

Optical Activity Can Be Created from "Nothing"

Lesley Caswell,¹ Miguel A. Garcia-Garibay,² John R. Scheffer,³ and James Trotter
University of British Columbia, Vancouver, Canada V6T 1Z1

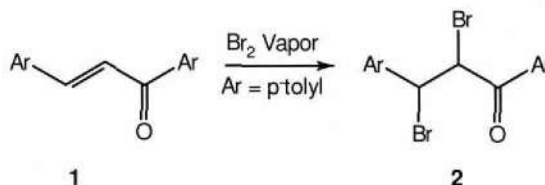
There is a common misconception that optically active products cannot be generated from achiral reactants without some form of external intervention involving pre-existing optical activity, the most common being the addition of a resolved chiral auxiliary to the reaction mixture in order to produce diastereomeric transition states or intermediates. This takes the form of phrases such as "it takes optical activity to create optical activity," or "optical activity cannot be created from nothing". The purpose of this article is to point out that optically active products can be formed from achiral precursors without the intervention of pre-existing optical activity, a process that has been termed "absolute asymmetric synthesis" (1).

Spontaneous Resolution

It has been known for some time that the combination of "spontaneous resolution" upon crystallization followed by a stereospecific chemical reaction of the resulting chiral crystals in the solid state is capable of producing optically active products with significant enantiomeric excesses. Spontaneous resolution is the process whereby an achiral molecule crystallizes in one of the 65 possible chiral space groups, the total number of crystallographic space groups (chiral plus achiral) being 230 (2). Although it is frequently observed that conformationally flexible molecules that have average planes or centers of symmetry in solution adopt homochiral conformations in the solid state, this is not required for spontaneous resolution, and even rigid, highly symmetrical compounds (e.g., maleic anhydride (3) and 9,10-ethenoanthracene (4) to name but two) crystallize in chiral space groups. Thus, it is the three-dimensional packing arrangement of the molecules in the crystal that determines a chiral space group and not the chirality of the molecules themselves. Crystals that have chiral space groups are characterized by being enantiomorphous. They exist in "right-handed" and "left-handed" forms that may or may not be visually distinguishable. It is not uncommon to find both enantiomorphs present in a given batch of crystals from the same recrystallization.

Absolute Asymmetric Synthesis

The first example of an absolute asymmetric synthesis was provided by Penzien and Schmidt in 1969 (1). They showed that 4,4'-dimethylchalcone (1), although itself achiral, crystallizes spontaneously in the chiral space group $P2_12_12_1$, and when single crystals of this material are treated with bromine vapor in a gas-solid reaction, the chiral dibromide 2 is produced in 6% enantiomeric excess (53% of one enantiomer, 47% of the other). In this beautiful experiment, it is the reaction medium, the chiral crystal lattice, that provides the asymmetric influence that favors the formation of one product enantiomer over the other, and the chemist has done nothing but provide a non-chiral solvent (ethyl acetate) for crystallization and a non-chiral reagent (bromine) for reaction. To the caveat that the



chemist has exerted an optically active influence by selecting a "right-handed" single crystal over a "left-handed" one, it has been noted by McBride (5) that spontaneous resolution of achiral molecules upon crystallization frequently gives a predominance of one enantiomorph, particularly when the reaction is stirred during the recrystallization process. Thus, solid state reaction of one batch of crystals may lead to an excess of levorotatory product; whereas, another batch from a different recrystallization may give a predominance of dextrorotatory material. We shall see an example of this type of behavior later in the paper. Over time, however, equal amounts of both product enantiomers should be formed provided that the crystallization process is truly spontaneous, i.e., that it produces equal amounts of enantiomorphous chiral crystals. The best example of a true spontaneous resolution process was provided by Pincock et al. (6), who showed in 200 separate trials that crystallization of racemic 1,1'-binaphthyl from the melt gave optically active material whose specific rotation fitted a Gaussian distribution curve from -218° to $+206^\circ$ with a mean of $+0.18^\circ$; optically pure 1,1'-binaphthyl has a specific rotation of $\pm 245^\circ$.

Crystallization of Achiral Molecules

The crystallization of achiral molecules in chiral space groups, while rare and unpredictable, is well documented (7). Even rarer is to find materials exhibiting this behavior that also react chemically in the solid state and produce chiral products. As a result, very few absolute asymmetric syntheses have been reported, and those that have are the result of serendipity rather than planning. Their interest at the moment, therefore, lies not so much in their potential as a general method of asymmetric synthesis, but rather as a mechanistic probe of solid state chemical reactivity as well as a possible model for the prebiotic origins of optical activity on earth. Review articles on both of these topics have appeared (8, 9).

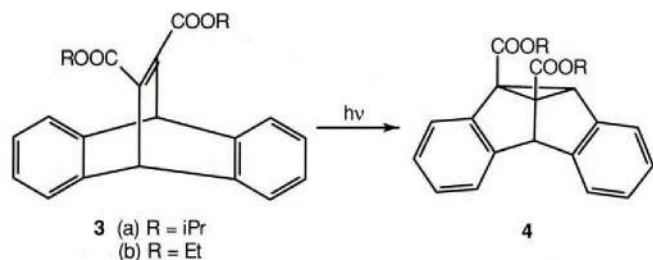
Photorearrangement Reactions

During our studies in the field of solid state organic chemistry, we have discovered several photorearrangement reactions that convert achiral reactants into optically active products in much higher enantiomeric excesses than those reported heretofore. The remainder of this article will deal with some of the more dramatic findings from our laboratory along with a related example taken from the literature. Our original work in this area involved diisopropyl 9,10-dihydro-9,10-ethenoanthracene-11,12-dicarboxylate (3a) (10). This compound reacts photochemically both in solution and the solid state to afford the

¹Natural Sciences and Engineering Research Council of Canada Undergraduate Summer Research Fellow, 1991.

²Present address: Department of Chemistry, University of California at Los Angeles, Los Angeles, CA 90024.

³Author to whom correspondence should be addressed.



so-called dibenzosemibullvalene derivative **4a**, an example of the well-studied (11) di- π -methane or Zimmerman photorearrangement. The photorearrangement of **3a** into **4a** satisfies one of the requirements for an absolute asymmetric synthesis, namely the conversion of an achiral compound into a chiral one.

Crystals of diester **3a** grown from cyclohexane were found to be formed in the chiral space group $P2_12_12_1$, and irradiation of large, carefully grown single crystals to less than 25% conversion by using a nitrogen laser (or a medium pressure mercury arc lamp) gave photoproduct **4a** in greater than 95% enantiomeric excess! The enantiomeric excesses were measured by the chiral shift reagent NMR method (12). Diester **3a** adopts a homochiral conformation in the solid state to which an absolute configuration can be assigned, and in later X-ray crystallographic work (13), we were able to correlate the absolute configuration of **3a** in one crystal with the absolute configuration of photoproduct **4a** formed via irradiation of the same crystal, thereby gaining an insight into the structural features responsible for the very high stereospecificity of the solid state reaction.

Diester **3a** also was found to crystallize in the nonchiral space group $Pbca$ (10). This is an example of the phenomenon of polymorphism, whereby a substance packs in more than one crystallographic space group. Depending on the number of polymorphs present, the substance is said to be dimorphic, trimorphic, tetramorphic, etc. Both the $P2_12_12_1$ and the $Pbca$ dimorphs were present in the same batch of crystals prepared by recrystallization of **3a** from cyclohexane. Although the dimorphs had identical melting points and were difficult to distinguish visually, they could be differentiated easily through solid state infrared spectroscopy in potassium bromide matrices. X-ray crystallography revealed that the $Pbca$ crystals of diester **3a** are racemic-composed of equal amounts of enantiomeric conformations related by crystal symmetry. This predicts that photolysis of these crystals should give racemic photoproduct, and this was found to be the case; no optical activity could be detected in compound **4a** following nitrogen laser irradiation of single crystals of the $Pbca$ dimorph.

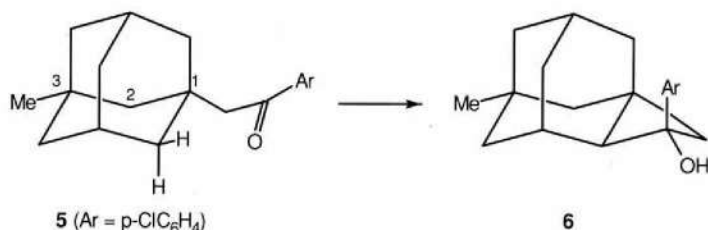
Racemic **4a** also was produced when diester **3a** was irradiated in solution. This is not surprising, as NMR spectroscopy shows that **3a** possesses average C_{2v} symmetry in solution. Because of this symmetry in solution, the optical activity produced in each solid state photolysis is easy to determine by simply dissolving the entire sample in chloroform and measuring its rotation at the sodium D line. The specific rotation of photoproduct **4a** can be calculated from the weight of the crystal photolyzed and the percent conversion as determined by capillary gas chromatography. The unreacted starting material contributes nothing to the rotation, because it is achiral in solution.

When crystals of compound **3a** were prepared by heating powdered material above the melting point in sealed tubes and the molten liquid allowed to solidify into a polycrystalline mass, the sample

appeared to be composed largely of a single enantiomorph of the $P2_12_12_1$ modification. This conclusion was based on the finding that photolysis of such polycrystalline samples affords photoproduct **4a** in enantiomeric excesses that approach those produced in the single crystal irradiations (14). In order to eliminate self-seeding of the molten sample by unmelted $P2_12_12_1$ microcrystallites, which could lead to a bias in determining the randomness of the spontaneous resolution process, these experiments were carried out by melting racemic ($Pbca$) material and allowing it to solidify. In eight separate photolyses of samples prepared in this way, four gave (+)-**4a** and four gave (-)-**4a**.

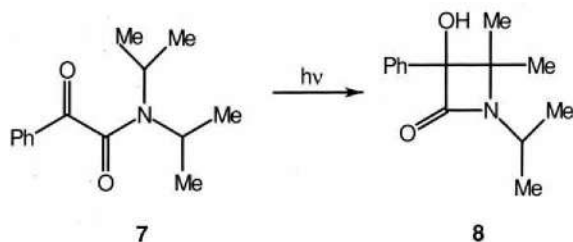
Of over 20 symmetrical and unsymmetrical dialkyl 9,10-ethenoanthracene-11,12-dicarboxylates that we have prepared and investigated (14, 15), only two were found to undergo an absolute asymmetric di- π -methane photorearrangement in the solid state. One is the diisopropyl diester **3a** discussed above and the other is the diethyl diester analogue **3b**. This latter material, which is trivial to prepare via a Diels-Alder reaction between commercially available diethyl acetylenedicarboxylate and anthracene, crystallizes from ethanol solution to afford colorless crystals of two different morphologies. One, mp 93–94 °C, which appears as thin, rectangular plates, was found to have an achiral space group, $P2_1/c$; the other, mp 97–98 °C, which crystallizes as stout prisms, has the familiar chiral space group $P2_12_12_1$. If, instead of pure ethanol, a 1:1 (vol/vol) mixture of ethanol and ethyl acetate is used as the recrystallization solvent, the $P2_12_12_1$ dimorph is always obtained. As with diester **3a**, both dimorphs photorearrange in the solid state to afford a chiral dibenzosemibullvalene derivative, in this case compound **4b**. When large, carefully grown single crystals of each dimorph were irradiated, the achiral, centrosymmetric crystals gave racemic photoproduct while the chiral crystals yielded optically active material. The optical activity obtained in this case was much more variable than in the case of diisopropyl diester **3a**. Enantiomeric excesses ranging from barely detectable to nearly quantitative were obtained. In general, lower photolysis temperatures gave higher enantiomeric excesses, and when the crystal melted or disintegrated during photolysis, noticeably lower enantiomeric excesses were observed.

We turn now to a third example of an absolute asymmetric photorearrangement discovered in our laboratory (10). In this case, the chemical change involved is an example of the Norrish type II reaction, a well-known excited state process of ketones that is initiated by an intramolecular hydrogen atom transfer from carbon to oxygen through a six-membered transition state (16). The compound studied was the adamantane derivative **5**, which is achiral due to a plane of symmetry that runs through C(1), C(2) and C(3). Ketone **5** was found to crystallize from ethanol in very large prisms that have the chiral space group $P2_12_12_1$, and irradiation of these crystals to approximately 10% conversion gave the chiral cyclobutanol derivative **6** as the major



product. Analysis of the reaction mixture by polarimetry revealed that substantial optical activity had been created, and chiral shift reagent NMR measurements of the purified photoproduct indicated an enantiomeric excess of approximately 80%.

As a final example of an absolute asymmetric photorearrangement reaction in the solid state, we include a reaction originally discovered by Aoyama et al. (17) and subsequently studied in more detail by Toda and co-workers (18). This concerns the photochemical conversion of the achiral α -oxoamide derivative **7** into the chiral β -lactam alcohol **8**, a process that is similar to the photorearrangement of ketone **5** in that it also is thought to involve initial hydrogen atom transfer from carbon to oxygen followed by coupling of the 1,4-biradical so produced (Norrish type II process). When grown from benzene, crystals of compound **7** were found to occupy the chiral space group $P2_12_12_1$, and irradiation of one of the enantiomorphs (as a powder) was found to give (+)-**8** in 93% enantiomeric excess, while photolysis of the other enantiomorph gave (-)-**8**, also with an ee of 93%. Samples of each enantiomorphous form of α -oxoamide **7** were saved for use as seeds in later recrystallizations, and in this way, substantial quantities of either enantiomorph could be prepared as desired. The crystalline phase rearrangement of **7** to **8** is noteworthy also for the high conversions (up to 75%) that can be tolerated without significant loss of enantioselectivity. As a result, the reaction has genuine preparative utility.



Conclusion

The examples discussed above are by no means the only absolute asymmetric solid state chemical reactions that have been reported. For example, several intermolecular [2+2] photocycloaddition reactions are known that convert achiral alkenes into optically active dimers or oligomers (19, 20). The results are sufficient, however, to illustrate the main theme of this article, namely that certain achiral compounds can be transformed simply and directly into enantiomerically enriched products without the intervention of an external, pre-existing source of optical activity. At first sight this conclusion appears to provide an attractive mechanism through which the first optically active molecule could have arisen on earth. It is entirely conceivable that an achiral, "prebiotically relevant" organic com-

pound could have crystallized from water in a chiral space group and then been transformed in the solid state by sunlight into an optically active photoproduct. While there is little doubt that such events could have generated local pockets of intense optical activity, when considered on a global scale or integrated over a long period of time, such a mechanism should not lead to any net optical activity for reasons already discussed. Therefore, most current thinking favors mechanisms based on the long term accrual of minute amounts of optical activity from constant natural sources of chirality such as polarized electromagnetic radiation (9).

Regardless of the implications that solid state absolute asymmetric reactions may have for the origins of optical activity on earth, classroom discussions of such processes offer an attractive method of introducing the concepts of molecular symmetry, crystal symmetry, optical activity, solid state chemistry, and organic photochemistry into an upper level course in organic chemistry. In addition, students and instructors alike will learn to avoid blanket prohibitions against the possibility of de novo generation of optical activity.

Acknowledgment

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