

Crystal growth, polymorphism and structure–property relationships in organic crystals

Joel Bernstein

Department of Chemistry, Ben-Gurion University of the Negev, PO Box 653, Beer Sheva 84105, Israel

Abstract. Understanding the role of structure in determining the properties of materials is a crucial aspect of the design of new materials. The existence of polymorphic crystal structures provides a unique opportunity to study structure–property relationships, since the *only* variable among polymorphic forms is that of structure, and variation in properties must be due to differences in structure. Systematic characterization of the polymorphic forms and acquisition of the ability to grow crystals of a desired form are additional elements in the design strategy of new materials. The conditions and techniques required to obtain a particular polymorph, combined with knowledge of the crystal structures, can also provide information on the relative stability of the different structures. Studies of representative systems which illustrate the intimate connections between polymorphism, structure–property relations and crystal growth are presented.

1. Introduction

The design and preparation of materials with desired properties is one of the principal goals of chemists, physicists and structural biologists. Achieving that goal depends critically on understanding the relationship between the structure of a material and the properties in question. Systematic studies of structure–property relationships generally require eliminating as many as possible of the structural variables in an attempt to isolate the one or few structural parameters which play the most important role in determining the particular property under investigation. For organic molecules a typical strategy might involve, for instance, a systematic variation in the mode or type of substitution on one part of the molecule in order to test a particular hypothesis. Variations in substituents, while they do often result in changes in structure, and the corresponding changes in properties, also lead to perturbations in the electronic structure of the molecules in question. In such cases, changes in properties cannot always be correlated directly with changes in structure. The existence of polymorphic forms provides a unique opportunity for the investigation of structure–property relationships, since by definition the only variable among polymorphs is that of structure. For a polymorphic system, differences in properties among the polymorphs must be due to differences in structure. As a corollary to this principle, a constancy in properties for a polymorphic system indicates a lack of structural dependence on that property, at least within the limitations of the structural

variations through that particular series of polymorphic structures.

For organic materials, studies of structure–property relations fall into two broad categories. In the first, the properties under investigation are due to strong interactions between neighbouring molecules, and we wish to study the changes in bulk properties resulting from differences in the spatial relationships between molecules in the crystal, i.e. the crystal structure. In the second category we seek information related to variations in molecular structure, generally molecular conformation. The existence of different molecular conformations in different polymorphic structures, known as conformational polymorphism, also provides an opportunity for the study of the influence of crystal forces on the molecular conformation, since variations in conformation must be a result of different crystalline environments.

Our intention in this paper is to provide a brief overview, with suitable examples, of the utilization of polymorphism in organic materials to investigate structure–property relations.

2. How widespread is polymorphism in organic materials?

Although the phenomenon of polymorphism was recognized by Mitscherlich (1822, 1823) at the dawn of modern chemistry, relatively little effort was devoted to the systematic search for and investigation of

polymorphic forms of organic materials until the last twenty-five years or so†. The extent of the phenomenon is evident in the fact that over 3000 of the entries in the Cambridge Structural Database (Allen *et al* 1991) contain qualifying descriptions as being members of polymorphic systems.

While most examples of polymorphism are still discovered through serendipity, there are a number of areas of chemical research and development where full characterization of solid materials is critical in the determination of their ultimate use. These include pharmaceuticals (Haleblian and McCrone 1969, Haleblian 1975, Clements 1976), dyes (Walker *et al* 1972, Griffiths and Monahan 1976, Etter *et al* 1984, Tristani-Kendra *et al* 1983, Morel *et al* 1984) and explosives (Karpowicz *et al* 1983). Various aspects of the subject have been treated in books (Varna and Krishna 1966, Byrn 1983, Kuhnert-Brandstatter 1971) and a number of reviews (McCrone 1963, Haleblian and McCrone 1969, Haleblian 1975).

The proliferation of examples of polymorphism in these areas would seem to lend credence to the widely quoted statement by McCrone (1963) that 'Virtually all compounds are polymorphic and the number of polymorphs of a material depends on the amount of time and money spent in research on that compound'. However, it is still not possible to predict with any reasonable level of confidence the crystal structure of an organic material, much less the existence of polymorphism, although considerable progress is being made in these endeavours (Roberts 1992, Sato 1992, Desiraju 1991, Gavezzotti 1989, 1991, Maddox 1988, Scaringe and Perez 1987, Fagan and Ward 1992). Moreover, since scientists do not make a practice of reporting negative results, we are generally not aware of unsuccessful systematic searches for polymorphs. When required, a systematic search for polymorphic forms should be carried out on solid materials, involving a wide variety of techniques and conditions for growing crystals and enlisting a diversified armoury of analytical techniques to detect them. The range and combinations of crystal growth conditions are virtually infinite, and there is no way to guarantee the preparation of additional polymorphs of a substance, much less the generation of 'all' of them.

In spite of the considerable efforts and progress in understanding and controlling polymorphic behaviour (Weissbuch *et al* 1987) the phenomenon still seems to be at least partially shrouded in mystery and folklore, with tales of metastable crystal forms 'disappearing' in favour of more stable ones (Woodard and McCrone 1975, Jacewicz and Nayler 1979, Webb and Anderson 1978, Scheidt *et al* 1983). To fuel this debate there have been reports of successful attempts (Catti and Ferraris 1976, Czugler *et al* 1981, Bar and Bernstein 1982), after considerable efforts, to overcome the 'poisoning' of a laboratory or even vast areas of the earth (Woodard and McCrone 1975).

† One notable exception is the relatively obscure but very useful compilation by Deffet (1942) of polymorphic organic materials.

3. Comparing polymorphic crystal structures

The crystal structure representation containing most information is a stereo diagram of the packing, with a suitably chosen view of a central reference molecule and its immediate surroundings. Comparison of polymorphic structures is best made by preparing the same type of drawing on the same reference plane of the reference molecule for all of the polymorphs. While this pictorial approach is very helpful to a viewer it is difficult to translate the graphic information into a form which can be communicated to others. The traditional method of doing so involves the preparation of a listing of the 'short' intermolecular contacts (i.e. those less than the sum of the van der Waals radii) including the symmetry operations relating the neighbouring molecules. This representation falls at the opposite end of the information spectrum: it contains all the necessary analytical data, but is virtually impossible for the reader to visualize.

A solution to this dilemma may lie in the use of graph sets which have been developed recently to represent the patterns of hydrogen bonds (Etter 1990, Etter *et al* 1990), but which, in principle, may be applied to any type of intermolecular interaction. In this representation all hydrogen bonds may be classified as belonging to one of only four different patterns: intramolecular, finite dimeric, finite ring, or infinite chain. A complete definition of the pattern is given by specifying the number of donors (hydrogens) and the number of acceptors (basic atoms) as well as the total number of atoms contained in the pattern. The hydrogen-bond networks may then be summarized in a concise shorthand way which carries a great deal of information that may be used to compare readily the structures of polymorphic systems. Examples of such a treatment are given for the trimorphic system of iminodiacetic acid (Bernstein *et al* 1990) and the dimorphic L-glutamic acid (Bernstein 1991a).

Because of their highly directional nature, as compared with other types of interactions, this approach has been applied initially to hydrogen-bonded structures. Other intermolecular atom–atom interactions also exhibit characteristic patterns (Desiraju 1991) which are now much more amenable to study because of the ready accessibility of the structural data from the Cambridge Structural Database and the analytical and statistical software associated with it. The extension of the graph set approach for cataloguing structures from hydrogen-bond systems to other types of interaction is a natural one which should allow for much more facile understanding and comparison of polymorphic systems.

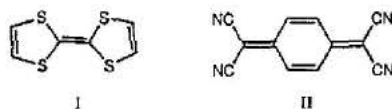
4. Examples of structure–property studies on polymorphic systems

4.1. Bulk properties

For historical reasons, the properties of organic materials have been considered in terms of the molecular structure. This was a natural result of the fact that most of the

chemistry of these materials was carried out in solution, where molecules might interact or react in a pairwise fashion. Even three-body interactions were considered quite unusual. The last two decades have witnessed a revolution in this point of view, as the wealth of possibilities for designing and utilizing the solid state properties of organic materials have become evident. These properties intrinsically depend on both the nature of the molecules and the way in which they interact with each other in the solid. Important information about the role of these solid state interactions can be obtained from the study of polymorphic materials, and variation of physical properties from one polymorph to another. Moreover, the recognition of the conditions required for the growth of the different polymorphs can provide additional information on the energetic relationships among them, and the crystallization conditions necessary to obtain the crystal architecture with the desired intermolecular interactions required for a particular physical property. Two examples from the realm of bulk properties will serve to illustrate these points.

4.1.1. Electrical conductivity. Organic materials are traditionally considered to be electrical insulators, but the discovery twenty years ago of metallic conductivity in crystals of the π molecular complex of tetrathiafulvalene **I** and tetracyanoquinodimethan **II**



(Ferraris *et al* 1973, Coleman *et al* 1973) led to a revolution in thinking about these materials in particular and the potential for organic materials in general, as the basis for the next generation of electronic components (Wudl 1984, Williams *et al* 1985). In contrast to the vast majority of known π molecular complexes that crystallize with plane-to-plane stacks of alternating donors and acceptors (mixed stack, figure 1(a)) (Herbstein 1972), the complex of **I** and **II** crystallized with segregated stacks of molecules along the same crystallographic axis (but not mutually parallel), each stack containing only one type of molecule.

This structural feature has been shown to be a necessary condition for electrical conductivity in these materials, although the mixed mode of stacking is generally the thermodynamically preferred one (Shaik 1982). What means do chemists have at their disposal to overcome the tendency to form mixed stacks rather than segregated stacks? One method is to choose either a donor or acceptor with a completely different molecular shape. The principles of close packing in organic crystals (Kitaigorodskii 1973) then suggest that molecules will pack in segregated stacks in order to most efficiently fill the space. Such reasoning led, for instance, to the 2:1 'Bechgaard salts' (Bechgaard *et al* 1980, 1981) based on **III** as a donor, and a similar series based on **IV** ('ET') as a donor, in which the acceptors are

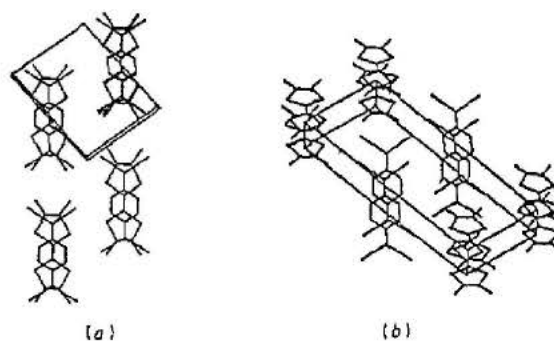
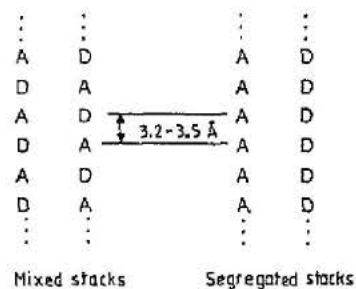
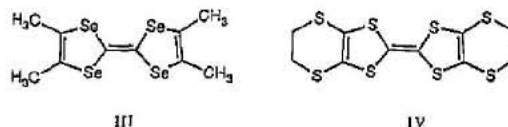


Figure 1. Upper part: schematic diagram of the mixed stack and segregated stack motifs for packing of molecular charge-transfer complexes; lower part: views of the two polymorphic structures of **I:II**. In both cases the view is on the plane of the π molecule (**I**). (a) The red, transparent, mixed stack complex, a semiconductor; (b) the black, opaque, segregated stack complex, a conductor. (From Bernstein (1991b) with permission.)

nearly spherical (i.e. octahedral or tetrahedral) or short linear anions that fill the voids between stacks of donors.



The 2:1 stoichiometry ensures the partial charge on the donor stack, another necessary condition for conductivity, and many of these salts are conductors or superconductors.

Proof of the relative stability of the mixed and segregated stack packing motifs and a recipe for obtaining crystals of the latter came with the discovery of a pair of polymorphic 1:1 complexes of **II** with **III** (Bechgaard *et al* 1977, Kistenmacher *et al* 1982). The red, transparent, mixed stack form of the complex is a semiconductor, while the black, opaque, segregated stack is a conductor (figure 1(b)). This finding demonstrated conclusively that the segregated stacks are a necessary condition for electrical conductivity. Reflecting the relative stabilities for the two stacking modes noted above, crystals of the red semiconductor form are obtained by a 'thermodynamic' or 'equilibrium' crystallization: equimolar solutions of the donor and acceptor in acetonitrile are mixed and allowed to evaporate slowly. Crystals of the black form are obtained by a 'kinetic' or nonequilibrium crystallization: hot equimolar solutions of the donor and acceptor in acetonitrile are mixed and cooled rapidly. Some microcrystals of the resulting black powder are then used

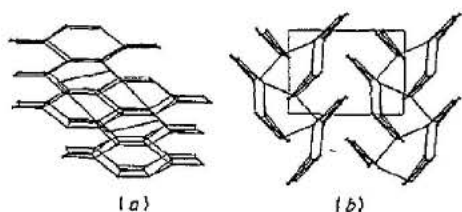


Figure 2. Network of ET (V) molecules in two phases of the salt $(\text{ET})_2^+\text{I}_3^-$. The unit cell is included in each figure and thin lines indicate short intermolecular S...S contacts. (a) β form; (b) κ form. (From Williams *et al* (1991) with permission.)

as seeds to obtain larger crystals of the mixed stack black form. Non-equilibrium crystallization methods, in particular electrochemical techniques, have become standard procedure for obtaining crystals of organic conductors, in part because of the ability to control and reproduce the crystallization conditions. However, as we indicate below, control and reproducibility do not guarantee obtaining a single or unique crystal phase.

The role of polymorphism in understanding the connection between structure and properties is most poignantly represented by the ET_2X salts of IV. No fewer than 20 have been reported to be superconductors, having among them the highest known T_C values (Williams *et al* 1991). For $\text{X}=\text{I}_3^-$ alone, there are at least fourteen known phases, and learning to understand and control the crystal growth conditions in these polymorphic systems is one of the greatest challenges facing workers in this rapidly expanding field. As above, crystals are typically obtained by electrocrystallization methods, using Pt electrodes and an H tube, and a constant current of $\sim 1 \mu\text{A cm}^{-2}$. Crystal growth experiments can extend up to periods of months, with a number of polymorphs simultaneously appearing on the same electrode, in many cases with indistinguishable colours or crystal habits. For instance, Kobayashi *et al* (1987) identified the presence of the α , β , γ , δ , θ and κ polymorphs of $(\text{ET})_2^+\text{I}_3^-$ in the same crystallization experiment.

Intense activity in this field has led to the definition of some conditions for preferentially obtaining one, or a limited number, or phases (Williams *et al* 1991), but very often the isolation and identification of the various phases requires characterization of each individual crystal (Kato *et al* 1987).

As an example of the type of variation observed, we can compare the β and κ phases of $(\text{ET})_2^+\text{I}_3^-$ (figure 2). The former, apparently favoured by thermodynamic crystallization conditions (e.g. low current density) is a centrosymmetric triclinic structure with one formula unit of the salt in the unit cell. The symmetry arguments require that the anion lie on a crystallographic inversion centre, and that the donor molecules all be parallel, as shown in figure 2(a). The structure is thus characterized by stacks along the diagonal of the unit cell, with strong intermolecular S...S interactions between stacks. T_C for this phase is 1.4 K.

The κ phase may be obtained, together with the α and θ phases, in a THF solution under N_2 with

a mixed supporting electrolyte of $(n\text{-C}_4\text{H}_9)_4\text{NiI}_3$ and $(n\text{-C}_4\text{H}_9)_4\text{NAuI}_2$ at 20 °C and constant current of 1.0 μA (Kato *et al* 1987). It is characterized by the formation of dimers, but a number of different salts exhibit more variability in this type of structure than in the β phase (Williams *et al* 1991). $\kappa\text{-}(\text{ET})_2^+\text{I}_3^-$ is centrosymmetric, with one layer per unit cell in a $P2_1/c$ structure (Kato *et al* 1987) (figure 2(b)) and has a T_C of 3.6 K.

Understanding the structure–property relationship in these materials is crucial to the rational development of organic conductors and superconductors with increasingly high T_C values. The plethora of polymorphic structures can easily lead the unwary investigator astray, but it provides an opportunity not available in many other systems for isolating the structural characteristics required for a very specific physical property. Williams *et al* (1991) have also pointed out that the isostructural series of salts are important for the information they can yield. In this case, the structural parameter is kept nearly fixed (or only slightly perturbed) and the effect of chemical perturbations can then be evaluated.

4.1.2. Aggregation of dyes. The aggregation of organic dye molecules has held the attention of dye chemists since its discovery over half a century ago (Smith 1974, Herz 1974). A lack of understanding of the phenomenon did not prevent extensive use being made of it, for instance, in the spectral ‘tuning’ of the response of photographic silver halide emulsions (Nassau 1983). Jelley (1936) found that when the solution concentration of many dyes is increased, the intensity of the characteristic molecular absorption band decreases in favour of the growth of a new intense, narrow absorption band on the long-wavelength side of the original molecular absorption band (figure 3). The new absorption, called a J band after its discoverer, is commonly attributed to the formation of aggregates of dye molecules, and results from the coupling of transition dipoles within the aggregate structure.

Since the aggregates are generally believed to contain only a few tens of molecules (Smith 1974) it has been difficult to study directly the relationship between their structure and spectral properties. While there is no certainty that a crystal structure represents the structure of the aggregate, the existence of polymorphic structure of a dye does allow one to probe directly the relationship between structure and spectral properties. For many years great difficulty was encountered in obtaining crystals of most dyes, to say nothing of polymorphic forms. However, as a result of the energy crises during the 1970s, considerable research effort was expended on many dyes with potential applications as photovoltaic materials (Morel *et al* 1978, Morel 1979, Forster and Hester 1982). True to McCrone’s dictum some were found to be polymorphic, and one, the squarylium dye V was the subject of a combined crystallographic and spectroscopic study to investigate the relationship between the structure and spectral properties of such dyes.

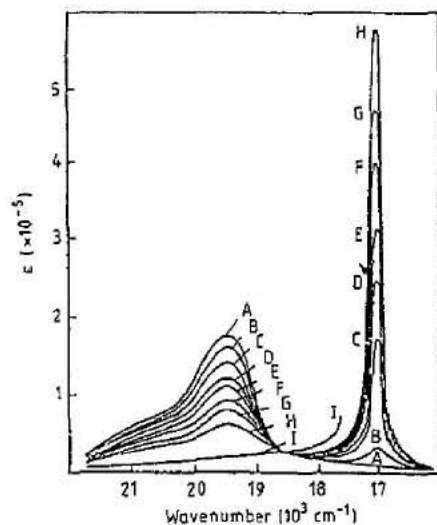
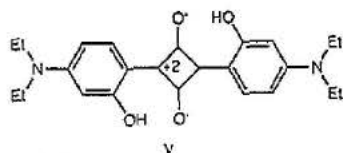


Figure 3. Solution spectra of a dye exhibiting J banding. Solutions numbered 1–9 range in concentration from 8.8×10^{-7} M to 1.4×10 M. The molecular absorption band is on the left; the J band on the right (see text). (From Bernstein (1991b) with permission.) A, 8.81×10^{-9} M; B, 1.76×10^{-6} M; C, 2.20×10^{-6} M; D, 2.64×10^{-6} M; E, 3.08×10^{-6} M; F, 3.53×10^{-6} M; G, 4.40×10^{-6} M; H, 6.16×10^{-6} M; I, 1.44×10^{-3} M.



The material is dimorphic, forming well developed crystals of both a violet triclinic structure and a green triclinic structure. Representative views of the crystal structures are given in figure 4. Here again, the crystal growth process is instructive in understanding the energetic relationships between the two observed phases. The two polymorphs appear simultaneously in the same beaker, and hence they grow under identical conditions, indicating that they are of very similar energies. The energetic similarity would appear to be coincidental since the difference in space groups and crystal structures indicated by figure 4(a) and (b) would suggest at least some difference in lattice energy and hence different crystallization conditions. The key to this conundrum lies, in part at least, in the way the crystal structures are viewed. When the reference plane is the molecular plane (figure 4(c) and (d)) it is clear that the plane-to-plane stacking in the two structures is essentially identical. This apparently is the dominant interaction, and the one that governs the crystallization process. The only difference between the triclinic and monoclinic structures, then, is the relationship between the stacks, a translation in the triclinic structure, and a screw axis in the monoclinic structure. These must be either subsidiary to the plane-to-plane stacking interaction or equal to each other for the crystals to appear simultaneously (Bernstein and Chosen 1988).

What are the spectroscopic manifestations of these structural differences? The molecule is essentially flat in both structures, so differences in the spectroscopic

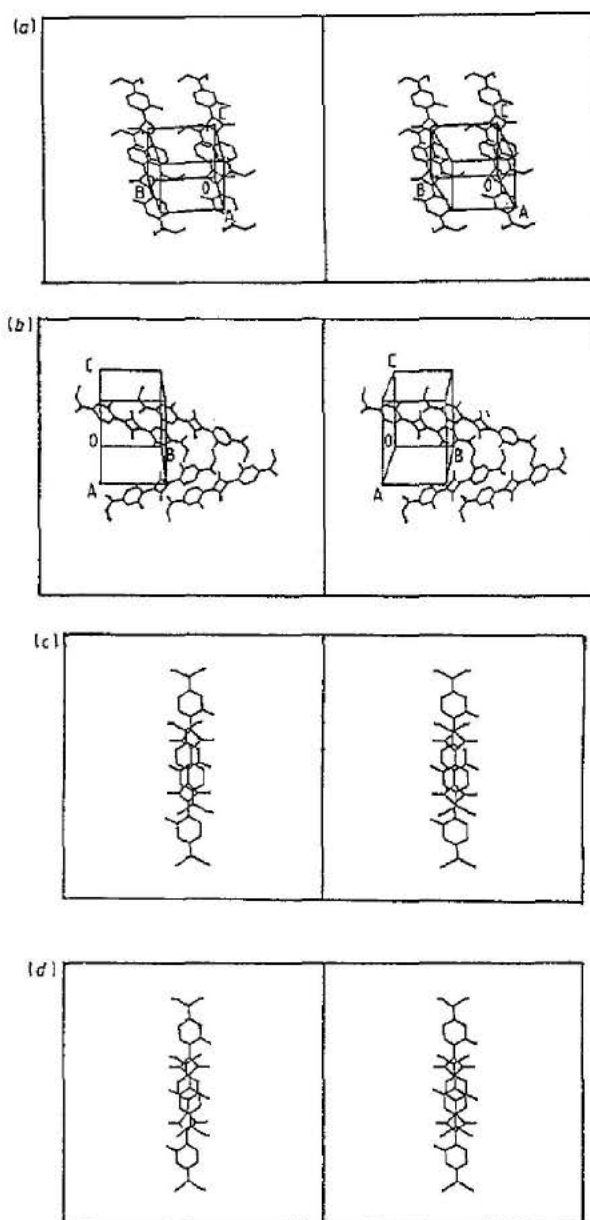


Figure 4. Stereo views of the crystal structure of the squarylium dye V: (a) triclinic structure, (100) face; (b) monoclinic structure, (100) face (from Tristani-Kendra *et al* (1983) with permission.); (c) view of the molecular plane, triclinic structure; (d) view of the molecular plane, monoclinic structure. (From Bernstein and Chosen (1988) with permission.)

properties must be an expression of the differences of intermolecular relationships in the two structures. The polarized normal incidence reflection spectra of the two crystals are given in figure 5, and it can be readily seen that the spectra are significantly different between the two forms for light polarized along the long axis of the molecules. This must be a consequence of the difference in the interaction of a single molecule with its surroundings. The reflection spectrum of the band in the monoclinic form has been interpreted as being composed of two oscillators, while that of the triclinic form contains three, or possibly four, oscillators

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.