

## Entropic control in green chemistry and materials design\*

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*Abstract:* The traditional construction of materials is usually driven by classical synthetic transformations involving the making and breaking of covalent bonds. These processes often require high-energy input and highly reactive and hazardous materials. In natural systems, one typically encounters synthetic control schemes that are based on entropic forces rather than these human-designed enthalpic manipulations. In natural processes, phase changes and triggered mixing are often employed to direct systems toward or away from equilibrium conditions. The recognition of these “natural tendencies” allows one to design processes that have reduced toxicological and environmental impact. Results in noncovalent derivatization (NCD) and bioinspired photopolymers that illustrate this shift toward entropic control are described.

*Keywords:* green chemistry; phase diagrams; entropy; photopolymers; thymine.

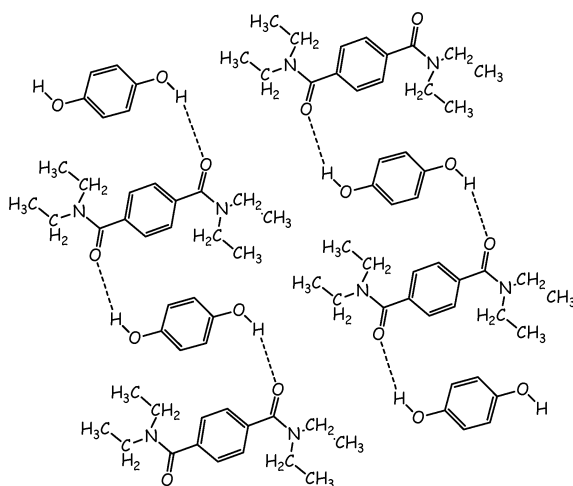
In the early 1990s, the concept of noncovalent derivatization (NCD) was developed and applied to controlled diffusion and solubility of hydroquinones in Polaroid Instant Photography [1]. NCD employs the techniques of crystal engineering and molecular self-assembly to purposefully control the physical and chemical properties of a substance by incorporating basic building blocks within binary or ternary cocrystalline matrices [2]. Basically, NCD involves constructing materials with unique properties by manipulating the *noncovalent* interactions rather than a series of traditional *covalent* derivatizations. Because these processes often occur spontaneously at ambient conditions, this technique [3] was described in 1998 as an example of green chemistry [4].

Specifically, the Polaroid technology sought to create a neutral stable entity that would release hydroquinone at elevated pH. As an alternative to traditional covalently modified hydroquinones with base labile protecting groups, the researchers at Polaroid created self-assembled binary cocrystals of hydroquinones and bis-(*N,N*-dialkyl)terephthalamides (Fig. 1) [5]. The dissolution rate and relative neutral stability could be controlled by the nature of the terephthalamide complexing agent. This technique was shown to be viable at industrial scale through processes using aqueous suspension milling. Process analytical methods were developed using a combination of X-ray powder diffraction, solid-state NMR spectroscopy, and differential scanning calorimetry [6].

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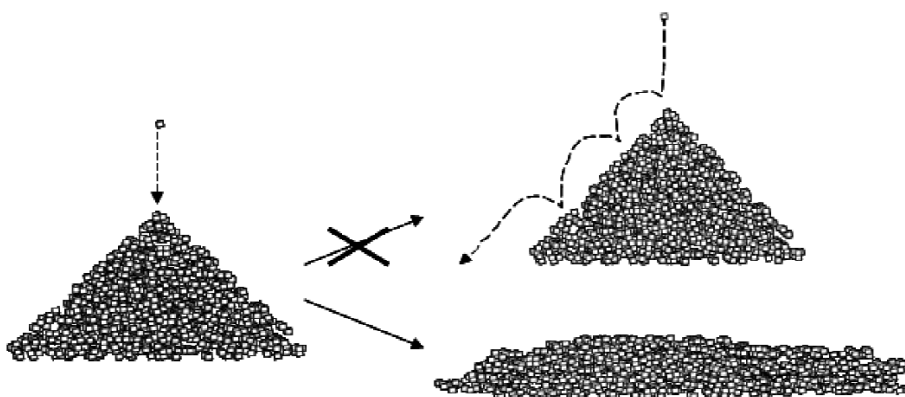
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**Fig. 1** Hydroquinone-bis-(*N,N*-diethyl)terephthalamide cocrystal.

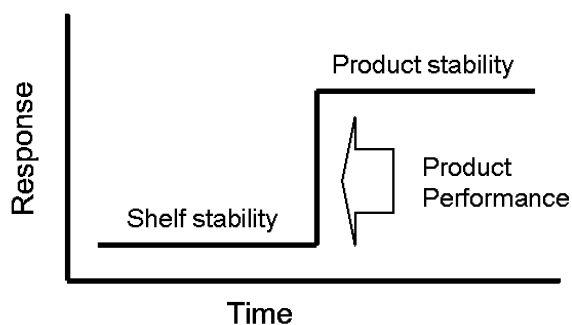
When one considers the thermodynamics involved in such processes, it is useful to separate out the enthalpic [ $\Delta H$ ] and entropic [ $\Delta S$ ] components. While certainly this leads to an oversimplification of these complicated processes, a few generalizations are worth noting. In general, conventional organic synthesis can be seen as a series of covalent bond-breaking and -forming reactions. While entropy plays a role in these transformations, for the most part, these processes are governed by bond energies and relative enthalpies. Natural systems, on the other hand, are controlled in a very different way. Many “natural” reactions are often driven by compartmentalization, mixing, and phase separation. Glycogen exists as phase-separated microdomains in liver and muscle cells. Adipose cells store triacylglycerols as discrete oil droplets. In these cases, the release of the material for bioavailability requires a triggered molecular event that ultimately allows for coalescence of phases. For example, significant amplification is observed during the release of neurotransmitters at a synaptic junction. Triggered by a small number of molecular events, a flood of molecules is released as a consequence of permeation and mixing processes. In some cases, the level of chemical amplification can exceed  $10^{20}$ ! In these examples, one can identify a unique event that creates a “tipping point” where a rapid transition from one stable equilibrium state to another occurs. NCD is uniquely poised to create and control phenomena such as this.

Imagine the formation of a pile of salt crystals on a surface. As one drops the salt into the center of the pile, the forming mound increases in mass and height. After a certain critical amount of material has been accumulated, one reaches a point (the proverbial straw that breaks the camel’s back) where that very last grain of salt is not capable of balancing on the top of the pile. At this moment, what does not typically occur, is that the grain of salt tumbles simply down the side of the pile. Instead, a catastrophic event occurs, causing the entire pile of salt to collapse (Fig. 2). It is control of that specific moment of catastrophe that NCD seeks to capture: a “tipping point” where one quickly jumps from one stable equilibrium to another.



**Fig. 2** Catastrophic collapse of a growing pile of salt.

From a manufacturing perspective, the stability of the pre-catastrophic state translates into shelf-life stability (Fig. 3). The catastrophic event itself represents product performance, and the post-catastrophic equilibrium is equated with product stability. If one can control this type of process at the level of intermolecular forces, one should be capable of designing a differentiated and robust product.



**Fig. 3** Product characteristics between stable equilibria.

Consider a typical simple binary-phase diagram of compounds A and B that forms a eutectic composition at approximately 50 % (Fig. 4). At the termini of this diagram, 100 % A and 100 % B, the compositions are of pure crystalline material. The inherent stability of these compositions is based on the enthalpic forces of attraction between their individual components. But this enthalpic stability comes at the expense of entropy because of the highly ordered, minimum entropy structure. At the eutectic composition, however, the situation is reversed. The composition has settled with maximum entropy and disorder at the expense of enthalpic forces.

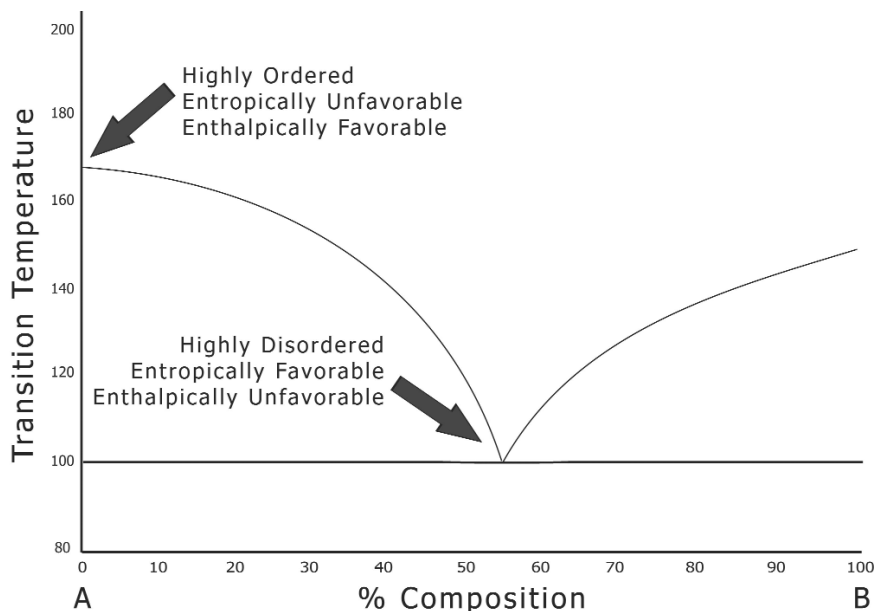


Fig. 4 Typical binary-phase diagram.

With NCD, one metaphorically fuses two phase diagrams together where the compounds C and D form some unique molecular complex consisting of some integer molar ratio. In Fig. 5, C and D form a 1:1 molar complex CD, with two eutectics, one between pure C and the complex CD and one between the complex CD and pure D. The complex CD is the “noncovalent derivative”. And for applications in the solid state, CD has properties and behavior entirely different from either pure parent compounds C or D.

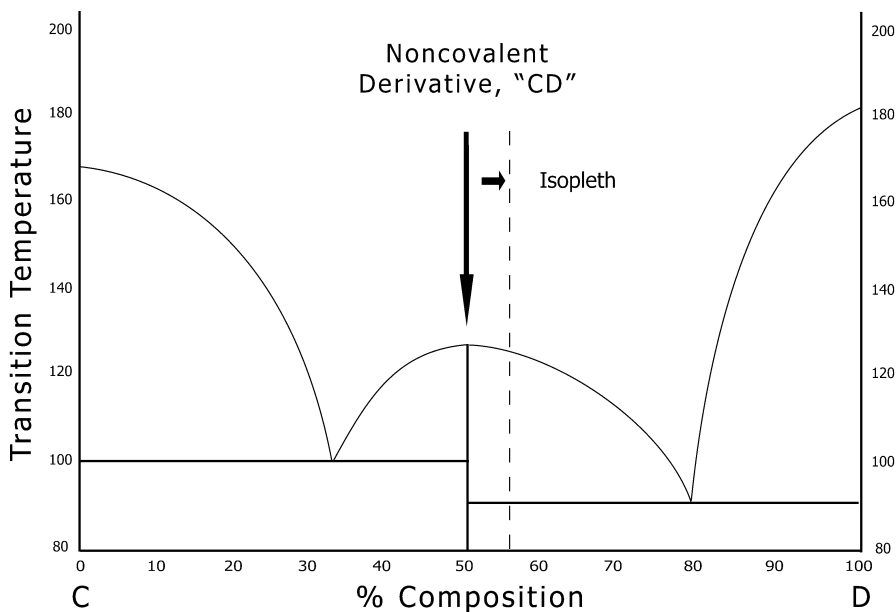


Fig. 5 Binary-phase diagram of a system that forms a 1:1 complex.

If one monitors the bulk physical properties of the CD complex while introducing small amounts of “impurity” C or D, one experiences an initial resistance to change, and is hard pressed to measure or even identify the presence of the additional material. However, after a certain threshold amount is reached, the physical behavior of the material “jumps” to the properties better defined for the eutectic composition.

This process is best illustrated by imagining a pure 3D binary cocrystal of some system. This material will have a determinable solubility within any given solvent. If some number of minimum threshold point defects are created within the matrix, where the trans-crystal hydrogen bonding pattern is somehow interfered with, one can significantly alter the solubility of the bulk material (Fig. 6). This is accomplished by exponentially increasing the surface area exposed to the solvent.

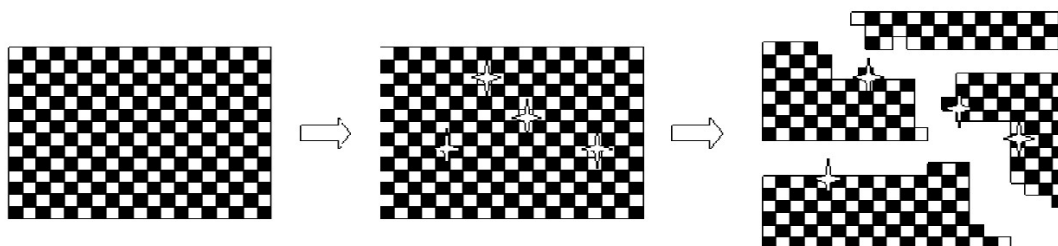


Fig. 6 Dissolution of a solid with point defects.

The field of NCD seeks to correlate precisely the impact of individual noncovalent interactions with various physical properties. In the same way that structure–activity relationships are established for the covalent reactivity of molecules through traditional physical-organic chemistry, NCD seeks to establish a series of quantitative relationships that correlate crystallographic measurements with bulk physical properties.

Another example of entropic control in materials design is observed with photocrosslinkable polymers (Fig. 7) [7]. Thymine has been shown to undergo a  $2\pi + 2\pi$  photocyclodimerization reaction upon exposure to short-wavelength UV light. With minimal amount of irradiation, these thymine-containing polymers become insolubilized. This technology is useful for the construction of photoresists [8].

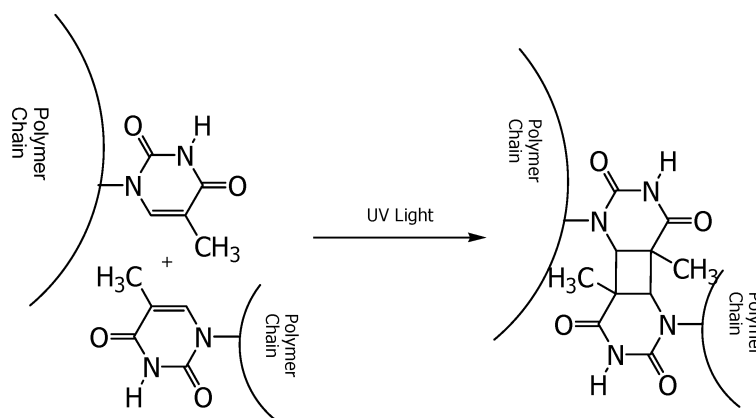
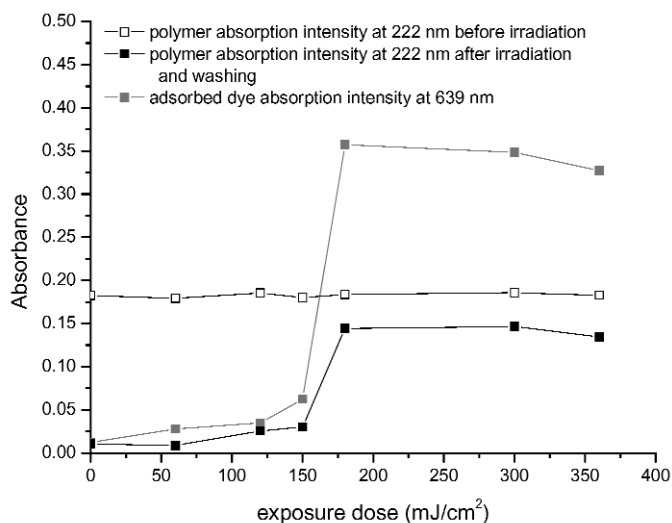


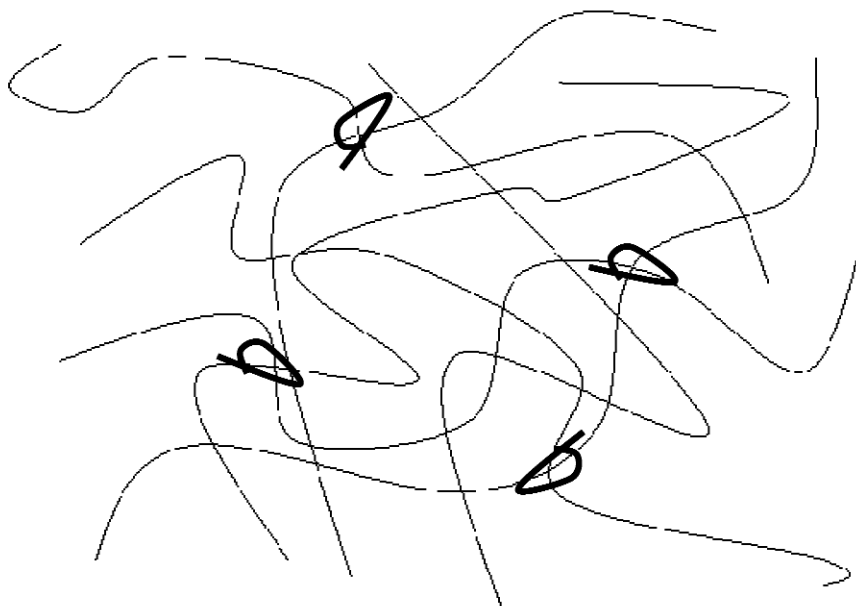
Fig. 7 Polymer crosslinks through thymine photocyclodimerization.

An interesting phenomenon associated with these systems is the ability to precisely control the amount of energy required to insolubilize a particular copolymer, and additionally the extent to which the insolubilization occurs (Fig. 8) [9].



**Fig. 8** Control of insolubilization of thymine-based polymers.

This process can be viewed as a “reverse” catastrophic event (Fig. 9). The polymer begins as a freely soluble material with independent random polymer chains. As photons are absorbed and thymine units undergo the photocyclodimerization reaction, crosslinks and corresponding networks and entanglements are created, rendering the system dynamically restricted and hence insoluble. This rapid



**Fig. 9** Crosslink formation as reverse catastrophic events.

“jump” from soluble to insoluble is due to achieving a threshold limit of crosslink density required. If one views the process in reverse, it is not significantly dissimilar to the dissolving crystals and point defects described for NCD. This technology has been applied to the templated formation of conductive polymers [10], dissolution control in release systems [11], and even control of hair curling [12].

From the perspective of green chemistry, entropic control holds a great deal of potential. With the intrinsic chemical amplification factors observed with these processes and the freedom from high temperatures and hazardous reagents, there are many opportunities to design truly unique and benign materials and technologies. If one considers the entropic implications of many other traditional synthetic processes, one is likely to discover additional mechanisms that illustrate this concept.

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