Table II. Some Results on Asymmetric Crystallization of Monomers 1, 3, and 4 Induced by Impurity,[a] Given as Specific Rotation of Dimers

monomer	impurity (dimer of 5) chirality	impurity (dimer of 5) %[c]	solvent	$[\alpha]_D$ of product dimer,[b] deg
1	+	10	CH_2Cl_2	−92, −52, −80
	+	5	CH_2Cl_2	−71
	+	10	hexane[d]	−106, −89, −101
	+	5	hexane[d]	−100
	+	10	ethyl acetate	−81, −78
3	−	10	CH_2Cl_2	+61, +53, +62
	−	10	hexane[d]	+85, +82, +70
	+	10	hexane[d]	−89, −66, −66
	−	10	ethyl acetate	+43, +43, +51
4	−	10	CH_2Cl_2	+62, +60, +50
	−	5	hexane[d]	+59, +92, +87
	−	10	ethyl acetate	+26, +31, +61

[a] Reference 4. [b] See footnote *b* of Table I. [c] % in weight of substrate. [d] With a few drops of methylene chloride to improve solubility.

Westinghouse lamps, 40 W), for 2 weeks at 5 °C. The reaction products were separated by preparative TLC (silica, cyclohexane:ethyl acetate 3:1) from unreacted monomer and impurity, and their specific rotations were used as a measure of the asymmetric induction in crystallization. Table I summarizes some typical results from monomers **1**–**6**.

The studies were extended to crystallization from solution[5] (Table II). For artifact exclusion, blanks (i.e., polycrystalline monomer samples without impurity) were run simultaneously in both series of experiments. No significant optical activity was found in any of them.

From these results we conclude as follows: the crystallization of monomers **1**–**6**, which pack in chiral structures as in Scheme I, is strongly affected by the presence of products which originated from the same three-dimensional motif of Scheme I. On the other hand, under the same conditions, no induced chirality was observed from similar monomer systems whose crystal structures are based on other motifs (**7**, **8**, and the second polymorph of **2**). Further, the enantiomorphic crystal with an absolute configuration opposite to that of the impurity always precipitates in excess, the enantiomeric yield ranging from 30 to 100%, depending on the monomer. Experiments were carried out also when products of different monomers **1** or **2** were used as additives, and similar results were observed, implying that the asymmetric induction is due mainly to the rigid chiral skeleton of the additive and not the *sec*-butyl groups attached to it. Finally, change of conditions, such as rate of crystallization, solvent, and temperature, affects the induction only quantitatively. Concentrations of additives from 3 to 15% lead to effects of the same order of magnitude.[6]

A possible interpretation of the results here described derives from the knowledge that, especially in inorganic systems, tiny amounts of impurities which are selectively adsorbed on specific faces of crystals may cause a dramatic decrease in the growth rates of these faces. The overall result is a habit change and a decrease in the growth rate of the affected crystals.[7] In our systems we postulate a process in which, by virtue of the stereochemical resemblance between the impurity and one of the two enantiomorphic phases, namely, the parent phase, the products selectively poison the growing surfaces of crystals of that phase, thus inhibiting their growth while not influencing the growth of the enantiomorphic crystals. This mechanism may provide a common explanation for a number of as yet unexplained results on induced crystallization by resolved impurities or additives.[2,8] In the following two papers, experimental evidence is given indicating that this mechanism is indeed correct and has important implications in the kinetic resolution of chiral materials crystallizing in the form of conglomerates.

We conclude, further, that the precipitation of the "unwanted" enantiomorph, both in the experiments of Green and Heller and in our systems, is not an unpredictable property of the specific systems but is an unavoidable and general consequence of the mechanism of the effect. The solution of the amplification problem will thus require very specially designed experiments.

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(5) In this second series of experiments, the monomers were dissolved in different solvents together with a small concentration of impurity and left to crystallize to dryness (12–48 h). The workup procedure is identical with the one used in the first set.

(6) It was observed in several cases that when more than 3% impurity was used, in crystallization from the melt, some of this impurity separated in the form of an oil. Recent studies on the crystallization of **1** in the presence of 1% dimer as impurity resulted in enantiomeric excess of the same size.

(7) For the effect of impurities on crystal growth and morphology see: Brice J. C. "The Growth of Crystals from Liquids"; Wohlharth, E. P., Ed.; North Holland: Amsterdam, 1973; Chapter 3. Palm, J. H.; McGillavry, C. H. *Acta Crystallogr.* **1963**, *16*, 963.

(8) Pincock, R. E.; Perkins, R. R.; Ma, A. S.; Wilson, K. R. *Science (Washington, DC)* **1971**, *174*, 1018.

Useful Impurities for Optical Resolutions. 2. Generality and Mechanism of the Rule of Reversal

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We have reported studies on the preferential crystallization of one enantiomorphous form of conglomerates of photopolymerizable dienes in the presence of chiral products ("impurities") of topochemical photopolymerization within crystals of these dienes.[1] In all cases the crystal that precipitates in excess is of opposite absolute configuration to that of the chiral impurity (the "rule of reversal"). The effect can be interpreted by considering preferential adsorption of the additive at one or more of the growing surfaces of the stereochemically related parent crystal. This results in a decrease of growth rate of this crystal with respect to that of the enantiomorph. The process should then be of general applicablity to the resolution of racemic mixtures crystallizing in the form of conglomerates (Scheme I).

In order to achieve a successful resolution, the impurity *S'* needs to be "tailor-made" for each specific system.

First support for our hypothesis comes from inspection of the existing literature on induced asymmetric crystallization in the presence of resolved additives. Among all the systems investigated, there are a number for which inducing effects consistent with the pattern of Scheme I have been recorded. In these instances, a striking stereochemical resemblance indeed exists between the resolved impurity and one of the enantiomers of the racemic substrate. Thus, for example, (*R*)-glutamic acid was reported to crystallize preferentially from the racemic mixture in the presence of (*S*)-aspartic acid[2] or (*S*)-γ- methyl glutamate[3] and analogously (*R*,*R*)-sodium ammonium tartrate in the presence of (*S*)-sodium ammonium malate,[4] (+)-narwedine in the presence of (−)-galanthamine,[5] and (*R*)-Cu(Asp)$_2$ in the presence of (*S*)-alanine

(1) van Mil, J.; Gati, E.; Addadi, L.; Lahav, M. *J. Am. Chem. Soc.* **1980**, *103*, preceding paper in this issue.
(2) Purvis, J. L. U.S. Patent 2 790 001, 1958.
(3) Fike, H. L. U.S. Patent 2 937 200, 1960.
(4) Ostromisslenski, L. *Chem. Ber.* **1908**, *41*, 3035.
(5) Barton, D. H. R.; Kirby, G. W. *J. Chem. Soc.* **1962**, 806.

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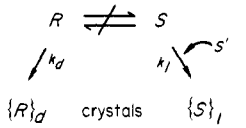
Table I

substrate	impurity[a]	crystallization,[b] ee crop I	crystallization,[b] ee crop II	dissolution,[c] ee	preferential adsorption S substrate,[d] S'/R'	morphology[e]
phenylene diacrylate monomers (1)	dimer	30–100%		*f*	5:1	–
	trimer	30–85%				
	oligomer	10–45%				
(*R,S*)-Cu(Asp)$_2$ (2)	*S*-Glu	66% *R*	*S*	25% *S*	3:1	–
	R-Glu	50% *S*	*R*			–
	S-Ala	25% *R*	*S*	18% *S*		–
	R-Ala	86% *S*	*R*			–
	S-iLeu	50% *R*	*S*	0		–
(*R,S*)-threonine (Thr) (3)	*S*-Glu	94% *R*	*S*[g]	82% *S*	5:2	+
	R-Glu	90% *S*	*R*			–
	S-Asn	90% *R*	*S*	68% *S*		–
	R-Asn	90% *S*	*R*			+
	S-Asp	70% *R*	*S*	65% *S*		–
	S-Cys	93% *R*	*S*			–
(*R,S*)-asparagine (Asn) (4)	*S*-Asp	98% *R*	*S*	46% *S*	6.5:1	+
	R-Asp	99% *S*	*R*			–
	S-Glu	85% *R*	*S*	5% *S*	30:1	+
	R-Glu	79% *S*	*R*			–
	S-Gln	10% *R*	*S*			+

[a] For system 1, see preceding paper in this issue. Systems 2, 3, 4: 10% impurity was added to the supersaturated solution of the racemate before filtration. Under these conditions, the impurity is always well below its saturation levels. [b] Workup for 1 in previous communication. 2: solvent buffer copper acetate/acetic acid, pH 4. 3, 4: solvent H_2O: Hot solutions are filtered and cooled to room temperature to perform crystallization from a 100% supersaturated solution. Time of crystallization from 4 h (2) to 48 h or more (3, 4) in absence of seeds. Stirring induces fast crystallization accompanied by loss of enantiomeric purity. Enantiomeric excesses are evaluated either by specific rotation ([*c* 3] in 1 N HCl for 2, H_2O for 3, and 5 N HCl for 4) or directly by integration of high-performance LC[11] with chiral eluants. Since the effect is kinetic, only maximum values of ee have been reported, with minimum values being 0 for long-time crystallization. [c] The substrate racemate consists of big crystals of pure conglomerate or of racemic material crystallized to equilibrium in the presence of impurity and are checked to be optically inactive before use. The solutions contain 10% of impurity. The experiment is stopped when ca. one-half of the crystalline material has dissolved. [d] In 1, *S* monomer was crystallized from EtOH in presence of racemic dimer, and the optical purity of the dimer extracted from the crystals of monomer was checked by $[\alpha]_D$. In 2–4 the ratio *S'*/*R'* was directly evaluated from high-performance LC (see *b*) of the crystals, redissolved after filtering and drying. [e] The results of the experiments marked + are discussed in the following paper. In systems 1 and 2 morphological experiments could not be carried out due to the bad quality of the crystals. [f] The experiments could not be carried out because of technical problems. [g] (2*R*,3*S*)-Threonine is D-threonine, (2*S*,3*R*)-threonine is L-threonine.

Scheme I[a]



[a] *S'* is a resolved impurity which stereochemically resembles the surface of the *S* crystals; in the absence of *S'*, $k_d = k_l$, in the presence of *S'*, $k_d >> k_l$.

or (*S*)-glutamic acid.[6] Explanations such as ligand exchange,[6] adsorption,[5] chiral seeding,[4] chiral solvent effects,[7] and the like were given, but in the absence of a unifying mechanism, these accidental observations remained as separate curiosities and were not investigated further. We suggest that in all these examples the same mechanism of selective adsorption and inhibition is responsible for resolution. The following pattern of events should occur if the proposed mechanism is correct.

(i) Upon crystallization of a racemic conglomerate *R,S* in the presence of a resolved impurity *S'*, the enantiomer *R* of absolute configuration opposite to that of the impurity should precipitate first. The molecule of *S'* must be stereochemically similar to the *S* molecule or to the *l* crystal (it may, for example, be a slightly modified substrate molecule or a dimer, trimer, or oligomer of it with a stereochemistry resembling that of two-, three-, or *n*-substrate molecules, respectively, in their crystalline arrangement), so that it can be preferentially adsorbed on the *l* crystal. Since the effect is kinetic, the optimal conditions for resolution must be determined experimentally. The affected enantiomer, *S*, should be found in the second crop of crystallization.

(ii) Impurities acting as inhibitors of crystallization should in general be inhibitors of dissolution as well.[8] The affected enantiomer should therefore dissolve more slowly. Partial dissolution of a racemic conglomerate in the presence of a resolved impurity should result in enrichment of the residual crystals in the enantiomer of the same absolute configuration as that of the impurity.

(iii) Crystallization of an optically pure substrate *S* in the presence of racemic impurity (*S'*,*R'*) must result in preferential adsorption of the impurity enantiomer of the same chirality (*S'*).[9]

(iv) Since the rate of growth of the impurity affected crystal is influenced differently in the various growth directions, this last should undergo a morphological change.[10]

Among a number of systems which have been successfully resolved in the presence of impurities, four have been subjected to the above tests: $Cu(Asp)_2$, already investigated by Harada,[6] and the polymerizing dienes, threonine, and asparagine, resolved by us on the sole basis of the stated hypothesis.

Table I summarizes the results of experiments on crystallization, dissolution, and preferential adsorption on the model compounds. Morphological studies on two of these systems will be described separately in the following paper. The results described in Table I are in agreement with the four criteria previously stated, demonstrating that resolution indeed takes place in all the systems by the same proposed mechanism.

Concentrations of 0.03–2% of impurity have been found in the crystallized material. In the preferential adsorption experiments,

(6) Harada, K. *Nature (London)* **1965**, *205*, 590.
(7) Secor, R. M. *Chem. Rev.* **1963**, *63*, 306. Since the information is sprinkled over the literature, we cannot assure that the list is complete.
(8) Cabrera, N.; Vermilyea, D. A. "Growth and Perfection of Crystals"; Wiley: London, 1958; Chapter 5. In practice the effect can be overwhelmed by other factors affecting dissolution.
(9) Sakata, Y.; Takenouchi, K. *Agr. Biol. Chem.* **1963**, *27*, 610.
(10) Wells, A. F. *Philos. Mag.* **1946**, *37*, 180, 217, 605.
(11) (a) Gil-Av, E.; Hare, P. E.; Tishbee, A. *J. Am. Chem. Soc.* **1980**, *102*, 5115. (b) Weinstein, S. In preparation. A full analysis will appear in a joint full paper with S. Weinstein.

both enantiomers S' and R' have been found in the S crystal. However, after dissolution of the first layers, the R' impurity is completely removed, while S' is still present in the bulk of the crystal.

In the dissolution experiments, the magnitude of the effect has been found to be strongly dependent on the size of the crystals and maximal when the impurity is preadsorbed on them, excluding the possibility that stereoselective solution interactions be responsible for resolution. Futhermore, these experiments indicate that the major role of the impurity is on crystal growth (or dissolution) rather than on the preferential nucleation of one of the enantiomorphs. Further investigation is, however, needed to clarify the exact contribution of nucleation to the overall resolution.[12]

The above information suggests that it should be possible, by exploiting this mechanism, to improve not only the resolution of enantiomers crystallizing in the form of conglomerates but also the separation in any process involving competition in the crystallization of two phases, such as diastereoisomers or polymorphic forms (reacemate against conglomerate[13] and the like).

This process is not competitive with seeding but can be efficiently coupled with it, by using the seeds of the wanted enantiomer while inhibiting the growth of the unwanted one by impurity. Further, there may be a connection between the process here and other processes involving chiral recognition by adsorption, such as chromatographic separation on chiral phases.[14] Studies in this direction are under investigation.

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(12) Nucleation of both enantiomers is in general delayed in the presence of impurity. We do not know, however, whether this influence is stereoselective. In several systems we found similar resolutions in the presence of seeds R,S as without seeds.

(13) Sakata, Y. *Agr. Biol. Chem.* **1961**, *25*, 829.

(14) (a) Mikes, F.; Boshart, G.; Gil-Av, E. *J. Chromatogr.* **1976**, *122*, 205. (b) Weinstein, S.; Leiserowitz, L.; and Gil-Av, E. *J. Am. Chem. Soc.* **1980**, *102*, 27.

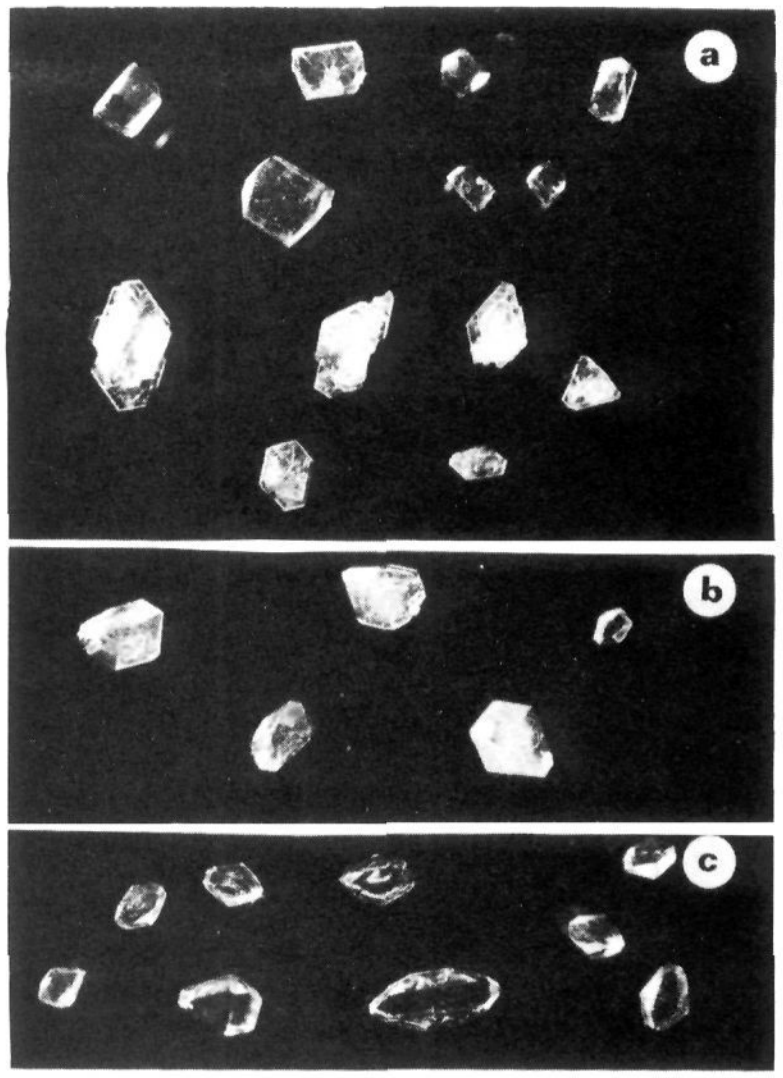

Figure 1. Crystal morphology of (*R*,*S*)-asparagine crystallized in the presence of *S* impurity: (a) (*R*,*S*)-Asn + (*S*)-Asp; manual separation: upper, unaffected *R* crystals; lower, *S* crystals; (b) (*R*,*S*)-Asn + (*S*)-Glu, *S* crystals; (c) (*R*,*S*)-Asn + (*S*)-Gln, *S* crystals; in (b) and (c) *R* crystals appear as in (a) upper.

Useful Impurites for Optical Resolutions. 3. An Improved Pasteur-Type Resolution of Conglomerates and a New Empirical Method for Assignment of Absolute Configuration

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In 1848 Pasteur separated for the first time the two antipodes from a racemic mixture by mechanically sorting enantiomorphous crystals of sodium ammonium tartrate tetrahydrate under a microscope.[1] This process was made possible by the fact that the enantiomorphous crystals developed appropriate hemihedral faces, which permitted their visual identification. This feature is very rare and introduces additional limitations to the already severe requirement that to allow resolution by this method the racemate must crystallize in the form of a conglomerate.[2,3]

Moreover, the correlation between the external morphology of the crystal and the absolute configuration of the enantiomer composing it is not straightforward.[4,5] We shall describe here a new method for visual separation of conglomerates and a new empirical method for assignment of absolute configuration of enantiomers.

In our studies[6,7] on the crystallization of conglomerates in the presence of chiral impurities, we have presented evidence for a mechanism involving preferential adsorption of the impurity at one or more of the faces of the stereochemically related crystal. Since the overall morphology of the crystal is determined by the rates of growth of the various faces, preferred adsorption on some of these, associated with changes of their relative growth rates, will result in an overall morphological change of the enantiomorph where adsorption took place,[7,8] while the antipode will be almost unmodified. We describe three examples of this phenomenon: asparagine·H_2O, threonine, and (*R*,*R*)- and (*S*,*S*)-ammonium hydrogen tartrate.

(*R*,*S*)-Asparagine (Asn) crystallizes from water at room temperature in the form of a conglomerate of space group $P2_12_12_1$.[9]

(1) Pasteur, L. *Ann. Chim. Phys.* **1848**, *24*, 442.

(2) Fieser and Fieser [Fieser, L.; Fieser, M. "Advanced Organic Chemistry"; Reinhold: New York, 1961; p 71] report that only nine other examples of this kind have been found.

(3) Collet, A.; Brienne, M. J.; Jacques, J. *Bull. Soc. Chim. Fr.* **1972**, 127.

(4) An assignment of the absolute configuration of tartaric acid from its morphology [Waser, J. *J. Chem. Phys.* **1949**, *17*, 498] turned out to be incorrect: Bijvoet, J. M.; Peerdeman, A. F.; Van Bommel, J. A. *Nature (London)* **1951**, *168*, 271.

(5) For a description of other methods for identification of chirality of crystals, see: Lin, C. T.; Curtin, D. Y.; Paul, I. C. *J. Am. Chem. Soc.* **1974**, *96*, 6199.

(6) van Mil, J.; Gati, E.; Addadi, L.; Lahav, M. *J. Am. Chem. Soc.*, first of three papers in this issue.

(7) Addadi, L.; van Mil, J.; Lahav, M. *J. Am. Chem. Soc.*, preceding paper in this issue.

(8) On the effect of impurities on crystal morphology, see: Miles, F. D. *Proc. R. Soc. London, Ser. A* **1931**, *132*, 266. Buckley, H. E. "Crystal Growth"; Wiley: New York, 1951.

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