J. Am. Chem. Soc. **1989**, *111*, 1029-1034

Absolute Asymmetric Photochemistry Using Centrosymmetric Single Crystals. The Host/Guest System (*E*)-Cinnamamide/(*E*)-Cinnamic Acid[†]

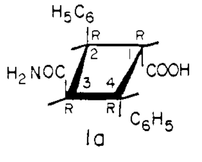
M. Vaida, L. J. W. Shimon, J. van Mil, K. Ernst-Cabrera, L. Addadi,* L. Leiserowitz,* and M. Lahav*

Contribution from the Department of Structural Chemistry, The Weizmann Institute of Science, 76100 Rehovot, Israel. *Received May 26, 1988*

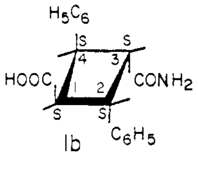
Abstract: Controlled reduction in crystal symmetry has been accomplished and exploited to perform an absolute asymmetric photoreaction. The principle is based on selective introduction of a guest molecule into a centrosymmetric host structure, thus reducing the symmetry of the mixed crystal. Crystallization of (*E*)-cinnamamide (space group $P2_1/c$) in the presence of (*E*)-cinnamic acid results in a mixed crystal composed of two enantiomorphous halves each containing 0.5–1.0% of the acid. The replacement of N–H···O hydrogen bonds between host molecules by O···O lone-pair repulsion between host and guest at the chiral surfaces of the growing crystal is responsible for the stereoselective occlusion of the guest and the reduction in symmetry. Irradiation of each half separately yielded the optically active cyclobutane dimer **1a** or **1b** in excess, with an enantiomeric yield in the range of 40–60%, varying from one single crystal to another. The absolute configuration of the chiral dimer **1a** formed in excess at the +*b* pole (1*R*,2*R*,3*R*,4*R*) was independently assigned by the Bijvoet method, NMR, and crystal-etching experiments and is in agreement with our proposed mechanism of molecular recognition.

Asymmetric transformations of nonchiral molecules packing in chiral space groups are well documented. These include both heterogeneous gas/solid[1] and topochemical[2–4] reactions. An important extension of these asymmetric transformation to centrosymmetric crystals has been proposed[4a,5a] and recently successfully accomplished for heterogeneous reactions by Richardson et al.[5] and for the resolution of racemates inside centrosymmetric crystals developing enantiotopic faces.[6] In these latter works we demonstrated, that when solid solutions are formed within single crystals of a centrosymmetric host, the symmetry of the mixed crystal can be reduced from centrosymmetric to chiral, thus providing a new means to design chiral crystals for the performance of spontaneous asymmetric transformations. This approach is illustrated here for the asymmetric photodimerization of guest (*E*)-cinnamic acid with host (*E*)-cinnamamide.

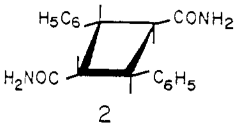
Mixed Crystal (*E*)-Cinnamamide/(*E*)-Cinnamic Acid. We selected (*E*)-cinnamamide as a host system.[7] The compound crystallizes in the centrosymmetric space group $P2_1/c$ (a = 9.56, b = 5.14, c = 16.01 Å; β = 94.1°) and is known to undergo a topochemical photodimerization[8] to yield the centrosymmetric dimer α-truxillamide (**2**).



1a



1b



2

Pure (*E*)-cinnamamide forms prismatic crystals elongated in *b* (Figure 1a). Within the lattice the molecules are arranged in hydrogen-bonded cyclic dimers across centers of inversion. The two molecules of such a hydrogen-bonded cyclic dimer are enantioconformers and reside at sites arbitrarily labeled *d* and *l* (Figure 2a). The dimers are interlinked by N–H···O hydrogen bonds along the *b* axis to form ribbons (Figure 2b,c). The nearest-neighbor ribbons are related to each other in the *c* direction by 2-fold screw symmetry and in the *a* direction by translation to form close-packed centrosymmetric pairs (Figure 2a,b). Photochemical dimerization takes place across these pairs, between molecules of a *d* and an *l* stack (Figure 2a,c). Figure 2b shows the relative orientations of the four symmetry-related molecules with respect to the unique *b* axis. We note that the glide and $\bar{1}$ symmetry elements reverse both the chirality and polarity of the molecules vis-à-vis the *b* axis, whereas the 2-fold screw leaves them unchanged. The four symmetry-related molecules sit at different surface sites at the four chiral $\{011\}$ faces (Figure 2b). By virtue of the $2/m$ point group, the (011) and $(01\bar{1})$ faces at the +*b* end of the crystal are homotopic and enantiotopic to the $(0\bar{1}1)$ and $(0\bar{1}\bar{1})$ pair at the −*b* end of the crystal. At the (011) and $(01\bar{1})$ faces, the N–H (anti) bonds of the *d* molecules emerge from the crystal surface, whereas the N–H (anti) bonds of the *l* molecules point into the crystal (Figure 2b). The roles of the *d* and *l* molecules are reversed at the opposite $(0\bar{1}1)$ and $(0\bar{1}\bar{1})$ faces. A cinnamic acid guest molecule may replace cinnamamide at *d* sites on the (011) and $(01\bar{1})$ faces. At such sites the N–H···O amide bond between host molecules can be replaced by an N–H···O bond between host and guest, even if the carbonyl oxygen atom is a somewhat weaker proton acceptor than the corresponding amide oxygen atom.[9] (*E*)-Cinnamic acid is expected to less easily occupy

---

[†] Dedicated to Prof. D. Y. Curtin on the occasion of his retirement from teaching.

(1) Penzien, K.; Schmidt, G. M. J. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 608.

(2) (a) Elgavi, A.; Green, B. S.; Schmidt, G. M. J. *J. Am. Chem. Soc.* **1973**, *95*, 2058. (b) Addadi, L.; van Mil, J.; Lahav, M. *J. Am. Chem. Soc.* **1982**, *104*, 3422.

(3) Evans, S. V.; Garcia-Garibay, M.; Omkaram, N.; Scheffer, J. R.; Trotter, J.; Wireko, F. *J. Am. Chem. Soc.* **1987**, *109*, 5648.

(4) For some leading reviews see: (a) Green, B. S.; Lahav, M.; Rabinovich, D. *Acc. Chem. Res.* **1979**, *12*, 191. (b) Green, B. S.; Arad-Yellin, R.; Cohen, M. D. *Top. Stereochem.* **1986**, *16*, 131. (c) Ramamurthy, V. *Tetrahedron* **1986**, *42*, 5753. (d) Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433. (e) Addadi, L.; van Mil, J.; Weissbuch, I.; Berkovitch-Yellin, Z.; Leiserowitz, L.; Lahav, M. *Chem. Scr.* **1985**, *25*, 91.

(5) (a) Holland, H. L.; Richardson, M. F. *Mol. Cryst. Liq. Cryst.* **1980**, 58, 311. (b) Chinna Chenchallah, P.; Holland, H. L.; Richardson, M. F. *J. Chem. Soc., Chem. Commun.* **1982**, 436. (c) Chinna Chenchallah, P.; Holland, H. L.; Munoz, B.; Richardson, M. F. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1775.

(6) (a) Weissbuch, I.; Addadi, L.; Berkovitch-Yellin, Z.; Gati, E.; Weinstein, S.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1983**, *105*, 6615. (b) Weissbuch, I.; Addadi, L.; Leiserowitz, L.; Lahav, M. *J. Am. Chem. Soc.* **1988**, *110*, 561.

(7) Berkovitch-Yellin, Z.; van Mil, J.; Addadi, L.; Idelson, M.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1985**, *107*, 3111.

(8) (a) Cohen, M. D.; Schmidt, G. M. J.; Sonntag, F. I. *J. Chem. Soc.* **1964**, *384*, 2000. (b) Schmidt, G. M. J. *J. Chem. Soc.* **1964**, *385*, 2014.

0002-7863/89/1511-1029$01.50/0

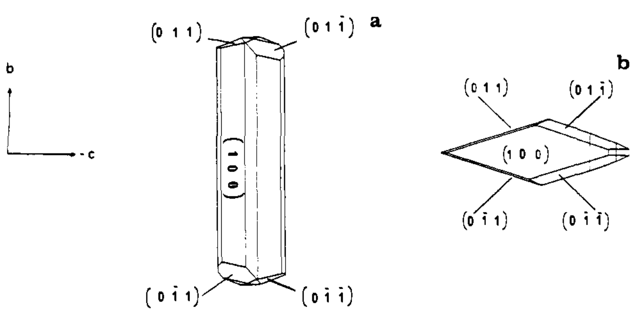


Figure 1. (a) Crystal morphology of pure (*E*)-cinnamamide viewed down the *a* axis. (b) Crystal morphology of (*E*)-cinnamamide grown in the presence of (*E*)-cinnamic acid viewed down the *a* axis.

l surface sites on the (011) and $(01\bar{1})$ faces since in this case the N–H···O amide bonds between host molecules would be replaced by a guest–host O(hydroxyl)···(amide) repulsion involving the lone-pair electrons (Figure 2c).[10] Consequently, (*E*)-cinnamic acid should be preferentially adsorbed and occluded through the *d* surface sites on the (011) and $(01\bar{1})$ faces and by symmetry through the *l* surface sites at the opposite $(0\bar{1}1)$ and $(0\bar{1}\bar{1})$ faces. This proposed mechanism of occlusion is compatible with the growth and dissolution properties of cinnamamide in the presence of cinnamic acid.[7,11] We had reported that cinnamic acid strongly inhibits the growth of cinnamamide along the *b* axis (Figure 1b). Moreover, partial dissolution of cinnamamide crystals in the presence of cinnamic acid yields etch pits formed only on the $\{011\}$ faces.[11b] These results are indicative of a strong preferential adsorption of cinnamic acid on the $\{011\}$ faces during dissolution and are compatible with growth experiments. As a consequence of the above-mentioned analysis a mixed crystal of cinnamamide/cinnamic acid will be composed of two enantiomorphous halves, each of symmetry $P2_1$, and the absolute orientations of the enantioconformers in the crystal will be unambiguously assigned with respect to the crystal axes.[12] We anticipate that topochemical photocyclodimerization of a cinnamic acid guest molecule in a *d* stack with a cinnamamide molecule of an *l* stack will take place at the +*b* end of the crystal preferentially yielding the chiral mixed dimer (*t*-3-carbamoyl-*t*-2,*c*-4-diphenyl-*r*-1-cyclobutane carboxylic acid) **1a** (*RRRR*). Symmetrically, we expect the enantiomeric dimer **1b** (*SSSS*) to be formed in excess at the –*b* end (Figure 2c).[13a]

Results

Large single crystals of (*E*)-cinnamamide were grown from supersaturated solutions of (*E*)-cinnamamide containing 10% (wt/wt) (*E*)-cinnamic acid in ethyl acetate, with a seed crystal placed in each vessel (see Experimental Section). Figure 3 shows a photograph of a crystal in its natural size, containing 0.5–1% (*E*)-cinnamic acid. The boundaries between the starting seed and the newly grown segments at the +*b* and the –*b* ends are seen. The crystal cleaves easily along these boundaries, thus allowing total separation of its enantiomorphous segments. Material from the top parts of these segments was crushed and exposed to UV irradiation. The mixed dimers were isolated, as described in the Experimental Section, and the hetero acid/amide dimers were finally purified by preparative TLC. The chiral dimers were transformed into the corresponding *N*-(trifluoroacetyl)-*O*-isopropyl derivatives and analyzed for their enantiomeric excess by GC on a capillary chiral column. The enantiomeric excess was in the range of 40–60%, differing from one segment to another (Figure 4).

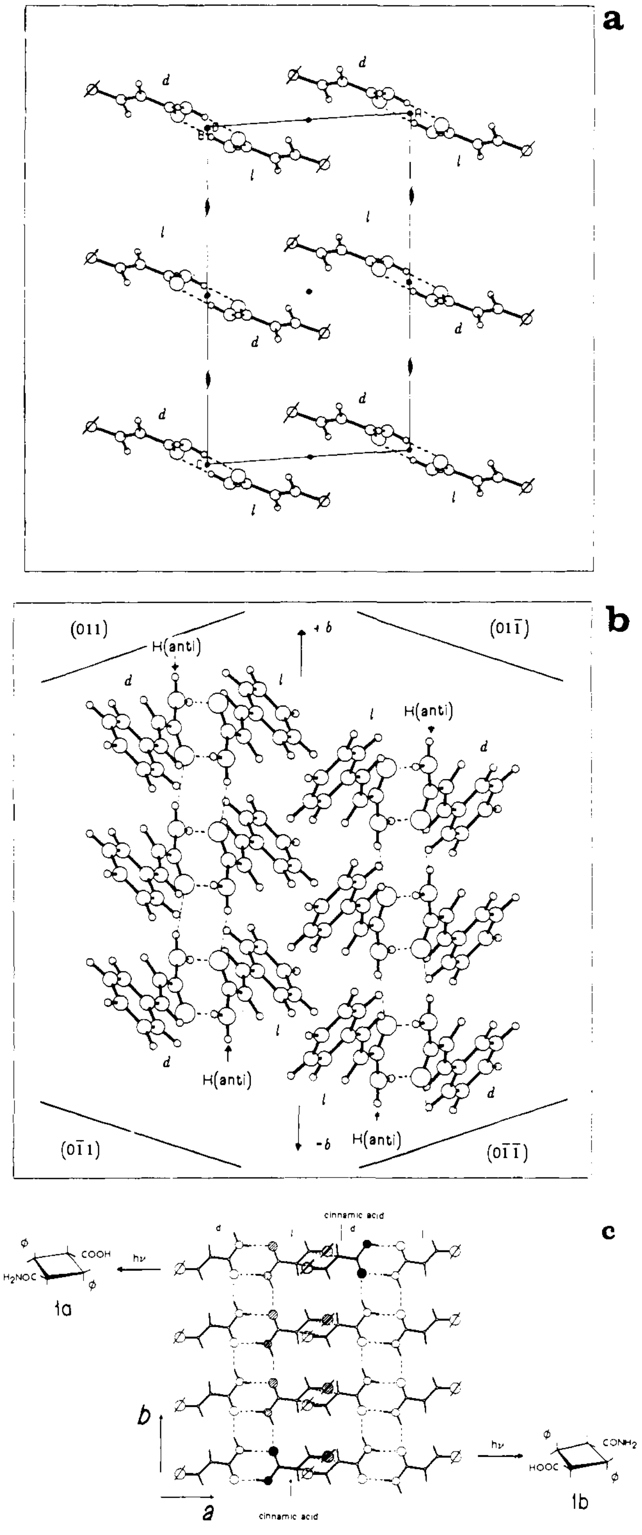


Figure 2. Packing arrangement of (*E*)-cinnamamide. (a) View along the *b* axis, with the *d* and *l* molecules shown. (b) View along the *a* axis. The $\{011\}$ faces are shown. (c) View along the *c* axis showing hydrogen-bonded dimers related by translation along *a* and *b*. The shaded *l* molecules belonging to one hydrogen-bonded dimer ribbon are lying above the *d* molecules of the other dimer ribbon.

Absolute Configuration of the Mixed Dimer. The proposed mechanism of preferential adsorption and occlusion of the guest molecules may be further confirmed by correlating the proposed absolute structure of the mixed crystal with an independent assignment of the absolute configurations of the chiral mixed dimers formed in excess at each end of the crystal. The absolute con-

---

(9) Berkovitch-Yellin, Z.; Ariel, S.; Leiserowitz, L. *J. Am. Chem. Soc.* **1983**, *105*, 765.

(10) (a) Huang, C.; Leiserowitz, L.; Schmidt, G. M. J. *J. Chem. Soc., Perkin Trans. 2* **1973**, 503. (b) Leiserowitz, L. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1976**, *B32*, 775. (c) Berkovitch-Yellin, Z.; Leiserowitz, L. *J. Am. Chem. Soc.* **1983**, *104*, 4052.

(11) (a) Shimon, L. J. W.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.* **1985**, *107*, 3375. (b) Shimon, L. J. W.; Lahav, M.; Leiserowitz, L. *Nouv. J. Chim.* **1986**, *10*, 723.

(12) Addadi, L.; Berkovitch-Yellin, Z.; Weissbuch, I.; Lahav, M.; Leiserowitz, L. *Top. Stereochem.* **1986**, *16*, 1.

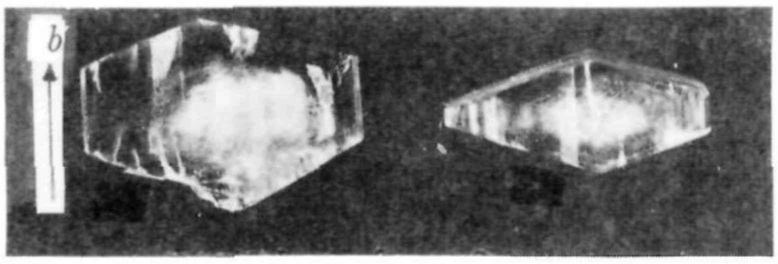


Figure 3. Crystals of cinnamamide grown in presence of cinnamic acid. View perpendicular to the *b* axis. The seeds can be clearly seen.

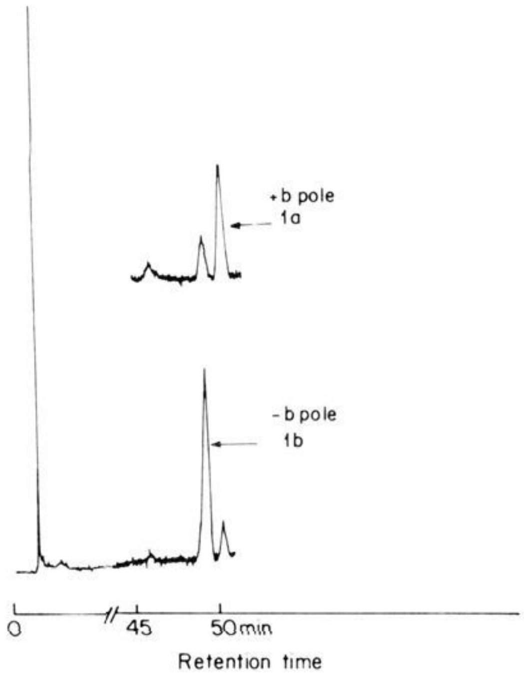


Figure 4. GC chromatograms of the *O-i*-Pr-*N*-TFA derivatives of compounds **1a** and **1b** isolated from the +*b* and −*b* pole (Chirasil-L-valine capillary column).

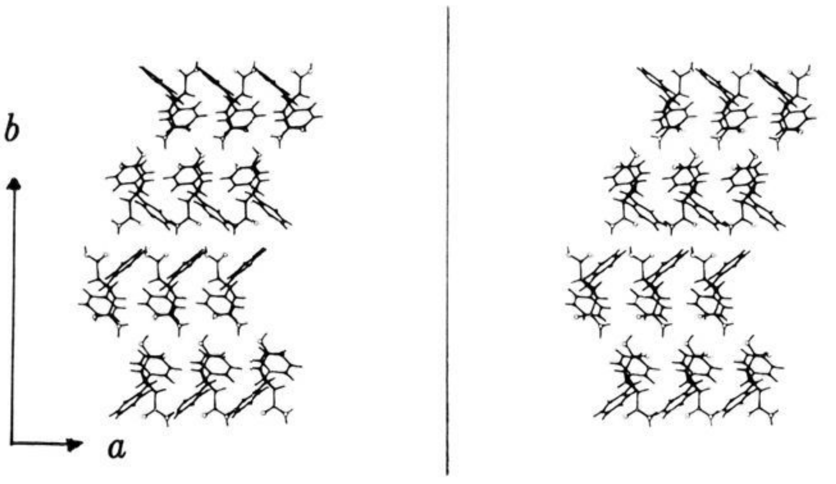


Figure 5. Stereoscopic view of the packing arrangement of the truxillic acid monoamide dimer **1a** as seen down the *c* axis.

figuration of the mixed dimer was assigned as follows.[13b]

Bijvoet Analysis. The racemic mixed dimer **1** undergoes spontaneous segregation upon crystallization into homochiral crystals of space group $P2_1$, with $z = 4$, i.e., 2 independent molecules per asymmetric unit. The X-ray crystal structure was determined with a crystal grown from optically pure material obtained by resolution of a racemic mixture (see Experimental Section). The resolved dimer used for the X-ray structure determination was assigned by CD ($\Delta\epsilon = +2$, $\lambda = 220$) and by GC to have the same absolute configuration as the mixed dimer **1a** formed in excess at the +*b* side of the amide crystal. The crystal structure was determined and refined by structure-factor least squares, yielding a final agreement factor of $R(F) = 0.034$ (Table I). The packing arrangement is shown in Figure 5. Paradoxically, **1** crystallizes in a pseudocentrosymmetric arrangement, with the two independent molecules related by a pseudocenter of inversion. The subtle deviations from a true center of symmetry made it possible to assign the absolute configuration of the photoaddition product **1a** to be (*R,R,R,R*) using the Bijvoet method (see Experimental Section). However, the pseudocentrosymmetric arrangement of the crystal structure of **1a** still raised the possibility of an ambiguous assignment of the absolute structure from the Bijvoet method, thus demanding an independent confirmation.

Table I. Truxillic Acid Monoamide **1**. X-ray Intensity Measurements and Crystal Structure Refinement

(a) Crystal Data	
formula	$C_{18}H_{17}NO_3$
space group	$P2_1{}^a$
a, Å	5.530 (1)
b, Å	32.629 (6)
c, Å	8.610 (1)
β, deg	107.97 (1)
V, Å^3	1477.8
Z	4
X radiation	Cu Kα (1.5418 Å)
no. of reflcns measd	3320
crystal size, 10^{-1}mm	2 × 2 × 3
$R(\mathrm{av})^b$	0.0110
(b) *Crystal Structure Refinement*	
no. of independent reflcns	3070
no. of parameters refined	499
R(*F*)	0.034
$R_w(F)$	0.039

[a] For convenience the general atom positions are (x, y, z) and $(^1/_2 - x, {}^1/_2 + y, -z)$, i.e., the 2-fold screw axis lies at $x = {}^1/_4$, $z = 0$. [b] $R(\mathrm{av})$ is the agreement between equivalent reflections and is $\sum|\bar{F}_o{}^2 - F_o{}^2|/\sum F_o{}^2$ where $\bar{F}_o$ is the average value of the observed symmetry-related structure factor and F_o is the individual structure factor.

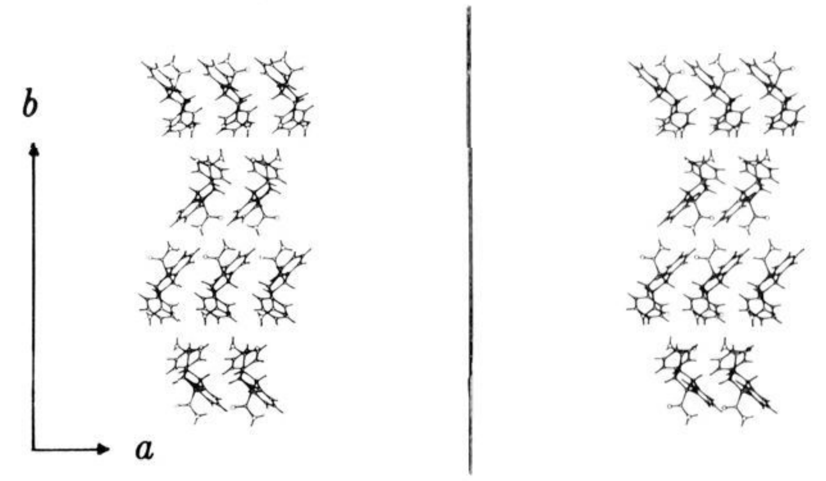


Figure 6. Stereoscopic view of the packing arrangement of the truxillic acid diamide **2** as seen down the *c* axis.

Absolute Configuration by Etching. Recently we have developed an independent crystal-etching method for the direct assignment of the absolute configuration of chiral molecules.[11] The method is based on molecular recognition involving a direct correlation between the ability of an etchant molecule to bind to a crystal surface and the development of etch pits on that surface during partial dissolution. Centrosymmetric crystals of the nonchiral truxillic diamide **2** were an ideal substrate for this purpose. The chiral acid/amides **1** were used as etchants in a manner equivalent to cinnamic acid used as etchant for cinnamamide (vide supra).[11b] The diamide crystals grow as well-developed {010} plates. By inspection of the crystal structure of the diamide (see Experimental Section) (Figure 6) we expect that the acid/amide **1a** molecules of absolute configuration (*R,R,R,R*), will be adsorbed on the (010) face and, upon dissolution, etch this face. By symmetry, the (*S,S,S,S*) enantiomer **1b** will be adsorbed upon and etch the $(0\bar{1}0)$ face. Indeed, when crystals of the diamide were dissolved in the presence of the acid/amide of the same absolute configuration

---

(13) (a) The absolute configurations of **1a** and **1b** in the present work are designated as *RRRR* and *SSSS* according to the convention of: Prelog, V.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 567. It should be noticed that this notation will be different according to a previous convention of: Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem.* **1966**, *5*, 385. Following this convention, the absolute configuration of **1a** and **1b** should read *RRSR* and *SSRS*, respectively. (b) Assignment of absolute configuration of chiral-resolved **1** by forming the diastereomeric *sec*-butyl-containing derivative proved unsuitable, for the crystals were poor and the structure thereof was found to contain 4 molecules per asymmetric unit.

Figure 7. Etch pits on the (010) face of **2** after partial dissolution in presence of **1a**.

as had been assigned by X-ray diffraction, i.e., **1a**, the crystals were etched only at the (010) face (Figure 7). The (0$\bar{1}$0) face remained smooth and unetched.

NMR. The absolute configuration of resolved **1b** could also be assigned by the NMR analysis of the corresponding *sec*-butyl esters. This enantiomer was reacted with *R*-(−)- and *S*-(+)-*sec*-butyl alcohols to yield the two diastereomeric esters **3** and **4**, respectively. In accordance with previous observations on similar systems,[14] the relative intensities of the doublet A(**3**) at δ 0.93 and of the triplet B(**3**) at δ 0.51 for **3**, with respect to the doublet A(**4**) at δ 0.55 and the triplet B(**4**) at δ 0.72 for **4**, suggest that the absolute configuration of dimer **1b** is in agreement with that derived by the other two methods (Figure 8).

All these three independent studies demonstrate unambiguously that the absolute configuration of the dimer is in agreement with our proposed mechanism.

Discussion

An asymmetric synthesis involving two nonchiral host and guest molecules was accomplished inside a single crystal of an originally centrosymmetric host. This is an important extension of previous studies, where such absolute asymmetric photoreactions were limited to the narrow class of chiral space groups; statistics on the packing modes of nonchiral molecules or racemates have shown that these molecules have a tendency higher than 80% to crystallize in centrosymmetric space groups.

The prime factors responsible for the reduction in symmetry in the present system are the interactions between host and guest molecules at the chiral crystal surfaces, on the one hand an N–H···O(guest carbonyl) hydrogen bond of −7 kcal/mol favoring guest occlusion and on the other hand a repulsive O···O interaction of +2 kcal/mol inhibiting guest occlusion.[7] Direct experimental evidence for such O···O repulsion is provided by the packing arrangement of two crystal structures, the molecular 2:1 complex of benzamide/succinic acid[10a] and the mixed dimer **1a** described in the present work. In the crystal structure of benzamide/succinic acid a distorted hydrogen-bond network is induced so as to prevent two neighboring O(carbonyl) and O(hydroxyl) oxygen atoms, whose lone-pair electrons are directed at each other, to approach to within less than 3.6 Å. This distortion manifests itself in a dihedral angle of 20° between the planes of amide and carboxyl groups forming a hydrogen-bonded dimer. In the crystal structure of **1a**, a similar distortion is observed. Indeed the evidence for such a distortion is strengthened by a comparison of the crystal structure of **1a** and of truxillic acid diamide (**2**). These two crystal structures have similar packing arrangements, (Figures 5 and 6, respectively). Both molecules form cyclic dimers with OH···O and NH···O hydrogen bonds. These dimers are then weakly linked along the translational *a* axis by NH···O interactions. Additional NH···O and OH···O hydrogen bonds link the molecules related across the glide (or pseudoglide) plane.

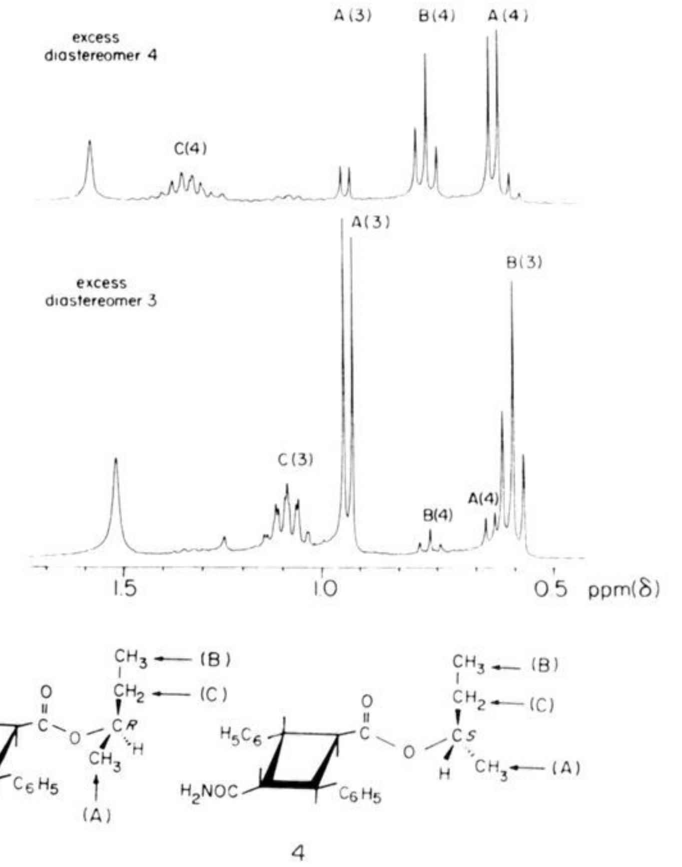


Figure 8. NMR spectrum of the methyl region of diastereomers **3** and **4**. The relative intensities of the doublet A(**3**) at δ 0.93 and of the triplet B(**3**) at δ 0.51 for **3**, with respect to the doublet A(**4**) at δ 0.55 and the triplet B(**4**) at δ 0.72 for **4**, suggest that the absolute configuration of dimer **1b** is in agreement with that derived by the other two methods.

Comparison of these two crystal structures shows certain indicative changes in intermolecular distances, arising from the replacement of one amide nitrogen by an oxygen. The *a* axis (the hydrogen-bonding axis) of the acid/amide is 5.53 Å, increased from the diamide axial length of 5.26 Å, a difference of 0.27 Å. This increase in axial length is manifested in NH···O distances of 3.34 and 3.60 Å in the acid/amide, increased from the corresponding NH···O distances in the diamide of 3.06 and 3.34 Å, respectively. Within the acid/amide itself, the O···O distances are 3.59 and 3.79 Å, increased from the corresponding NH···O distances of 3.34 and 3.60 Å, respectively. This is an effective increase of approximately 0.5 Å which can be directly ascribed to a repulsion between the oxygen lone pairs. We may envisage that absorption of cinnamic acid at a less favorable {01$\bar{1}$} surface site may be achieved by a similar rotation of the carboxyl group, so as to lower the repulsive interaction between the oxygen atoms. The reduction in crystal symmetry brought about by relatively small differences in molecular volume involving host and guest molecules calls for a general revision of the structure and symmetry of solid solutions, where it had generally been assumed that the symmetry of the mixed crystal be the same as that of the host. In the following paper, we demonstrate such a reduction of symmetry by a direct neutron diffraction study on a single mixed crystal of asparagine·H_2O/aspartic acid containing as much as 16% aspartic acid.[15]

The present approach also provides us with a tool for pinpointing weak interactions between functional groups of molecules at surfaces. Finally, the ability to transform centrosymmetric crystals into chiral or polar mixed crystals provides us with new means for obtaining phases for frequency doubling. Studies along these lines are described elsewhere.[16]

Experimental Section

All CD spectra were taken on a Jasco 500 spectrophotometer. All NMR spectra were taken on a Bruker 270-MHz or Varian 80-MHz spectrophotometer. GC spectra were made on a Hewlett-Packard 5890

---

(14) Addadi, L.; Lahav, M. *J. Am. Chem. Soc.* **1978**, *100*, 2838.

(15) (a) Weisinger-Lewin, Y.; Frolow, F.; McMullan, R.; Koetzle, T. F.; Lahav, M.; Leiserowitz, L. *J. Am. Chem. Soc.*, following paper in this issue. (b) Vaida, M.; Shimon, L. J. W.; Weisenger-Lewin, Y.; Frolow, F.; Lahav, M.; Leiserowitz, L.; McMullan, R. *Science* **1988**, *241*, 1475.

(16) Weissbuch, I.; Lahav, M.; Leiserowitz, L.; Meredith, G. R.; Vanherzeele, H. *Chem. Mater.*, in press.

gas chromatograph equipped with a 25-m fused silica Chirasil-L-valine capillary column (purchased from Chrompack) at 180 °C, 0.9 bar, He carrier gas. The truxillic acid monoamide was derivatized on the carboxylic acid functional group with 5 N HCl in *i*-PrOH at 100 °C for 1 h to obtain the ester and at the amide functional group for 1 h at 0 °C with 25% trifluoroacetic anhydride in $MeCl_2$ to obtain the imide. HPLC analyses were done on a Waters HPLC equipped with 240 × 4.6 mm Rp 18 Chromosorb 5-μm column, eluent buffer acetate (0.05 M, pH 4) with 30% acetonitrile at flow rate 1 mL/min, and UV detector (254 nm).

Preparation of Materials. Truxillic Acid Monoamide 1. A 10-g portion of truxillic acid was dissolved in 30 mL of dry dioxane and ~30 mL of dry DMF and cooled to 0 °C; 1.4 equiv (9.75 g) of 1,3-dicyclohexylcarbodiimide was added, followed immediately by 1.4 equiv of *N*-hydroxysuccinimide (5.5 g). The reaction was left for 1 h at 0 °C and 1 h at room temperature. The precipitated 1,3-dicyclohexylurea was filtered; the filtrate was added to dioxane through which dry ammonia was bubbled and left to stir for 40 h. The solvent was evaporated and the reaction mixture, which contained also truxillic acid and diamide, was separated by flash chromatography on silica gel with eluent *i*-PrOH/H_2O/NH_4OH 200:12:16. Finally, the nearly clean truxillic acid monoamide **1** fractions were recrystallized from ethanol.

Resolution of 1. One gram of **1** was dissolved in 120 mL of acetone while heating, and 1.130 g of strychnine was added; ~100 mL of acetone and a few drops of ethanol had to be added to obtain a clear solution. The solution was filtered and condensed to a volume of 150 mL and kept at 5 °C. After a few days crystals of strychnine precipitated, which were filtered. The mother liquor was concentrated and kept at 5 °C. After 2 days, 280 mg of salt (106 mg of **1**, 8% ee) precipitated and was filtered. The mother liquor was concentrated again. This procedure was repeated two more times [81 mg (50% ee) and 6 mg (60% ee) of salt] until no more salt precipitated from the solution. The remaining 707 mg of material was hydrolyzed. The 345 mg of **1** obtained was dissolved with 465 mg of brucine in acetone and concentrated to a volume of 25 mL; 465 mg of salt (160 mg of **1**, 86% ee of the opposite enantiomer) precipitated and, after 2 days, 145 mg of salt (55 mg of **1**, 96% ee). After evaporation of the remaining acetone 101 mg of material (27 mg of truxillic acid monoamide, 56% ee) was left. Hydrolysis was done in a small volume of 5 N HCl while stirring and heating gently for 1 h, whereafter the truxillic acid monoamide was filtered off. The enantiomeric purity of each fraction was determined by GC.

Truxillic acid: ^{1}H NMR (80 MHz, $(CD_3)_2SO$) δ 3.7–3.9 (m, 2 H), 4.2–4.4 (m, 2 H), 7.3–7.5 (br s, aromatic 10 H).

Truxillic acid monoamide: ^{1}H NMR (80 MHz, $(CD_3)_2SO$) δ 3.6–3.9 (m, 2 H), 4.1–4.3 (m, 2 H), 7.3 (br s, aromatic 10 H).

Truxillic acid diamide: ^{1}H NMR (80 MHz, $(CD_3)_2SO$) δ 3.7–3.9 (m, 2 H), 4.1–4.3 (m, 2 H), 7.3 (br s, aromatic 10 H).

Truxillic acid monoamide *R*-(−)-2-butyl ester (3): ^{1}H NMR (270 MHz, CD_2Cl_2) δ 0.51 (tr, 3 H), 0.93 (d, 3 H), 1.06 (q, 2 H), 3.9 (m, 1 H), 4.05 (m, 1 H), 4.3 (m, 2 H), 4.47 (m, 1 H), 7.2–7.5 (m, aromatics 10 H).

Truxillic acid monoamide *S*-(+)-2-butyl ester (4): ^{1}H NMR (270 MHz, CD_2Cl_2) δ 0.51 (tr), 0.55 (d, 3 H), 0.72 (t, 3 H), 0.93 (d), 1.37 (m, 2 H), 3.8–3.9 (m, 2 H), 4.3, 4.5 (m, 3 H), 7.21–7.28, 7.3–7.4 (m, aromatics 10 H).

Truxillic acid monoamide 2-pentyl ester: ^{1}H NMR (270 MHz, CD_2Cl_2) δ 0.57 (d, $^3/_2$ H), 0.68 (tr, $^3/_2$ H), 0.79 (tr, $^3/_2$ H), 0.95 (d, $^3/_2$ H), 0.81–0.95 (m, H), 0.99–1.09 (m, H), 1.12–1.28 (m, H), 1.28–1.38 (m, H), 3.75–3.9 (m, 2 H), 4.32–4.45 (m, 2 H), 4.51–4.59 (m, 1 H), 7.25–7.4 (m, aromatics 10 H).

Crystal Growth. Small crystals for seeds and HPLC analysis were grown by slow evaporation at room temperature from a solution of 200 mg of cinnamamide with 20 mg of cinnamic acid in 10 mL of ethyl acetate. Crystals used for the experiments were grown by slow cooling in Erlenmeyer flasks containing 100 mL of ethyl acetate with 3.5 g of cinnamamide and 350 mg of cinnamic acid. In order to obtain large single crystals, a seed crystal was placed in each Erlenmeyer vessel. The vessels were kept in a thermostated water bath, whose temperature was lowered from 45 °C by 1 °C per day until the crystals were either large enough or 30 °C was reached. In this way, single crystals of approximately 1 g each were obtained, containing 0.5–1% of cinnamic acid.

Preparation for Irradiation. The crystals were washed with ethyl acetate. Their +*b* and −*b* directions were determined on a Siemens four-circle diffractometer. The top and bottom parts of each crystal at its +*b* or −*b* ends were scraped off with a scalpel, care being taken to remove material from the {011} faces only. The material was put in Petri dishes and irradiated for ~30 days under sunlamps and crushed every few days. The reaction could be followed on TLC (silica and toluene/dioxane/acetic acid 200:50:8).

Table II. Truxillic Acid Monoamide. Atomic Coordinates (×10^4) and Displacement Parameters (Å^2 × 10^3)

atom	*x*/*a*	*y*/*b*	*z*/*c*	U_{equiv}[a]
O(2)	1917 (4)	2091	518 (3)	49
O(3)	−1275 (4)	2093 (1)	1574 (3)	58
O(4)	616 (4)	488 (1)	17 (3)	49
O(1)	−815 (4)	−546 (1)	187 (3)	46
O(6)	2912 (4)	−229 (1)	763 (3)	63
O(7)	2538 (5)	−2091 (1)	−914 (4)	57
N(5)	−1242 (4)	−2144 (1)	−450 (3)	62
N(14)	−3350 (5)	248 (1)	−557 (4)	59
C(1)	−2773 (4)	979 (1)	−441 (3)	34
C(2)	−1261 (4)	1300 (1)	−1129 (3)	35
C(3)	−21 (4)	1457 (1)	667 (3)	32
C(4)	−1982 (4)	1215 (1)	1229 (3)	33
C(5)	1222 (5)	974 (1)	2793 (3)	37
C(6)	1173 (5)	1005 (1)	3926 (3)	47
C(7)	1791 (7)	776 (1)	5369 (4)	58
C(8)	51 (8)	522 (1)	5688 (4)	65
C(9)	−2367 (7)	491 (1)	4570 (4)	66
C(10)	−2983 (6)	718 (1)	3151 (4)	51
C(11)	−2905 (4)	1587 (1)	−2384 (3)	35
C(12)	−2482 (5)	1626 (1)	−3889 (3)	43
C(13)	−4010 (6)	1873 (1)	−5103 (3)	50
C(14)	−5972 (6)	2091 (1)	−4830 (4)	48
C(15)	−6418 (5)	−2060 (1)	−3338 (4)	48
C(16)	−4914 (5)	1808 (1)	−2133 (3)	43
C(17)	107 (4)	1913 (1)	975 (3)	31
C(18)	−1695 (5)	549 (1)	−312 (3)	38
C(19)	589 (4)	−1475 (1)	−336 (3)	31
C(20)	2437 (4)	−1197 (1)	−878 (3)	34
C(21)	2965 (4)	−950 (1)	768 (3)	35
C(22)	1665 (4)	1301 (1)	1451 (3)	36
C(23)	3360 (5)	−1569 (1)	2752 (3)	38
C(24)	2800 (5)	−1628 (1)	4204 (3)	45
C(25)	4258 (7)	−1889 (1)	5410 (4)	58
C(26)	6275 (8)	−2096 (1)	5174 (4)	53
C(27)	6899 (7)	−2036 (1)	3770 (4)	57
C(28)	5482 (6)	−1768 (1)	2580 (4)	51
C(29)	1579 (4)	−971 (1)	−2477 (3)	37
C(30)	−835 (5)	−1011 (1)	−3574 (3)	48
C(31)	−1535 (6)	−790 (1)	−5025 (3)	59
C(32)	171 (6)	−528 (1)	−5383 (4)	68
C(33)	2579 (5)	−486 (1)	−4305 (4)	69
C(34)	3299 (5)	−707 (1)	−2858 (3)	52
C(35)	1482 (4)	−557 (1)	544 (3)	37
C(36)	717 (5)	−1933 (1)	−605 (3)	39

[a] Where $U_{equiv} = (U_{11} + U_{22} + U_{33})/3$.

Table III. Observed and Calculated[a] Bijvoet Differences

hkl	B_o	B_c	*hkl*	B_o	B_c
0,15,3	0.018	0.034	011	−0.074	−0.038
2,35,3	0.114	0.049	−5,27,1	0.051	0.035
222	0.197	0.050	041	−0.091	−0.043
−3,2,2	0.052	0.061	−1,3,3	−0.052	−0.036

[a] The calculated Bijvoet differences, $B_c = [(F_c^2(hkl) - F_c^2(\bar{h}\bar{k}\bar{l})/0.5\text{-}(F_c^2(hkl) + F_c^2(\bar{h}\bar{k}\bar{l}))]$, were based on space group $P2_1$ with atomic *x*, *y*, *z* coordinates given in Table II. These reflections were chosen by an index of observability given by $[F_c^2(hkl) - F_c^2(\bar{h}\bar{k}\bar{l})]/0.5[\sigma(F_c^2(hkl) + \sigma(F_c^2(\bar{h}\bar{k}\bar{l}))]$.

Isolation of 1. The mixed dimer **1** was separated from the cinnamamide and the truxillic acid diamide by flash chromatography on Merck Silica 60 with *i*-PrOH/NH_4OH/H_2O 130:8:6. **1** was further purified on either TLC or PLC (depending on the quantity) in the same eluent.

Determination of the Absolute Crystal Structure of Resolved Truxillic Acid Monoamide. Crystals were grown for this experiment from resolved material that gave a CD spectrum of Δε of +2. The cell dimensions of the specimen crystal of truxillic acid monoamide were measured on a CAD-4 diffractometer (Table I). The X-ray intensities were measured with Ni-filtered Cu Kα radiation for all reflections within a hemisphere of reciprocal space out to sin θ/λ = 0.635 Å^{-1}. Experimental details are given in Table I. The crystal structure was determined by direct methods and refined by structure-factor least squares[17] with the complete measured hemisphere of reflections. The C, N, and O atoms were treated anisotropically, the H atoms isotropically. The final refinement cycle

---

(17) Sheldrick, G. M. *SHELX Program for Crystal Structure Determination*; Cambridge University: Cambridge, England, 1976.

Table IV. Truxillic Acid Diamide X-ray Intensity Measurements and Crystal Structure Refinement

(a) Crystal Data	
formula	$C_{18}H_{18}N_2O_2$
space group	$P2_1/a$
a, Å	5.256 (1)
b, Å	33.741 (5)
c, Å	8.706 (1)
β, deg	106.32 (2)
V, Å^3	1481.74
X radiation	Cu Kα (1.5418 Å)
no. of reflcns measd	2136
crystal size, 10^{-1}mm	2 × 2 × 3
R(av)^a	0.0116
(b) Crystal Structure Refinement	
no. of independent reflcns	1963
no. of parameters refined	272
R(*F*)	0.048
$R_w(F)$	0.055

[a] *R*(av) is the agreement between equivalent reflections and is $\sum[\bar{F}_o^2 - F_o^2|/\sum F_p^2$ where $\bar{F}_o$ is the average value of the observed symmetry-related structure factor and F_o is the individual structure factor.

Table V. Truxillic Acid Diamide. Atomic Coordinates (×10^4) and Displacement Parameters (Å^2 × 10^3)

atom	*x*/*a*	*y*/*b*	*z*/*c*	U_{equiv}^{a}
O(1)	2025 (3)	7043 (1)	4106 (2)	41
O(2)	6361 (3)	5518 (1)	5459 (2)	46
C(3)	2167 (3)	6194 (1)	4248 (2)	29
C(4)	4255 (4)	6891 (1)	4408 (2)	30
N(5)	6420 (4)	7103 (1)	4496 (2)	40
C(6)	5288 (4)	6294 (1)	6496 (2)	31
C(7)	3135 (4)	5972 (1)	5901 (2)	33
C(8)	4647 (3)	6455 (1)	4716 (2)	29
C(9)	1454 (4)	5962 (1)	2707 (2)	31
C(10)	4232 (4)	5565 (1)	5769 (2)	36
C(11)	4950 (4)	6568 (1)	7793 (2)	33
C(12)	2797 (5)	6009 (1)	1552 (2)	44
C(13)	6964 (5)	6602 (1)	6204 (2)	42
N(14)	2737 (5)	5265 (1)	5983 (3)	56
C(15)	−1383 (6)	5482 (1)	993 (3)	52
C(16)	−644 (5)	5698 (1)	2403 (3)	44
C(17)	4484 (6)	7079 (1)	10225 (3)	54
C(18)	2665 (6)	6788 (1)	7653 (3)	45
C(19)	6733 (6)	6853 (1)	10422 (3)	51
C(20)	2045 (6)	5797 (1)	132 (3)	53
C(21)	−22 (6)	5535 (1)	−147 (3)	53
C(22)	2445 (5)	7044 (1)	5546 (3)	53

[a] Where $U_{equiv} = (U_{11} + U_{22} + U_{33})/3$.

gave $R(F) = 0.034$, and its inversion image yielded the same *R* factor (see Table I). The *x*, *y*, *z* coordinates of the final cycle are listed in Table II.

The packing arrangement is shown in Figure 5. The two independent molecules are related by a pseudocenter of inversion situated at $x = 0.017$, $y = 0$, and $z = 0.016$. The entire structure may now be described in terms of pseudo-$P2_1/a$ space group symmetry with the true 2-fold screw axis positioned, for convenience, at $x = {}^1/_4$, $z = 0$ (for space group $P2_1$ the usual position is $x = 0$, $z = 0$). This pseudocenter of inversion is the center of gravity of the two molecules and lies very close to the point $x, y, z = (0, 0, 0)$, the point that would be the position of the center of inversion in a true centrosymmetric crystal. The extent to which the arrangement is pseudocentrosymmetric may also be evaluated from the root mean square radius $r = (\sum r_i^2/n - 1)^{1/2}$, where n is the number of non-hydrogen atoms in the molecule, $r_i = {}^1/_2[(x_i + x_i')a + (y_i + y_i')b + (z_i + z_i')c]$, and the atomic coordinates (x', y', z') and (x, y, z) refer to the two atoms related by the pseudocenter of inversion. Thus, r_i specifies the distance from the origin (0, 0, 0) to the mean position of the two atoms. The root mean square radius was calculated as low as 0.15 Å, indicating a pseudocentrosymmetric crystal structure.

The pseudocentrosymmetric nature of the crystal structure indicated that the Bijvoet differences may arise solely from differences in the anomalous scattering of the hydroxyl oxygen versus the amide nitrogen atom. The centrosymmetric nature of the carbon skeleton has the advantageous result of canceling out their anomalous contributions.

The eight most observable Bijvoet sensitive reflections were chosen and measured.[7,18] All symmetry-related Friedel pairs, totaling 72 reflections, were measured on the CAD-4 diffractometer with scan rates such that each $\sigma(I)/I$ of the integrated intensity was significantly lower than the corresponding calculated Bijvoet difference, $B_c = [(F_c^2(hkl) - F_c^2(\bar{h}\bar{k}\bar{l}))/0.5(F_c^2(hkl) + F_c^2(\bar{h}\bar{k}\bar{l}))]$. The observed Bijvoet differences B_o of the symmetry-related reflections were averaged. These results, together with the values of B_c for the eight reflections for the crystal structure given in the packing arrangement of Figure 5 are listed in Table III. This is the (*R*,*R*,*R*,*R*) configuration.

Crystal Structure Determination of Truxillic Acid Diamide. Crystals of truxillic acid diamide were grown by slow evaporation from acetonitrile. Cell dimensions were measured on a CAD-4 diffractometer (Table IV). X-ray intensities were measured with Ni-filtered Cu Kα radiation for all reflections within a quadrant of reciprocal space out to $\sin\theta/\lambda = 0.635$ Å^{-1}. Experimental details are given in Table IV. The crystal structure was determined by direct methods and refined by structure-factor least squares[17] with the complete measured quadrant of reflections. The C, N, and O atoms were treated anisotropically, the H atoms isotropically. The final refinement of the atomic parameters gave $R(F) = 0.0480$. The *x*, *y*, *z* coordinates are given in Table V.

Acknowledgment. We thank Prof. M. D. Cohen for his constructive remarks and the Israel Academy of Sciences and Humanities for financial support.

Registry No. 1a, 117940-53-1; **1b**, 118014-55-4; **2**, 117940-54-2; **3**, 117940-55-3; **4**, 118014-56-5; (*E*)-cinnamic acid, 140-10-3; (*E*)-cinnamamide, 22031-64-7.

Supplementary Material Available: Tables of hydrogen atom coordinates for truxillic acid monoamide and hydrogen atom coordinates and isotropic temperature factors for the diamide (2 pages); tables of observed and calculated structure factors for the monoamide (10 pages). Ordering information is given on any current masthead page.

---

(18) Hope, H., private communication.