Structural and conformational study of two solvates of a fulgenic acid derivative†

Valerio Giannellini,[a] Massimo Bambagiotti-Alberti,*[a] Bruno Bruni[b] and Massimo Di Vaira*[b]

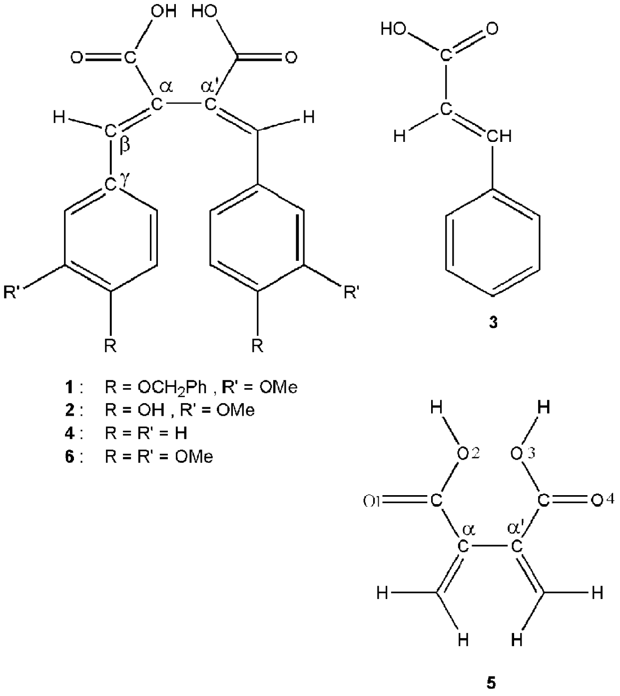
Received (in Montpellier, France) 8th November 2005, Accepted 20th January 2006
First published as an Advance Article on the web 14th February 2006
DOI: 10.1039/b515266f

The X-ray structures of two solvates of a fulgenic acid derivative (**1**), which is an essential intermediate in the synthesis of compounds with possible cancer-protecting properties, have been determined. The compound is closely related to those forming the class of fulgides, which are characterised by remarkable optical properties, that probably owe their existence to extensive electronic conjugation allowed by planarity of large parts of the molecules, a feature shared by **1**. A conformational study has been undertaken to investigate the conditions for the existence, or absence, of such geometrical features and to understand if possible intramolecular hydrogen bonds may play a structure-determining role. Computed energy barriers for rotations around three C–C bonds have shed light on the nature of conformational rearrangements operative for the equilibration detected on the NMR time scale. Intramolecular hydrogen bonds do not favour the planar arrangement of large moieties and are not found to be competitive with intermolecular hydrogen bonds.

Introduction

In previous papers[1,2] some of us reported that fulgenic acids (dibenzylidene-succinic acids), are well-suited intermediates for the synthesis of butanolide lignans (natural products characterised by the coupling of two C_6C_3 units[3]) and corresponding 1,4-butanediols. Among these, matairesinol [3,4-bis(4-hydroxy-3-methoxybenzyl)dihydrofuran-2-one] and secoisolariciresinol [2,3-bis(4-hydroxy-3-methoxybenzyl)butane-1,4-diol] in its glucosidic form, secoisolariciresinol diglucoside (SDG), have been recognised as the main precursors of the biologically active mammalian lignans enterolactone [3,4-bis(3-hydroxybenzyl)dihydrofuran-2-one] and, respectively, enterodiol [2,3-bis(3-hydroxybenzyl)butane-1,4-diol] which have gained reputation as cancer-protective agents.[4,5]

An essential intermediate of our synthetic route to matairesinol and secoisolariciresinol[1] is 2,3-bis(4-benzyloxy-3-methoxybenzylidene)-succinic acid, **1** (Scheme 1), obtained by an improved Stobbe condensation,[6] which is a benzyl-protected form of the "Stobbe acid" 2,3-bis(4-hydroxy-3-methoxybenzylidene)-succinic acid, **2**. The solid state structures of two solvates of **1**, a methanol solvate (**1a**) and a butanol solvate (**1b**), have now been determined by X-ray diffraction methods, not only to achieve a definitive assessment of the structure of this compound, but also to obtain detailed structural information, including possible effects on the molecular geometry due to packing in the solid state, for a species belonging to the class of fulgenic acids, strictly related to that of fulgides,[6,7] which owe the name to their intense and varied colours.[6,8] These compounds are now actively investigated for their photochromic properties.[9–12]



Scheme 1

Compound **1** may be viewed as resulting from the α,α′ coupling of two, properly substituted, (*E*)-cinnamic acid molecules (**3**) whose planarity, indicative of extensive electronic

---

[a] *Dipartimento di Scienze Farmaceutiche, Università di Firenze, via U. Schiff 6, I-50019 Sesto Fiorentino Firenze, Italy. E-mail: max@unifi.it*

[b] *Dipartimento di Chimica, Università di Firenze, via della Lastruccia 3, I-50019 Sesto Fiorentino Firenze, Italy. E-mail: massimo.divaira@unifi.it*

† Electronic supplementary information (ESI) available: Geometries and selected data for optimised computational models. See DOI: 10.1039/b515266f

delocalisation, is substantially preserved in the present solid state structures. Such geometrical and associated bonding features are likely at the origin of the interesting optical properties of compounds of this family, mentioned above. Similar structural features have been observed for 2,3-dibenzylidene-succinic acid,[13] **4**, which ideally results from the coupling of two molecules of unsubstituted (*E*)-cinnamic acid. To the best of our knowledge, compound **4** represents the only available example of a structure closely related to the present ones (we exclude from comparison, in this context, highly hindered tetraphenylbutadiene congeners,[14] as well as the anhydrides[13,15] or imides[7] of related dicarboxylic acids, that are considerably constrained, although they share several connectivity features with the parent acids). On the other hand, steric hindrance between phenyl and/or carboxylic groups in species like **1** and **2** would be hardly compatible with retention of planarity of extended parts of the molecules in the course of *free* rotations around the C_α–$C_{\alpha'}$ bond, which have been considered to occur in solution, to rationalise aspects of the NMR spectra.[13] In view of the continued interest in compounds of this family, it seemed worthwhile to evaluate by computational methods the activation energies for conformational rearrangements of the dibenzylidene-succinic acid and related species. A further point of interest consisted in verifying whether the possible formation of a hydrogen bond between the two carboxyls in **1** might play a structure-determining role.

Results and discussion

X-Ray structures

The structure of the methanol solvate **1a** consists of molecules of **1** and of the solvent in a 1 : 1 ratio, one molecule of each type occupying the asymmetric unit of the triclinic unit cell. Two views of the molecule of **1** are shown in Fig. 1 and values of selected geometrical parameters are collected in Table 1. Within each half of the molecule, approximate planarity is observed for the part corresponding to the cinnamic acid backbone. The atoms which deviate most from planarity are the carboxylic oxygens, involved in the formation of hydrogen bonds [O(5) exhibits the largest deviation, 0.471(2) Å, from the least-squares plane through the atoms of the pertaining cinnamic moiety]. The two nominally single C–C bonds adjacent to the olefinic bond in each half of the molecule [namely, bonds C(1)–C(2), C(3)–C(4), C(18)–C(19) and C(20)–C(21), for subsequent reference] are short, with a 1.47(1) Å mean [matching the 1.47(2) Å corresponding mean for **4**], apparently as a result of extensive conjugation. It should be noted that the longest of these four bonds in **1a** [C(18)–C(19), 1.486(2) Å] links the carboxylic group which deviates most from planarity. The 108.7(2)° value of the C(3)–C(2)–C(19)–C(20) dihedral angle (hereafter δ angle of the butadienic strand), measuring the relative tilt of the two main molecular planes, is close to the value reported for **4** [104.2(7)°].[13] This setting about the C_α–$C_{\alpha'}$ [C(2)–C(19)] bond implies loss of possible conjugation through the butadienic moiety but, as already noted,[13] it allows the release of strains between the two halves of the molecule. There is a system of intermolecular hydrogen bonds extending in one direction through the structure of **1a** (Fig. 2). One carboxyl is tightly linked head-on, through an inversion centre, to its counterpart from a second molecule. The other carboxyl of the first molecule interacts with a methanol molecule, both taking part in a four-membered ring of hydrogen bonds through the operation of an inversion centre distinct from the previous one. In this way a third molecule of **1** is involved in the hydrogen bond system: it is related to the second one by the *b* lattice translation so that the chain of these linkages extends along the *b* lattice direction. Within the above four-membered ring of hydrogen-bond interacting species, both the carboxyl and the solvate molecule act as donors as well as acceptors. This system of interactions, more complex than that undergone by the other carboxyl, is apparently at the origin of the large deviation of O(5) from the planar arrangement. The clearly defined orientations of the carboxylic hydrogens in this structure and the significant separation between the oxygen atoms of the two carboxylic groups belonging to the same molecule, due to the large δ angle, rule out the existence of an intramolecular hydrogen bond.

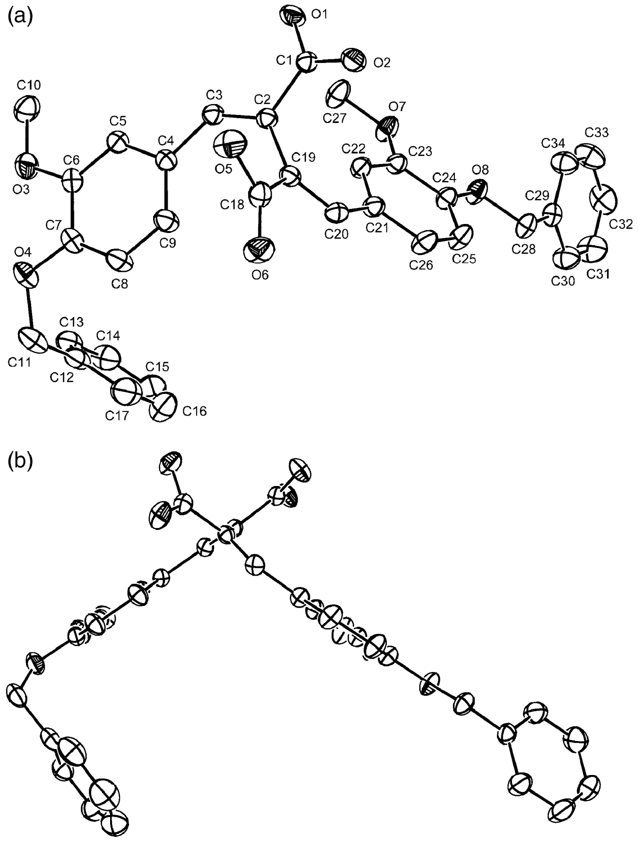


Fig. 1 (a) A view of the molecular structure of **1a**, with 30% probability ellipsoids, showing the atomic labelling. Hydrogen atoms are omitted for clarity. (b) Alternative view, showing the planarity of large parts of the molecule, discussed in the text.

The structure of the butanol solvate **1b** is formed by molecules of **1** and molecules from the solvent in a 1 : 1 ratio, the solvate molecules being arranged in a disordered fashion. Fig. 3 presents two views of the conformation attained by the molecule of **1** in this structure; selected values of geometrical parameters are listed in Table 2. Similarly to that found for the

Table 1 Structural parameters of **1a**: values of selected bond (Å) and hydrogen bond distances (Å), bond angles (°) and dihedral angles (°)

C(1)–O(1)	1.305(2)	C(18)–O(5)	1.326(2)
C(1)–O(2)	1.237(2)	C(18)–O(6)	1.210(2)
C(1)–C(2)	1.474(2)	C(18)–C(19)	1.486(2)
C(2)–C(3)	1.349(2)	C(19)–C(20)	1.345(2)
C(3)–C(4)	1.462(2)	C(20)–C(21)	1.461(2)
O(3)–C(6)	1.365(2)	O(7)–C(23)	1.364(2)
O(3)–C(10)	1.417(2)	O(7)–C(27)	1.428(2)
O(4)–C(7)	1.364(2)	O(8)–C(24)	1.368(2)
O(4)–C(11)	1.449(2)	O(8)–C(28)	1.442(2)
C(11)–C(12)	1.495(3)	C(28)–C(29)	1.493(2)
C(2)–C(19)	1.489(2)		
O(1)–C(1)–O(2)	121.9(1)	O(5)–C(18)–O(6)	122.1(1)
C(1)–C(2)–C(3)	119.3(1)	C(18)–C(19)–C(20)	116.3(1)
C(2)–C(3)–C(4)	130.7(1)	C(19)–C(20)–C(21)	130.3(1)
O(1)–C(1)–C(2)–C(3)	−12.1(2)	O(5)–C(18)–C(19)–C(20)	156.6(1)
C(1)–C(2)–C(3)–C(4)	−177.7(1)	C(18)–C(19)–C(20)–C(21)	−177.5(2)
C(2)–C(3)–C(4)–C(5)	−179.5(1)	C(19)–C(20)–C(21)–C(22)	−12.4(2)
C(1)–C(2)–C(19)–C(18)	102.9(1)	C(3)–C(2)–C(19)–C(20)	108.7(2)
O(1)···O(2)[a]	2.627(1)	O(5)···O(9)[b]	2.654(2)
O(5)···O(9)	2.876(2)		

[a] $2 - x, 1 - y, 2 - z$. [b] $2 - x, 2 - y, 2 - z$.

structure of **1a**, there is substantial planarity of extended parts of the molecule, corresponding to the cinnamic acid residues, whereas the flexible substituents on the benzylidene groups are arranged differently from **1a**. Apart from the latter differences, which may be ascribed to dissimilar packing interactions in the two structures, the main features of the cinnamic-type backbones are similar (excluding values of a few torsion angles) to those of the **1a** solvate, as appears from comparison of values in Tables 1 and 2. The largest deviation from the pertinent least-squares plane, 0.206(4) Å, is again exhibited by an oxygen, O(5), involved in the more complex system of hydrogen bonds (see below). The 1.47(2) Å mean of the four nominally single C–C bonds (already defined for **1a**) in the planar moieties, matches those of **1a** and **4**, again with the longest of such bonds [C(18)–C(19), 1.501(6) Å] being formed by the carboxyl which deviates most sensibly from the planar arrangement. The 97.6(6)° value of the δ angle in **1b** may be considered to be reasonably close to those found for **1a** and **4**, in view of the easy deformation with respect to the coordinate represented by that dihedral angle (see the Conformational study section). The system of hydrogen bonds in **1b** (Fig. 4) is similar to that detected for **1a**, with a close head-on interaction of centrosymmetric carboxyls and a more complex four-membered system involving the second carboxylic group of **1** [to which belongs the above-mentioned atom O(5)] and both fractions of the disordered butanol molecule. The comparable lengths of the two C–O bonds within the second carboxyl

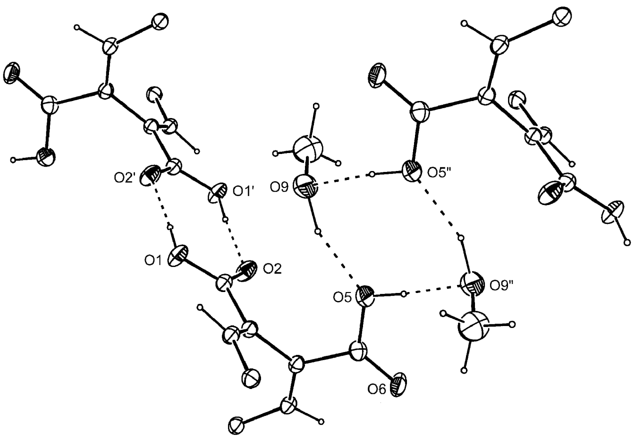


Fig. 2 Essential part of the repeat unit of the hydrogen bond system extending along the crystallographic b axis of **1a**. Only the butadiene dicarboxylic strand (including C_γ carbons) for three molecules of **1** is shown for clarity, in addition to two methanol solvate molecules. Symmetry operations: ′ $2 - x, 1 - y, 2 - z$, ″ $2 - x, 2 - y, 2 - z$.

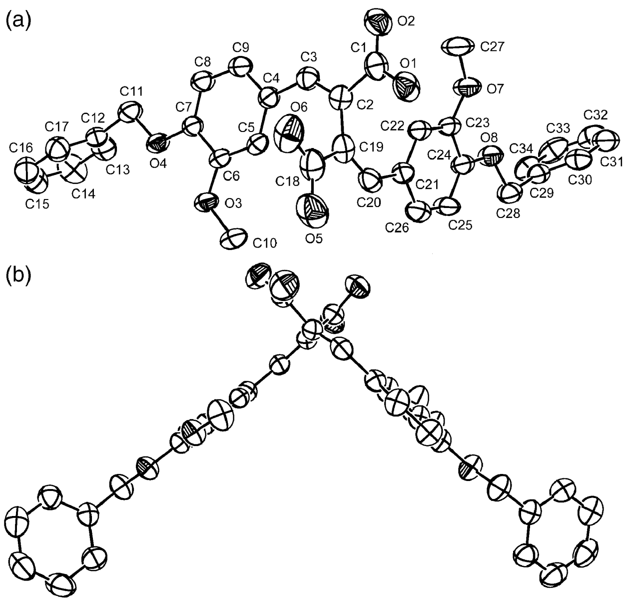


Fig. 3 (a) The molecular structure of **1b**, with 20% probability ellipsoids. The atomic labelling is shown; hydrogen atoms are omitted for clarity. (b) Alternative view, showing the molecular features discussed in the text.

Table 2 Structural parameters of **1b**: values of selected bond (Å) and hydrogen bond distances (Å), bond angles (°) and dihedral angles (°)

C(1)–O(1)	1.286(5)	C(18)–O(5)	1.255(6)
C(1)–O(2)	1.248(5)	C(18)–O(6)	1.274(6)
C(1)–C(2)	1.468(5)	C(18)–C(19)	1.501(6)
C(2)–C(3)	1.325(5)	C(19)–C(20)	1.338(5)
C(3)–C(4)	1.449(5)	C(20)–C(21)	1.473(5)
O(3)–C(6)	1.350(4)	O(7)–C(23)	1.362(4)
O(3)–C(10)	1.431(4)	O(7)–C(27)	1.408(4)
O(4)–C(7)	1.370(4)	O(8)–C(24)	1.361(4)
O(4)–C(11)	1.429(4)	O(8)–C(28)	1.441(4)
C(11)–C(12)	1.491(5)	C(28)–C(29)	1.476(5)
C(2)–C(19)	1.470(5)		
O(1)–C(1)–O(2)	123.3(4)	O(5)–C(18)–O(6)	124.6(6)
C(1)–C(2)–C(3)	118.7(5)	C(18)–C(19)–C(20)	117.8(5)
C(2)–C(3)–C(4)	132.9(4)	C(19)–C(20)–C(21)	130.3(4)
O(1)–C(1)–C(2)–C(3)	173.7(4)	O(5)–C(18)–C(19)–C(20)	−3.5(8)
C(1)–C(2)–C(3)–C(4)	−176.0(4)	C(18)–C(19)–C(20)–C(21)	−176.8(5)
C(2)–C(3)–C(4)–C(5)	−3.6(7)	C(19)–C(20)–C(21)–C(22)	14.6(8)
C(1)–C(2)–C(19)–C(18)	92.0(6)	C(3)–C(2)–C(19)–C(20)	97.6(6)
O(1)···O(2)[a]	2.558(5)	O(5)···O(9A)	2.771(6)
O(6)···O(9A)[b]	2.785(8)	O(6)···O(9A)	2.930(7)
O(5)···O(9B)	3.081(5)		

[a] 1 − *x*, −*y*, −*z*. [b] −*x*, −*y*, −*z*.

(considered to result from averaging, as an effect of disordered carboxyl orientation) and a set of contact distances formed by both of its oxygen sites with the two fractions of the butanol molecule (Table 2) suggest that both carboxyl oxygens participate, in a mutually exclusive way, to the hydrogen bond system. In the structure of **1b** the chain of hydrogen bonded molecules extends along the *a* crystallographic direction.

Conformational study

Quantum mechanical calculations have been performed on three types of model systems which, in the order of increasing complexity, correspond to the species **5**, **4** and **6** shown in Scheme 1; for convenience, these models will be referred to by the letters A, B and C, in the above order. Model A was essentially considered in order to investigate the conformational preferences of the butadiene dicarboxylic fragment with respect to rotations around the C_α–$C_{\alpha'}$ bond and to the arrangement of the carboxylic hydrogens. Model B has the connectivity of an experimentally determined structure[13] and C mimics the present compound **1**, with the simplifying substitution of an OMe group for the OPh one. Here are reported the essential results; most representations of geometries and the energy values in atomic units are given within the ESI.†

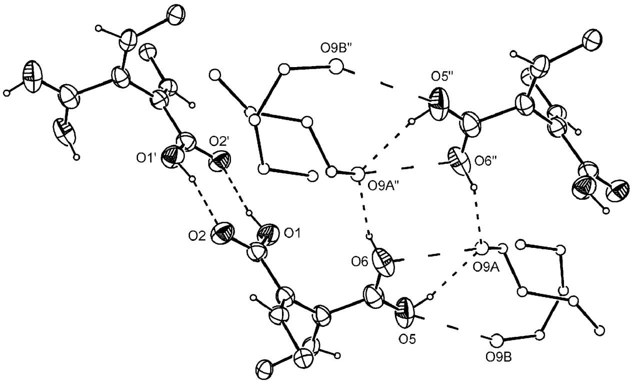


Fig. 4 Essential part, selected with the criteria of Fig. 2, of the repeat unit of the hydrogen bond system extending along the crystallographic *a* axis of **1b**. The non-hydrogen atoms of the two fractions of the disordered butanol molecule are represented by spheres of arbitrary radii, for clarity, and the uninformative (geometrically generated) butanol hydrogen positions are not shown. Symmetry operations: ′ 1 − *x*, −*y*, −*z*, ″ −*x*, −*y*, −*z*.

Calculations performed on model A have shown that, to a good approximation, planarity is attained within each half of the model molecule, formed by a carboxylic group and by the atoms of the adjacent ethylenic moiety. This sets some restraints on the overall flexibility, implying that different assignments of the positions of the carboxylic hydrogens produce small differences in the energy and overall shape. Of the three possible hydrogen arrangements, one had H atoms on O2 and O3, the two oxygens closest to each other (conformation A1: its optimised geometry is shown in Fig. 5 and in the ESI†), one had hydrogens on O2 and O4 (A2, this and following geometries are shown only in the ESI† unless differently stated), whereas according to the third arrangement (A3) the most distant oxygens, O1 and O4, were protonated. The energy difference between the least stable arrangement (A3) and the most stable one (A1) is, however, only 0.43 kcal mol^{-1}. The values attained by the δ angle, in the range 50.0° (A3) to 55.0° (A1), apparently determined by a balance between electrostatic interactions and steric repulsions, are smaller than those found for **1a**, **1b** and **4**. This may be ascribed to the existence of larger intramolecular repulsions between the bulky substituents in the experimental systems than between the two halves of model A. In none of the A1–A3 geometries is a hydrogen bond between the carboxylic groups established. A relative minimum energy geometry (A4), possessing the same connectivity as A2, but having hydrogen-bonded carboxyls and a 55.5° δ angle, lies 1.70 kcal mol^{-1} above A2 (1.89 kcal mol^{-1}

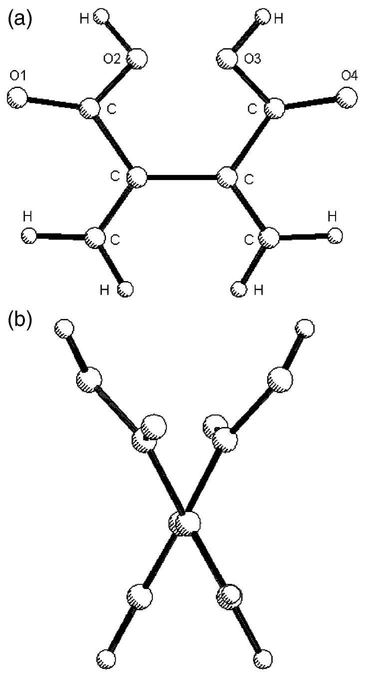


Fig. 5 Two views of the optimised geometry of the A model, with the A1 setting of the carboxylic hydrogens.

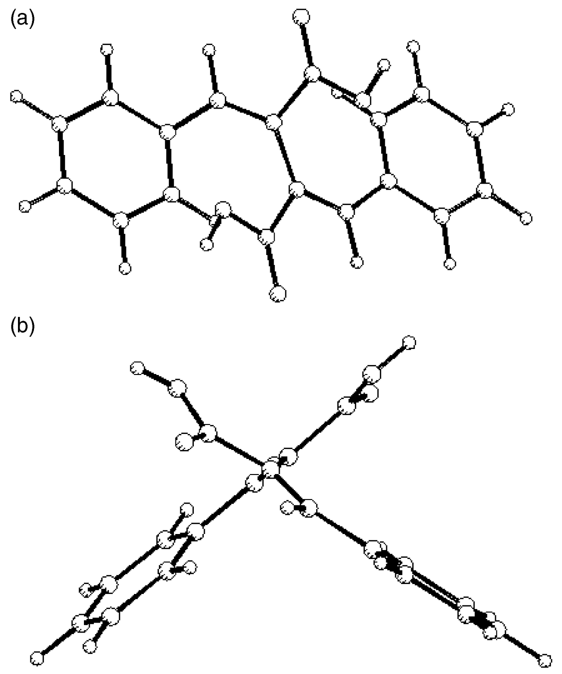


Fig. 6 Two views of the lowest minimum-energy geometry for model B (denoted B1 in the text).

above A1). Such a small destabilisation, which occurs in spite of the onset of a hydrogen-bond interaction absent in A2, should be ascribed to a moderate loss of planarity in the two halves of the model molecule, forced by the formation of the hydrogen bond in A4. It therefore appears that an intermolecular system of hydrogen bonds, when it can be established, as in the structures of **1a** and **1b**, is favoured over a possible intramolecular interaction. Extensive rotations may easily occur around the C_{α}–$C_{\alpha'}$ bond of model A: a minimum energy geometry with δ 136.2° (A5, lying 2.25 kcal mol^{-1} above A1) is reached through a transition state (A6, with δ 111.1°) lying only 2.36 kcal mol^{-1} above A1. On the other hand, *complete* rotation around the C_{α}–$C_{\alpha'}$ bond would imply at least partial loss of planarity for one or both sides of the model molecule, due to hindrance between the carboxylic groups. The rotation of one of these groups about its C–C_{α} bond occurs through a transition state geometry lying 7.45 kcal mol^{-1} (A7, δ 59.9°) or 8.00 kcal mol^{-1} (A8, δ 59.8°) above A1; the existence of more than one saddle point (along distinct paths) is due to the existence of alternative mutual arrangements of the (hydrogens of the) carboxyls.

Passing to the models with larger substituents on the skeleton of the succinic acid, higher values of the δ angle are found, close to those of the experimental systems, in line with the assumption that intramolecular repulsions play a major role in this respect. Values of 109.8° and 113.3° have been found for two optimised B conformations, respectively B1 (Fig. 6), having carboxylic H atoms allocations as in A1, and B2, with hydrogens as in A2. The energy separation between them (1.08 kcal mol^{-1}, with B2 at higher energy than B1) is significantly larger than that (0.19 kcal mol^{-1}) calculated for the above two A conformations. The δ value calculated for a C model with carboxyls arranged as in A1 (model C1) is 113.6°. In the conformations corresponding to such δ angles the separation between the carboxyls is large and no intramolecular hydrogen bond interaction may be established. A relative minimum geometry with hydrogen-bonded carboxyls (C2, δ = 84.1°) lies 1.57 kcal mol^{-1} above C1. The mean values of the bond lengths of the "nominally single" C–C_{α} and C_{β}–C_{γ} bonds are 1.479 Å for B1 and B2 and 1.473 Å for C1, quite close to the experimental means for **1a** and **1b**. Energy barriers to rotational motion around these bonds have been calculated in order to probe, on the one hand, the tendency to preserve the planarity of the cinnamic acid backbone and to investigate, on the other hand, the nature of possible rearrangements that may produce the equilibration in solution for compounds of this type, implied by NMR spectral features.[13,14] A barrier of 4.21 kcal mol^{-1} has been calculated for the rotation of a phenyl group around the C_{β}–C_{γ} bond of the B model, in correspondence with the transition state geometry B3. The height of the analogous barrier for C is 5.97 kcal mol^{-1} (C3). Apparently due to loss of electron delocalisation in the half part of the model affected by such rotation, the involved C_{β}–C_{γ} bond slightly lengthens in the transition state conformation, from 1.462 Å (B1) or 1.456 Å (C1) to 1.486 Å, for both B3 and C3. The rotation of a carboxyl around its C–C_{α} bond for model B involves a 7.45 kcal mol^{-1} barrier (B4), of identical height to that pertaining to the A7 saddle point of the simpler A model.

In order to detect possible limitations to relative rotations of the two halves of a B or C model molecule around the central C_{α}–$C_{\alpha'}$ bond, restrained optimisations were performed in steps, at fixed values of the δ angle. It was verified that a rotation of the order of 60° about C_{α}–$C_{\alpha'}$, from the global minimum geometry toward conformations with a δ angle of 50°, involves small energy increases, of 2.2 and 3.4 kcal mol^{-1}

for models B (B5) and C (C4), respectively. Energy increases of comparable amounts were experienced along the opposite path, in correspondence with *ca.* 40° δ increases from the values of the global minimum geometries. These two paths of δ angle variation will be referred to as $-\delta$ and $+\delta$ paths, respectively. It should be noted that in the proximity of $\delta = 50°$ the arrangement of the butadienic chain and of the phenyl groups is similar to that of the corresponding part of the crowded 2,3-bis(diphenylmethylene)butanedioic acid molecule.[14] This seems to represent a limiting condition for the approach of the two parts of the molecule. Forcing further rotation along the $-\delta$ path produces very high energy increases [a 30.9 kcal mol^{-1} energy barrier is encountered for the B model, from B1, and a 34.0 kcal mol^{-1} barrier for the C model, from C1, B6 and C5 being the transition state geometries] due to close contacts between the phenyl groups as well as between the carboxyls. In the saddle point region of each model, around $\delta = -40°$, a major rearrangement takes place, with rotations of both phenyls and carboxyls, yielding at $\delta = -50°$ a geometry approximately mirror-related to that existing at $\delta = 50°$; the mismatch from complete mirror symmetry is due to a change in the arrangement of carboxyls that switches from A1 to A3 type on crossing the barrier. On the other side, large rotations along the $+\delta$ path lead, at *ca.* $\delta = 200°$ (or $-160°$), to a 20 kcal mol^{-1} barrier for B (B7) and a 24 kcal mol^{-1} barrier for C (C6), caused in each case by carboxyl–phenyl hindrance. Crossing this saddle point, again, implies rotations of the two groups.

Finally, a study of the UV-Vis spectra of these compounds was not attempted, but the dependence of the HOMO–LUMO separation on the nature of substituent groups should be noted. The energy gap was found to be 131 kcal mol^{-1} for model A in the A1 conformation, 99 kcal mol^{-1} for B1, 88 kcal mol^{-1} for a model with R = OH and R′ = OMe (Stobbe acid, **2** in Scheme 1) and 87 kcal mol^{-1} for C1, revealing the importance of the presence of substituents on the phenyl ring. In the transition states B3 and B4 the energy gap was respectively, 105 and 100 kcal mol^{-1} (to be compared with the 99 kcal mol^{-1} gap of B1), showing that the loss of planarity due to phenyl rotation is more effective, in counteracting the substituent bathochromic effect, than the rotation of the carboxyl.

In conclusion, both the structural and the conformational studies have shown that planarity of the two cinnamic acid backbones, essential for the existence of the extensive electronic conjugation probably at the origin of the substituent-dependent optical properties of fulgides, is favoured. Departure from planarity produced by rotations of the substituents on the butadienic frame implies the crossing of substantial energy barriers. On the other hand, rotations of the two cinnamic moieties around the connecting C_α–$C_{\alpha'}$ bond are less restrained; it is therefore rather surprising that the values of the δ hinge angle about such a bond, from the structures of three non-isomorphous compounds, are grouped within a relatively narrow range and are also close to the values calculated for gas-phase model systems of similar complexity. However, *free* rotations around the C_α–$C_{\alpha'}$ bond, prevented by large energy barriers, should not be invoked to rationalise the equilibration on the NMR time scale of molecules belonging to the family of **1**. Rather, this is likely to occur through the combination of ample, although partly hindered, rotations around the C_α–$C_{\alpha'}$ bond, accompanied by rotations of the phenyl and/or carboxylic groups around the C_β–C_γ and, respectively, C–C_α bonds. Finally, the formation of an intramolecular hydrogen bond between the two carboxylic groups has not been found to yield significant stabilisation, apparently because the involved energy gain is overridden by the cost of small deviations from planarity. The formation of intermolecular hydrogen bonds is therefore favoured.

Experimental

Materials

The Stobbe acid, 2,3-bis(4-hydroxy-3-methoxybenzylidene)-succinic acid, was prepared according to the procedure previously reported.[1] Crystals of **1a**, suitable for the X-ray investigation, were obtained by slow recrystallisation from a 1 : 1 water–methanol solution and those of **1b** from a *ca.* 0.3 : 0.7 ethyl acetate–butanol solution.

X-Ray crystallography

X-Ray diffraction data were collected at room temperature, for both **1a** and **1b**, with an Oxford Diffraction Xcalibur PX Ultra CCD diffractometer, using Cu-Kα radiation ($\lambda = 1.5418$ Å). The pale yellow crystals employed had dimensions 0.26 × 0.38 × 0.42 mm (**1a**) and 0.18 × 0.35 × 0.60 mm (**1b**). Cell constants were obtained by least-squares refinements of the setting angles of 8905 reflections in the range $6 < \theta < 55°$ for **1a** and of 2297 reflections in the range $6 < \theta < 44°$ for **1b**. Details on data collection and structure refinement procedures are summarised in Table 3. Corrections for absorption were applied with SADABS.[16] The structures were solved by direct methods with SIR[17] and were extended and refined on F^2 with SHELXL-97.[18] The butanol molecule in **1b** was considered to be distributed between two orientations, which were assigned complementary population parameters, geometrical restraints being applied to the two fractions. In the final refinement

Table 3 Crystal data, data collection and structure refinement parameters for compounds **1a** and **1b**

	1a	**1b**
Formula	$C_{35}H_{34}O_9$	$C_{38}H_{40}O_9$
Formula weight	598.62	640.70
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
a/Å	10.6859(4)	10.929(1)
b/Å	10.7325(4)	11.708(1)
c/Å	14.5858(5)	15.385(2)
α/°	73.297(3)	101.68(1)
β/°	74.559(3)	106.69(1)
γ/°	77.321(3)	96.91(1)
U/Å^3	1525.7(1)	1812.9(3)
Z	2	2
μ(Cu-Kα/mm^{-1})	0.774	0.682
Reflections collected	16 190	14 403
Independent reflections (R_{int})	4927 (0.0264)	4790 (0.0352)
No. of parameters	500	477
R_1; wR_2 [$I > 2\sigma(I)$]	0.0369; 0.0954	0.0577; 0.1575
R_1; wR_2 (all data)	0.0455; 0.0991	0.1054; 0.1774
GOF	0.958	0.802

cycles all non-hydrogen atoms, including those in disordered positions for **1b**, were assigned anisotropic temperature factors. The positional parameters of the hydrogen atoms of **1a** were refined, whereas the H atoms of **1b** were in calculated positions, riding on the respective carrier atoms, the restraints $U_H = 1.2U_C^{eq}$ ($U_H = 1.5U_C^{eq}$ for methyl and carboxyl hydrogens) being applied for both models. The carboxyl hydrogen positions could be assigned unambiguously for **1a**, from ΔF maps and based on consideration of the C–O bond lengths and the network of hydrogen bonds. The net of possible hydrogen bonds formed with the two fractions of the solvate molecule by both oxygen sites of a **1b** carboxyl and the comparable values of its C–O bond distances suggested that such a carboxyl group might be affected by twofold orientational disorder, yielding complementary hydroxylic character for the oxygen sites: these were assigned equal fractions of the carboxylic hydrogen since the limited quality of data did not allow the refinement of the hydrogen occupancies. Peaks in the final difference syntheses, with heights ≤ 0.20 e Å^{-3} (**1a**) and ≤ 0.24 e Å^{-3} (**1b**), were devoid of chemical meaning. Computer programs used included PARST[19] for geometry calculations, and ORTEP[20] for graphics.

CCDC reference numbers 287354 (**1b**) and 287355 (**1b**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b515266f

Computational details

Calculations were performed using the GAUSSIAN98[21] suite of programs, at the B3LYP/6-31G(d,p) level.[22,23] Transition states were searched and identified by application of the synchronous transit-guided quasi-Newton procedure.[24] The nature of stationary points as true minima or first order saddle points, the latter characterised by one imaginary frequency, was checked by frequency calculations and unscaled ZPE corrections were applied to the energy values; the latter procedures were not applied to optimisations performed in the course of restrained energy surface scans, at fixed values of the δ dihedral angle. For graphics MOLDEN[25] and CACAO[26] were employed.

References

1 M. Bambagiotti-Alberti, S. A. Coran, F. F. Vincieri, N. Mulinacci and G. M. L. Pieraccini, *Heterocycles*, 1988, **27**, 2185–2196.
2 S. A. Coran, M. Bambagiotti-Alberti, F. Melani, V. Giannellini, F. F. Vincieri, N. Mulinacci, R. Sala and E. Moriggi, *Eur. J. Med. Chem.*, 1991, **26**, 643–650.
3 G. P. Moss, *Pure Appl. Chem.*, 2000, **72**, 1493–1523.
4 L. Q. Wang, *J. Chromatogr., B: Anal. Technol. Biomed. Life Sci.*, 2002, **777**, 289–309.
5 B. Raffaelli, A. Hoikkala, E. Leppala and K. Wahala, *J. Chromatogr., B: Anal. Technol. Biomed. Life Sci.*, 2002, **777**, 29–43.
6 H. Stobbe, *Justus Liebigs Ann. Chem.*, 1911, **380**, 1–129.
7 M. D. Cohen, H. W. Kaufman, D. Sinnreich and G. M. J. Schmidt, *J. Chem. Soc. B*, 1970, 1035–1039.
8 V. Ramamurthy and K. Venkatesan, *Chem. Rev.*, 1987, **87**, 433–481.
9 V. A. Kumar and K. Venkatesan, *Acta Crystallogr., Sect. B: Struct. Sci.*, 1993, **B49**, 896–900.
10 Y. Yokoyama, *Chem. Rev.*, 2000, **100**, 1717–1739.
11 Y. Yokoyama, in *Molecular Switches*, ed. B. L. Feringa, Wiley-VCH, Darmstad, ch. 4, 2001.
12 H. Port, P. Gärtner, M. Hennrich, I. Ramsteiner and T. Schöck, *Mol. Cryst. Liq. Cryst.*, 2005, **430**, 15–21.
13 P. A. Davidse, J. L. M. Dillen, A. M. Heyns, T. A. Modro and P. H. van Rooyen, *Can. J. Chem.*, 1990, **68**, 741–746.
14 F. Toda, K. Tanaka, Z. Stein and I. Goldberg, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun*, 1996, **C52**, 118–122.
15 F. Toda, K. Tanaka, Z. Stein and I. Goldberg, *Acta Crystallogr., Sect. B: Struct. Sci.*, 1995, **B51**, 856–863.
16 G. M. Sheldrick, *SADABS, Program for area detector adsorption correction*, Institute for Inorganic Chemistry, University of Göttingen, Germany, 1996.
17 A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. Moliterni, G. Polidori and R. Spagna, *J. Appl. Crystallogr.*, 1999, **32**, 115.
18 G. M. Sheldrick, *SHELXL-97, Program for refinement of crystal structures*, University of Göttingen, Germany, 1997.
19 M. Nardelli, PARST, *J. Appl. Crystallogr.*, 1995, **28**, 659.
20 L. J. Farrugia, *J. Appl. Crystallogr.*, 1999, **32**, 837.
21 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle and J. A. Pople, *GAUSSIAN 98 (Revision A.7)*, Gaussian, Inc., Pittsburgh, PA, 1998.
22 (*a*) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 1372; (*b*) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648; (*c*) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1988, **B37**, 785.
23 J. S. Binkley, J. A. Pople and W. J. Hehre, *J. Am. Chem. Soc.*, 1980, **102**, 939.
24 C. Peng, P. Y. Ayala, H. B. Schlegel and M. J. Frisch, *J. Comput. Chem.*, 1996, **17**, 49.
25 G. Schaftenaar and J. H. Noordik, MOLDEN: a pre- and post-processing program for molecular and electronic structures, *J. Comput. Aided Mol. Des.*, 2000, **14**, 123.
26 (*a*) C. Mealli and D. M. Proserpio, *J. Chem. Educ.*, 1990, **67**, 399; (*b*) C. Mealli, A. Ienco and D. M. Proserpio, *Abstracts XXXIII ICCC*, Florence, Italy, 1998, p. 510.