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ARTICLE *in* CRYSTAL GROWTH & DESIGN · MAY 2002

Impact Factor: 4.89 · DOI: 10.1021/cg0255218

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CRYSTAL GROWTH & DESIGN
2002
VOL. 2, NO. 4
255−257

Noncovalent Derivatization: Green Chemistry Applications of Crystal Engineering

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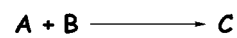
Received April 17, 2002; Revised Manuscript Received May 14, 2002

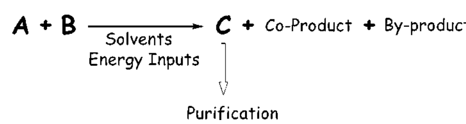
ABSTRACT: The field of crystal engineering is rapidly expanding. As our understanding of the mechanism of construction and relationship between structure and function of molecular crystals increases, it is important to recognize that this field offers significant toxicological and environmental benefits. The processes of molecular recognition and self-assembly are inherently benign in terms of its impact on human health and the environment. These benefits must be articulated and exploited.

As the field of crystal engineering continues to grow, it is worthwhile to consider some philosophical implications of its impact to the chemical sciences. We live in a society based on materials. We depend on chemical products for virtually every aspect of our lives. We have come to expect a continuous stream of new pharmaceuticals to cure life-threatening diseases or for the incremental improvement in the quality of our lives. We expect an ever-expanding food supply based on an agricultural industry that is designing new fertilizers and pesticides. We rely on new materials for the construction of buildings, clothing, and microelectronic gadgetry. Society has come to expect innovation from industry in the form of material goods. The economic fabric of our society is based for the most part on the design, manufacture, marketing, and sale of these materials, but the creation of these new "things" does not come without cost. Industry must use whatever state-of-the-art scientific tools available to meet the consumer's ever increasing appetite for new products. Under the pressure imposed by the expectations of "increased shareholder value" and patent timelines, there is less opportunity for industry to perform basic research. It must largely rely on the current literature for most of the new chemical processes and transformations it will use. Many of the chemical reactions available to the chemical industries use or generate substances that have a detrimental effect on human health and the environment. Ironically, at the same time that society has increased its expectations of materials production, it is also becoming more demanding in terms of toxicological and environmental issues. The negative reputation of the chemical industry on the general public has been propagated in large by the reoccurring reports in the media of chemical accidents, spills, leaks, and explosions. Much, if not all, of this criticism is well deserved. Green chemistry is the philosophy that the best method of pollution prevention, from an ethical and economic perspective, is to focus on toxicological and environmental implications at the earliest stage of product design. It is simply better to carry our processes that have minimal use of hazardous material. Industry certainly recognizes this fact. Unfortunately, most of the tools currently available are not environmentally benign.

Scheme 1



Scheme 2



Consider a simple schematic of a chemical reaction. In general, an ideal chemical transformation can be represented as a simple combination of reactants to form a single product (Scheme 1).

In practice, chemical reactions are rarely, if ever, this simple. There are many other implications (Scheme 2). Often there is the stoichiometric generation of coproducts and a number of byproducts that are formed during the reaction. These reaction products can have serious consequences from a toxicological or environmental analysis. The solvents that are used can constitute the majority of the total mass of the reaction materials. The energy used for the heating, cooling, or mixing of the reaction can account for the greatest cost, both environmentally and economically. It is also important to recognize that product isolation and purification, with the use of chromatography, distillation, or other solvent- or energy-intensive processes can have serious impact.

Why are chemical reactions carried out in the first place? What is the objective of chemical synthesis? It is safe to say that chemical synthesis is always carried out for the purpose of manipulating the chemical and physical properties of a material. Very often an individual molecule is identified that has several desirable physical and chemical properties for a specific application, but this molecule is not perfect. As an example,

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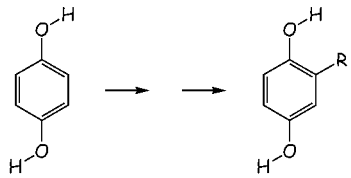
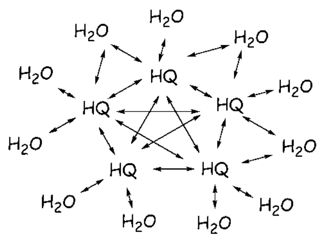
10.1021/cg0255218 CCC: $22.00
Published on Web 06/01/2002

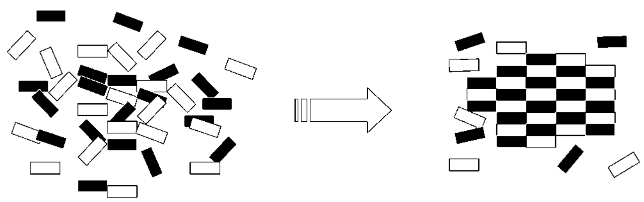
Scheme 3



Scheme 4



Scheme 5



imagine that the molecule hydroquinone (HQ) has many desirable properties for some application, except that it is too water soluble. The typical research and development approach would be to synthetically modify the molecule to increase its hydrophobicity. For example, a research effort could be undertaken to synthesize a number of alkyl derivatives (Scheme 3). Of course, these synthetic reactions will most likely produce coproducts and byproducts, make use of solvents and energy inputs, and require separation and purification.

What is being accomplished, at the molecular level, by adding an alkyl group to HQ? To render HQ less water soluble, the intermolecular interactions between the HQ molecules must be strengthened while simultaneously reducing the strength of the intermolecular interactions between the HQ molecules and water (H_2O) molecules (Scheme 4). The addition of the alkyl group will accomplish this by increasing the nonpolar, lipophilic surface area of the molecule, strengthening the van der Waals interactions between the HQ derivatives.

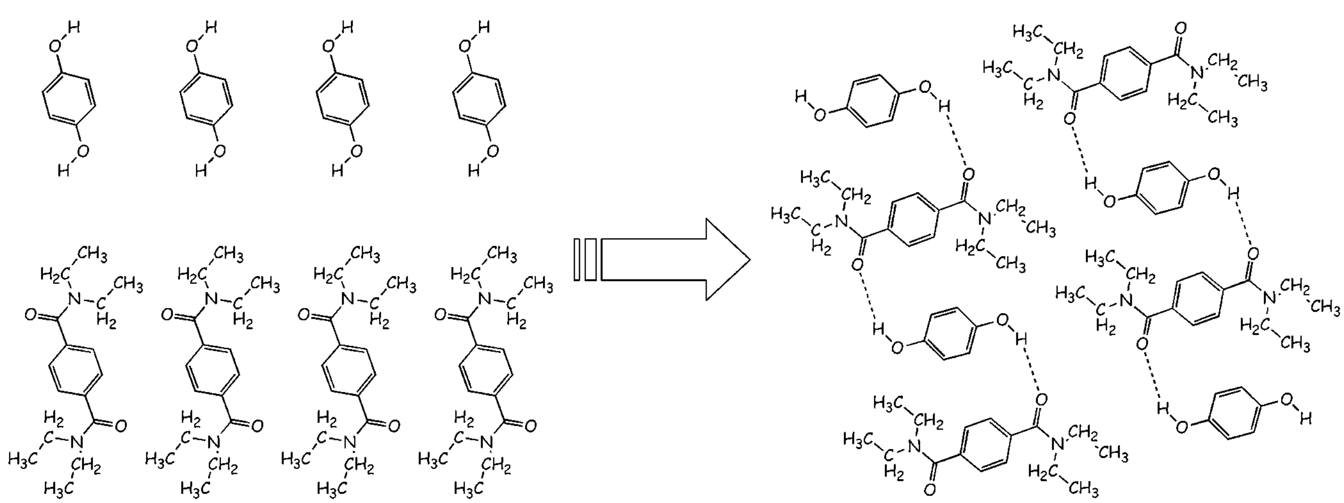
The process of molecular recognition and self-assembly occurs spontaneously in nature. Crystal engineering studies the mechanisms by which functional groups on molecules interact so as to align and orient molecular aggregates in ordered matrixes (Scheme 5).[1]

By taking advantage of this "natural tendency" of molecules to self-assemble in ordered matrixes, physical properties can be manipulated. In the same way that an HQ molecule can be made less water soluble by conventional covalent derivatization, its solubility can be equally reduced by incorporating it into a binary cocrystalline matrix.[2] For example, HQ can be cocrystallized with a terephthalamide molecule (Scheme 6). This 1:1 complex of HQ and, in this case, bis-[*N*,*N*-diethyl]terephthalamide can be considered a noncovalent derivative of HQ.[3]

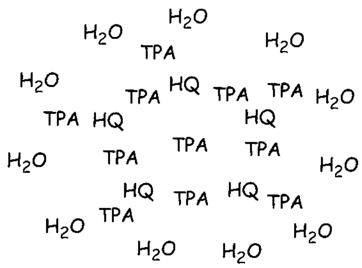
The physical properties of the HQ are now modified by the terephthalamide (TPA) molecule by interfering with the intermolecular interactions between the HQ molecules and between the intermolecular interactions between the HQ molecules and the H_2O molecules (Scheme 7).

Using molecular recognition and self-assembly in the design of materials is an example of green chemistry.[4] Because the coproducts, byproducts, solvents, energy inputs, and purification procedures are often unnecessary when constructing noncovalent derivatives, the process is more environmentally sound. In terms of economic and environmental cost, it is far better to manipulate intermolecular interactions than breaking and forming covalent bonds. Noncovalent derivatization is not amenable to all material syntheses, but there certainly is application for this technique in many instances. If we can learn what molecules "want" to do in the first place, and then design processes to be consistent with these "natural tendencies", the result will be more environmentally benign mechanisms in terms of materials and energy consumption. As the field of crystal engineering continues to advance, hopefully

Scheme 6



Scheme 7



practitioners will attempt to embrace these toxicological and environmental benefits that this field affords.

Acknowledgment. We wish to thank the EPA (R825327), the Massachusetts Toxics Use Reduction Institute, and Pfizer, Inc., for financial support.

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CG0255218