between glucose and water, thus dissolving glucose in water. When temperature rises, kinetic energy of H₂O is higher. H₂O molecules move faster to collide with glucose. Because of the five hydroxyl groups in glucose, water molecules can easily form hydrogen bonds with glucose. Before dissolution, the -OH groups in two glucose molecules are bonded together by intra-/inter-molecular hydrogen bonds, as shown in Figure 4B. As temperature increases, the surrounding water molecules move faster and faster due to increased kinetic energy, the intra-/inter-molecular hydrogen bonds in/among glucose molecules become weaker and weaker, and are finally broken by water molecules as shown in Figure 4C. Therefore, the temperature can strongly influence the solubility of glucose.

![Figure 4A](image1.png) ![Figure 4B](image2.png) ![Figure 4C](image3.png)

Figure 4. Glucose molecule and intra-molecular hydrogen bond in glucose molecules.

The case of sugar and salt is not rare. Taste of coffee is also related to the effect of temperature on solubility of ingredients in coffee. The higher the temperature is, the higher the solubility of fragrance substances is and the better the taste of the coffee will be. Adjusting temperature has been used as an approach to extract sweeter ingredients from coffee beans. Researchers found that the concentration of ketone (-C=O) and aldehyde (-CH=O) compounds in Espresso extracted at 92 °C hot water was higher than those in Espresso extracted at 88 °C hot water.[5] The finding can be explained with multiple theories. The carbonyl group in aldehyde has an O atom with high electron density to form hydrogen bond with water molecules and help it dissolve. In addition, aldehyde and ketone (Figure 5) are polar molecules whose negative part can attract the H atoms in water molecules which are partially positive, and verse visa. As temperature increases, water molecules move faster due to higher kinetic energy which endows them an opportunity to collide more often with ketones and aldehydes. After the collision, water molecules will interact with ketones and carbonyls by hydrogen bonds. On the macroscopic scale, a higher temperature helps extract more fragrant substances, which in turn makes the coffee taste better.
2.2. How temperature influences solubility of polymers

Different from glucose and edible salt, some polymers are found less soluble in water as temperature rises. One typical example is poly N-isopropylacrylamide (PNIPAAm). The structure of PNIPAAm is shown in Figure 6A. It contains hydrophilic side chains and a hydrophobic backbone. When PNIPAAm is added into the water at a low temperature (lower than 32 °C), hydrogen bonding is formed between water molecules and the side chain of PNIPAAm as presented in Figure 6B. At this time there are a bulk of water molecules surrounding the chain so that the polymer is dissolved. When the temperature increases, the water molecules have larger higher kinetic energy so that they move faster and tend to break hydrogen bonds between H₂O and hydrophilic motif since a hydrogen bond is not as strong as a covalent bond. When the temperature is at 32 °C, water molecules have higher kinetic energy and move fast enough to break all hydrogen bonds. The hydrophobic backbone of polymer collapses to a globule, which is insoluble in water. The hydrophobicity of backbone outweighs the hydrophilicity of pedants when the temperature reaches 32 °C, making soluble polymer collapsed and the solution cloudy.

The loss of water molecules hydrogen-bonded to a pedant leaves a vacancy behind and drives neighboring water molecules to break hydrogen bond and escape from neighboring pedant. As a result, all water molecules hydrogen-bonded to pedants are squeezed by collapsing hydrophobic carbon-carbon backbone, forming water-insoluble globules as shown in Figure 7. The cohesive force from the backbone makes PNIPAAm to solids, allowing the substance to occur phase change.
Figure 7. Collapse of PNIPAAm at lower critical solution temperature. (The graph on the left shows the solution when the temperature is below 32 °C, the solution is transparent. The graph on the right shows the solution when the temperature is above 32 °C. The collapse of molecules leading the solution to be turbid.\[7,8\])

As mentioned before, the phase change will only occur when the temperature is high enough, enabling water molecules to have adequate kinetic energy to break hydrogen bonds. The lowest temperature which can allow polymers to have phase change is called a lower critical solution temperature (LCST). Specifically, the LCST of PNIPAAm is 32 °C. The LCST behavior of polymers are dependent on the interaction between hydrophobic backbone and hydrophilic pendent.

Figure 8. Other typical polymers like PNIPAAm (from left to right: Ploy(N,N-diethylacrylamide) (PDEAAm), Poly(N,N-dimethylaminoethylmethacrylate) (PDMAEMA)) (The hydrophobic backbone and hydrophilic side chain of these polymers cause their LCST behaviors).\[9\]

Besides PNIPAAm polymer, other similar pendent polymers like PDEAAm and PDMAEMA (Figure 8) also demonstrate LCST behaviors. They both have hydrophobic backbones and hydrophilic pendants. In addition, polyethylene oxide PEO and polypropylene oxide PPO\[10\] are additional examples of polyether polymer with LCST behaviors. Although these polyether polymers have been utilized in many scenarios, it is worth mentioning that the solubilities of these polyether polymers are significantly dependent on structures. For example, polyethylene oxide (PEO, [-CH2-CH2-O-]n), as shown in Figure 9A, is extremely water-soluble. When n ≤ 600, PEO is infinitely soluble in water and can be widely used in the cosmetics industry due to such property.\[11\] However, polyformaldehyde (POM, [-CH2-O-]n) as shown in Figure 9B, whose repeating unit has one methylene group (-CH2-)
less than the repeating unit of PEO polymer, is a completely water-insoluble plastic. The simulation of the electron density of the molecules gives a possible explanation for the phenomenon.\cite{12} In the PEO chain, the induction effect of oxygen atoms can fully influence the carbon atoms on both sides. The nearby oxygen atoms will have higher electron density and stronger polarity, forming stronger hydrogen bonds with water molecules, which is helpful for dissolving (Figure 9C). However, in the case of POM, each oxygen atom needs to "share" the electrons of its adjacent carbon atoms with its spaced oxygen atoms, so the density of the surrounding electron cloud drops sharply, preventing it from dissolving in water (Figure 9D).

![Figure 9. PEO and POM and their oxygen induction effect.](image)

As polyether polymers, PPO can bond with other polymers with LCST behaviors. When PPO forms copolymers with other substances, the new substance shows LCST behavior in a different way. A typical example is PNIPAAm-PEO-PPO-PEO-PNIPAAm. When the temperature is below 31°C, PNIPAAm, polyphenyl ether (PPO) and polyethylene oxide (PEO) are all soluble. When the temperature is higher than 34°C, the LCST of PPO and PNIPAAm, \cite{10}these two substances become hydrophobic so that the copolymer will form a structure with PPO core and PNIPAAm surroundings, which is a kind of association and represent as an educt (similar to the structure of the cell membrane as shown in Figure 10).

2.3. Solubility of small molecules decreases with the increase of temperature

Amphiphilic block copolymers have a distinct explanation for their LCST behaviors. Aggregation/association is the process that primary particles collide with each other to form aggregates with the help of hydrogen bonding and covalent bonds, etc. The aggregation of the macromolecules is different from precipitation. The aggregations can always exist steadily in solution, forming colloid-like solutions. The forming of micelle is an important aspect of aggregation. Originally an aggregate molecules of surfactant is called micelle when spitting in a liquid colloid with the hydrophilic head regions exposed to solvent and hydrophobic single-tail in the center. This phase is caused by the packing behavior of single-tail lipids in a bilayer (as shown in Figure 10). The resistance exists when filling interior of a bilayer, while satisfying the area per lipid head group had on the molecule by the hydration. The resistance leads to the formation of a normal-phase micelle (oil-in-water micelle). Inverse micelles (water-in-oil micelle) have the head groups at the center and single-tail lipids exposed to surroundings.
During the process, the hydrophilic segments inhibit the tendency to form aggregations, forming a micelle that the hydrophilic segments surround the insoluble segments. The amphiphilic block copolymers are polymers composed of segments with diverse affinities, i.e., a part of the copolymer is hydrophobic while another is hydrophilic. They are also called polymeric surfactant. Similar to common surfactant, the polymeric surfactant has lower Critical Micelle Concentration (CMC).

Micelles are constructed only when fulfilling two prerequisites. Firstly surfactant’s concentration is larger than the critical micelle concentration. Secondly the temperature of the system is larger than Krafft temperature.

2.4. LCST behaviors of small molecules in water solutions

LCST behavior does not only appear in polymers such as PNIPAAm, but also shows in small molecule water solutions. The phenomenon is unusual as the solubility of typical small molecules such as edible salt, sugar and caffeine often increases with temperature, while an anthraquinone derivative breaks the rule. The molecule with structure A (AQ-1,8-3E-OCH₃: 1,8-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)anthracene-9,10-dione) in Figure 11 is a typical example of small molecule solution with LCST behavior and is occasionally discovered in the laboratory. At 25 °C, a temperature approximate to room temperature, the solution of AQ-1,8-3E-OCH₃ is transparent and brown. When the temperature rises to 45 °C, the small molecule solution turns to be turbid and yellow, showing in 45°C, AQ-1,8-3E-OCH₃’s solubility decreases and occurs phase change. As AQ-1,8-3E-OCH₃ becomes phase separated at a specific temperature, it is regarded as having LCST behavior. After cooling, the solution becomes transparent again, showing the phase change of AQ-1,8-3E-OCH₃ is reversible. The temperature can, therefore, be regarded as a switch to control the phase change of AQ-1,8-3E-OCH₃. However, the switch is not going to work for another anthraquinone derivative B (AQ-1,8-3E-OH: 1,8-bis(2-(2-hydroxyethoxy)ethoxy)ethoxy)anthracene-9,10-dione), even though it has similar structures with A (AQ-1,8-3E-OCH₃). A just substitutes the hydroxyl groups (-OH) of B with methoxy groups (-OCH₃). It is reasonable to speculate that B has similar chemical properties with A and has LCST behavior due to the similarity in their structures. Surprisingly, at 25 °C, the solution of B is red and transparent, at 45 °C, the solution is still red and transparent, without showing LCST behavior.
Figure 11. Comparison of two small molecule water solutions at an elevated temperature (45 °C). The two molecules are composed of hydrophobic 9,10-anthraquinone core and hydrophilic ethylene oxides chains. The sole difference of the two molecules are the ending groups in the chains: one is capped with methoxy groups while another one is capped with hydroxyl groups (right).[14]

The solubility of A and B can be partially explained by the structures when compared to the molecules mentioned above. Both AQ-1,8-3E-OCH_3 and AQ-1,8-3E-OH have simple structures, but they have remarkable differences with the structure of edible salt (NaCl) as A and B are organic molecules while NaCl is inorganic. A and B are much more like glucose and caffeine in structure and nature. The solubility of the molecules is determined by bonds and forces. NaCl crystal has ionic bonds, which can be easily broken in water solutions and form hydrated ions Na^+(H_2O)_x(l) and Cl^-(H_2O)_y(l). With the increment of temperature, the reaction goes forward. However, as organic compounds, AQ-1,8-3E-OCH_3 and AQ-1,8-3E-OH molecules are bonded with each other by intermolecular forces including London dispersion forces, dipole-dipole force, and hydrogen bonds instead of ionic bonds. Their change of solubility with temperature cannot be explained using the theory of hydrated ions. In this case, glucose and caffeine may be better references to understand the solubility of AQ-1,8-3E-OCH_3 and AQ-1,8-3E-OH. The solubility of AQ-1,8-3E-OH can be explained, referring to the solubility of glucose as both of them have hydroxyl groups (-OH). With stable hydration energy and lattice energy, glucose’s five -OH groups form hydrogen bonds when colliding with H_2O to help glucose dissolve. As for AQ-1,8-3E-OH, it also has two -OH ending groups, so hydrogen bonds are also formed with water molecules and hence AQ-1,8-3E-OH dissolves in water solution (Figure 12). When the temperature rises, the water molecules have higher kinetic energy to move, which increases the collision frequency of water molecules and AQ-1,8-3E-OH to increase its solubility. Whereas, The hydroxyl group is not existing in AQ-1,8-3E-OCH_3. A and B have a carbonyl group (-CH=O) in common, which is also shown in a caffeine molecule and allows a caffeine molecule to attract water molecules. The double bond between C and O has high electron density, while water molecules are partially positive in H (O has higher electron negativity and attracts the electrons to its part). As a result, H_2O molecules can be attracted by the carbonyl groups and help dissolve both A and B theoretically.
Ether groups are important for the solubility of polymers, especially polyethers. PEO and POM are both polyethers with similar structures, as shown in Figure 9. Their only difference in structure is the number of methylene (-CH₂-) groups between two neighboring O atoms. However, the small difference influences the electron density of the molecules and leads to huge discrepancy between their properties \cite{12} – PEO shows LCST behavior, while POM does not. Similarly, AQ-1,8-3E-OCH₃ and AQ-1,8-3E-OH have ether groups, more specifically, ethylene oxide groups. To sum up, the only difference between A and B is their different ending groups, which lead to different solubility in water.

Without hydroxyl end group, AQ-1,8-3E-OCH₃ shows different properties as the temperature rises due to its structure. As shown in Figure 13, the anthraquinone cores are relatively hydrophobic as only two carbonyl groups (-C=O) can interact with water molecules. Ethylene chains are hydrophilic since there are eight ester groups (-O-) to form hydrogen bonds with water molecules. Such structure is quite comparable with the structure of phospholipids. At 45 °C, we speculated that the molecule A might form micelle structure, in which the relatively hydrophobic anthraquinone cores stay inside of the micelle, and the hydrophilic ethylene oxide chains as the sphere of the micelle, directly contacting with water molecules in the surrounding.

Similarly, in another literature, Ogoshi et al. reported that a pillar [5]arenes modified with oligoethylene oxide groups (Figure 14) demonstrated LCST behavior with a transition temperature of 55 °C, as shown in Figure 15.\cite{15} Such pillar[5]arenes act as another example presenting temperature-sensitive behavior as AQ-1,8-3E-OCH₃.
Figure 15. Pictures of solution of 2 (2mM) at (a) 25°C and (b) 55°C.\textsuperscript{[15]} When it is lower than 25°C, the solution is clear, while at 55°C, the solution turns to be turbid. When the temperature is lower, the solution is clear again.

Combined with the information above, the molecules showing LCST behavior usually have hydrophobic cores as well as hydrophilic chains and therefore can be considered as amphiphilic molecules. Such molecules can form water-in-oil micelles with tails exposed to surroundings at elevated temperatures. The hydrophilic part attracts each other to form the outermost layer, and the hydrophilic side chains form the inner side. The cohesion force shapes the molecule to a sphere, as shown in Figure 16.

![Proposed structure of AQ-1,8-3E-OCH$_3$ at elevated temperature](image)

Figure 16. Proposed structure of AQ-1,8-3E-OCH$_3$ at elevated temperature

3. Conclusions
As the temperature rises from room temperature to 45°C, AQ-1,8-3E-OH solution appears to have no change, but AQ-1,8-3E-OCH$_3$ becomes cloudy, indicating AQ-1,8-3E-OCH$_3$ phase changed at 45°C, which is not high temperature. The LCST property of AQ-1,8-3E-OCH$_3$ is similar to certain kind of polymers such as PNIPAAm and PEO. The structure of AQ-1,8-3E-OCH$_3$ is similar to that of sugar, both of which are small organic molecules. In other words, LCST behavior should not, and is not expected to be observed in AQ-1,8-3E-OCH$_3$, as the solubility of small organic molecules usually increases with temperature. By discussing the solubility of small molecules such as sugar, inorganic salt such as edible salt, and polymers with LCST behaviors such as PNIPAAm and comparing the structure of AQ-1,8-3E-OCH$_3$ with molecules mentioned above, LCST behavior of not only AQ-1,8-3E-OCH$_3$ but also pillar[5]arenes modified with oligoethylene oxide groups can be well explained.

The reversible swelling - contraction process of PNIPAAm-like thermo-sensitive hydrogels can be used to achieve controlled release of drugs. As its low critical dissolution temperature (LCST) is near human body temperature and the process is convertible, thermo-sensitive macromolecule can automatically sense abnormal changes in temperature and chemical environment around the lesion to release the drug or to stop the releasing. The critical temperature for AQ-1,8-3E-OCH$_3$ is also approaching to body temperature of mammals, and reversely changes between transparent at 25 °C and cloudy at 45 °C. Therefore, in the future, it is expected that small molecules with LCST behaviors can be potentially applied for releasing drugs or as a thermal switch. For example, medicine for hypothermia can be surrounded by molecules similar to AQ-1,8-3E-OCH$_3$. When it is lower than LCST of the molecule, the outermost molecules are expected to dissolve in plasma, releasing drugs to
cure hypothermia; when it is higher than LCST, the molecules aggregate to separate out in form of micelle, surrounding medicine.

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