A Study on the Photochemical Dimerization of Coumarins in the Solid State

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Solid-state photochemical behavior of 28 substituted coumarins has been investigated. Of these twelve underwent photodimerization and this is remarkable in light of the inertness of coumarin itself in the solid state. X-ray crystallographic investigation of eight coumarins was undertaken with the view of understanding the role of packing in the crystal on their solid-state reactivity. Important findings include the identification of acetoxy and chloro substituents as useful "crystal engineering" groups and the results pertaining to subtler aspects of topochemical postulates. X-ray crystal structure analyses of 7-chlorocoumarin and 7-methoxycoumarin reveal packing modes which are not commonly met. The former is arranged in a β-type packing, the center–center distance between the reactive double bonds being 4.454 Å, which lies beyond the so far accepted limit of 3.5–4.2 Å. The reactive double bonds of 7-methoxycoumarin, on the other hand, are rotated by 65° with respect to each other with the center–center distance between the double bonds being 3.83 Å. Inspite of these unfavorable arrangements photodimerization of the above two coumarins in the solid state occurs through a topochemical process with large dimer yields. A careful analysis of the X-ray crystallographic results obtained from our investigations reveals that the two double bonds in the reactive crystals may be displaced with respect to each other both along the molecular plane as well as along the double bond axis. Thus the normally accepted dictums that in the photoreactive crystals the doube bonds should be within a distance of 4.2 Å and that they be parallel are no longer operational.

The reactions of cinnamic acids in the crystalline state are well-known examples of (2 + 2) photodimerization and the studies by Schmidt and his co-workers have demonstrated that such reactions are strictly controlled by the packing arrangement of the molecule in the crystal.[1] A correlation between molecular alignment in the reactant crystal and steric configuration of the product has been established. Schmidt has drawn attention to the fact that not only must the double bonds of the reacting monomers of cinnamic acid be within ~4.2 Å they must also be aligned parallel for cycloaddition to occur. Recently there has been growing interest in organic reactions in the crystalline state and many such reactions have been studied from the synthetic and mechanistic points of view.[2] The utility of such photoreactions as a synthetic tool is limited by the difficulty of achieving the desired type of crystal structure in any given case, for the factors that control the crystal packing are not fully understood. Scope undoubtedly exists for "engineering" organic crystals. The approaches to "crystal engineering", i.e., controlling packing geometry, have included introduction of a dichlorophenyl group into unsaturated systems, cocrystallization of mercuric chloride–organic mixtures, and the strategy involving the strong tendency for oxygen or carbonyl group of esters to pack over the center of the benzene ring of a neighboring molecule.[3]

In order to examine factors which affect the molecular packing and to identify the chemical groups which may be of value in bringing about the photoreactivity we have embarked on a detailed systematic crystallographic and photochemical study of a large number of substituted coumarins.[4] Coumarin is known to be photostable in the solid state although it readily dimerizes in solution.[5] Therefore, this appeared to be a good molecular framework to study the role of substituents in bringing about the preferred molecular packing for photodimerization. Substituents such as hydroxyl, methyl, chloro, acetoxy, and methoxy were utilized to engineer the crystals of coumarins toward photoreactivity. Also we have investigated the effects of the interchange of chloro and methyl substituents on the crystal packing. A study of a large number of substituted coumarins provided an opportunity to reexamine the subtler aspects of the topochemical postulates. Results obtained from our studies on coumarins are presented below.

Results

Table I shows the 28 coumarins investigated in the solid state for their photobehavior. Of these, 12 underwent photodimerization. Corresponding dimers are the only products isolated in these cases. While mass spectra confirmed the products to be the dimer, ^{1}H NMR was helpful in assigning the configuration. Spectral data of dimers are provided in Table IV. The structure of the dimer of 7-methoxycoumarin was confirmed by X-ray crystal structure analysis. The method of irradiation consisted of crushing the crystals between glass plates and irradiating them with a 450-W medium-pressure mercury arc lamp as the external light source. The temperature of the sample was maintained at 0 °C, if needed, by a cooling bath. Dimerization was followed by micro TLC and ^{1}H NMR. Plots of time of irradiation vs. the yield of the dimer as measured by ^{1}H NMR are shown in Figure 1. In all cases the dimer yield reached a plateau and the yields represented in Table I correspond to this number. Further irradiation did not bring about any change. Powder diffraction experiments carried out with 7-methoxy-, 7-acetoxy-, 6-chloro-, and 4-methyl-6-chlorocoumarins indicated that the reaction proceeded from one crystalline phase to another crystalline phase and in no case did the reactants become amorphous.

(1) Cohen, M. D.; Schmidt, G. M. J. *J. Chem. Soc.* **1964**, 1996, 2000, 2014.
(2) Scheffer, J. R. *Acc. Chem. Res.* **1980**, *13*, 283. Thomas, J. M.; Morsi, S. E.; Desvergne, J. P. *Adv. Phys. Org. Chem.* **1977**, *15*, 63.
(3) Schmidt, G. M. J. *Pure Appl. Chem.* **1971**, *27*, 647. Nakanishi, H.; Hasegawa, M.; Sasade, Y. *J. Polym. Sci.* **1977**, *15*, 173.
(4) Ramasubbu, N.; Guru Row, T. N.; Venkatesan, K.; Ramamurthy, V.; Rao, C. N. R. *J. Chem. Soc., Chem. Commun.* **1982**, 178. Ramasubbu, N.; Gnanaguru, K.; Venkatesan, K.; Ramamurthy, V.; Can. *J. Chem.* **1982**, *60*, 2159.
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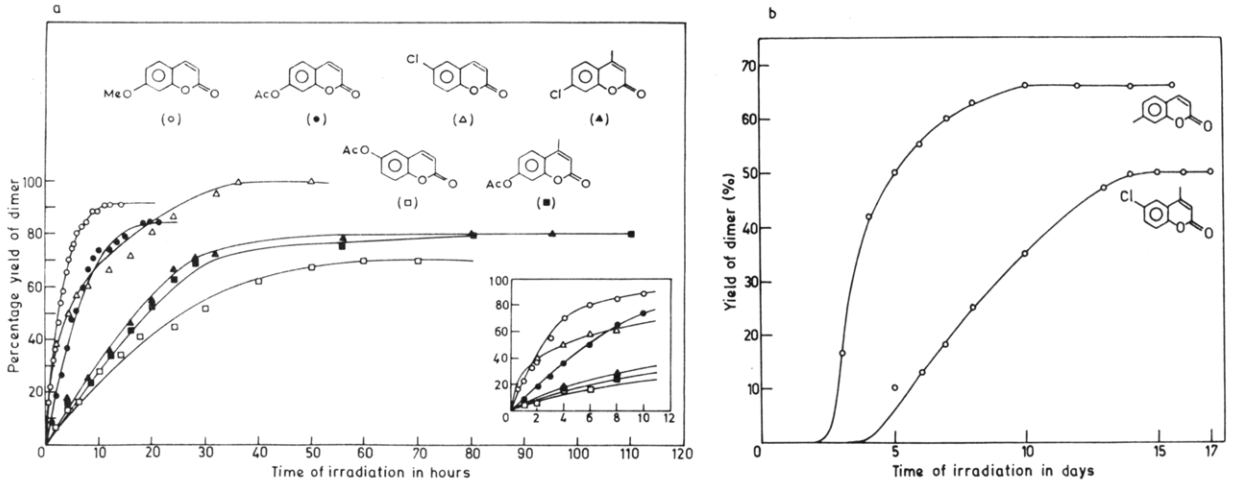

Figure 1. Duration of irradiation vs. yield of the dimer plots. (a) Topochemical dimerization. (b) Nontopochemical dimerization.

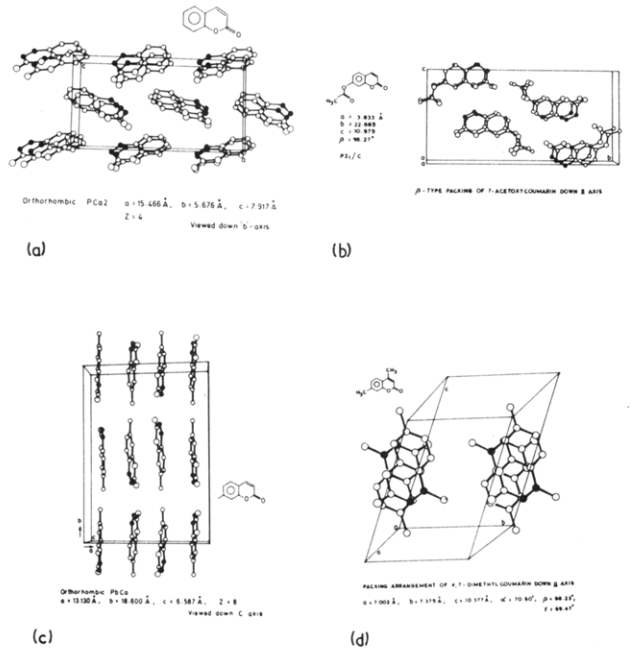

Figure 2. Packing arrangement of (a) coumarin, (b) 7-acetoxycoumarin, (c) 7-methylcoumarin, and (d) 4,7-dimethylcoumarin. Darkened circle corresponds to reactive double bond.

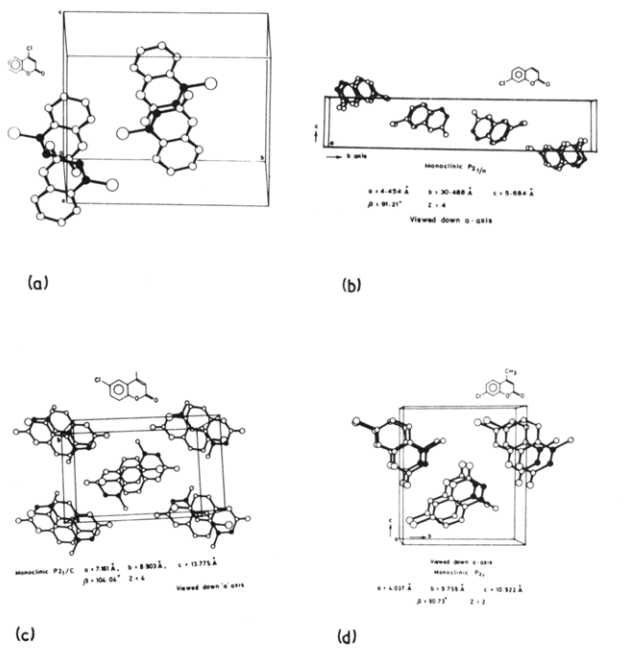

Figure 3. Packing Arrangement of (a) 4-chlorocoumarin, (b) 7-chlorocoumarin, (c) 4-methyl-6-chlorocoumarin, and (d) 4-methyl-7-chlorocoumarin. Darkened circle corresponds to reactive double bond.

In order to correlate the solid-state reactivity of coumarins with their three dimensional arrangement in the crystal lattice, X-ray crystal structure investigation of a few coumarins, wherever suitable crystals could be grown, was taken up. Crystal data are provided in Table II. Attempts to carry out detailed structure analysis of all the compounds were not successful. For example, suitable single crystals of 6-acetoxy- and 4-methyl-7-acetoxycoumarins could not be obtained. Only the cell parameters could be measured for 6-methoxy- and 6-chlorocoumarins. A crystallographic study of all the nonreactive coumarins was not considered essential and therefore only a selected few were investigated. Packing arrangements essential for the interpretation of solid-state reactivity are illustrated in Figures 2–4. Indeed the nonreactive coumarins possess packing arrangements not suitable for dimerization. Geometrical parameters relevant for representing the reactive double bonds are shown in Figure 5 and the data are provided in Table III. X-ray crystal structure analysis of 7-methoxycoumarin showed that the potentially reactive double bonds of the monomer molecules within the asymmetric unit are rotated by 65° with respect to each other. In order to interpret the topochemical dimerization of 7-methoxycoumarin, lattice energy calculations for the monomer crystal were carried out. The results are briefly discussed in the discussion (part c) and the details are published elsewhere.[6]

Discussion

(a) Structure of Dimers. Four different cis-fused dimers may theoretically be formed: syn head–head, anti head–head, syn head–tail, and anti head–tail. Spectral data of dimers are provided in Table IV. In general the mass spectra of the dimers showed a very strong peak corresponding to the monomer ion and in most cases a small peak due to the dimer (molecular ion) is also located. Configurational assignment of the dimers are made based on their ^{1}H NMR spectral data. Cyclobutyl protons showed a distinct pattern for each of the four isomers.[7] In

(6) Bhadbhade, M. M.; Murthy, G. S.; Venkatesan, K.; Ramamurthy, V.; *Chem. Phys. Lett.* **1984**, *109*, 259.

Table I. Photodimerization of Coumarins in the Solid State

no.	coumarins	duration of irradiation, h[a]	dimerization in the solid state and yield, %	nature of dimer[b]
1	coumarin	200	no	
2	4-hydroxy-coumarin	200	no	
3	6-hydroxy-coumarin	200	no	
4	7-hydroxy-coumarin	200	no	
5	4-methyl-6-hydroxy-coumarin	200	no	
6	4-methyl-7-hydroxy-coumarin	200	no	
7	4-methoxy-coumarin	200	no	
8	6-methoxy-coumarin	120	yes, 60	syn H–H
9	7-methoxy-coumarin	15	yes, 90	syn H–T
10	8-methoxy-coumarin	140	yes, 50	anti H–T
11	4-methyl-6-methoxycoumarin	200	no	
12	4-methyl-7-methoxycoumarin	200	no	
13	5,7-dimethoxy-coumarin	200	no	
14	4-acetoxy-coumarin	200	no	
15	6-acetoxy-coumarin	60	yes, 70	syn H–H
16	7-acetoxy-coumarin	15	yes, 90	syn H–H
17	4-methyl-6-acetoxycoumarin	200	no	
18	4-methyl-7-acetoxycoumarin	80	yes, 80	syn H–H
19	4-chlorocoumarin	200	yes, 25	anti H–H and syn H–T
20	6-chlorocoumarin	24	yes, 100	syn H–H
21	7-chlorocoumarin	40	yes, 70	syn H–H
22	4-methyl-6-chlorocoumarin	140	yes, 50	syn H–H
23	4-methyl-7-chlorocoumarin	80	yes, 80	syn H–H
24	4-methyl-coumarin	200	no	
25	6-methyl-coumarin	200	no	
26	7-methyl-coumarin	120	yes, 65	syn H–H
27	4,6-dimethyl-coumarin	200	no	
28	4,7-dimethyl-coumarin	200	no	

[a] All irradiations were conducted with a 450-W medium-presure mercury lamp. [b] H–H: head to head dimer. H–T: head to tail dimer.

general, this pattern itself is quite valuable in assigning the dimer configuration. Based on the analysis of a large number of dimers of coumarins[8] we find that the cyclobutyl protons of syn dimers resonate around δ 4.0–4.2

(7) Cyclobutyl protons of syn head–head dimer appears as two multiplets (2 H each) centered around δ 4.1 and 4.3; anti head–head dimer comes as a multiplet (4 H) centered around δ 4.3 and anti head–tail appears as a clean two sets of doublet of doublets around δ 3.5 and 4.1.

(8) (a) Muthuramu, K.; Ramamurthy, V. *Ind. J. Chem.* 1984, *23B*, 502. (b) Ramnath, N.; Ramamurthy, V. *J. Org. Chem.* **1984**, *49*, 2827. (c) Henders, L. H.; Schoutden, E.; de Schryver, F. C. *J. Org. Chem.* **1973**, *38*, 957. (d) Muthuramu, K.; Ramnath, N.; Ramamurthy, V. *J. Org. Chem.* **1983**, *48*, 1872.

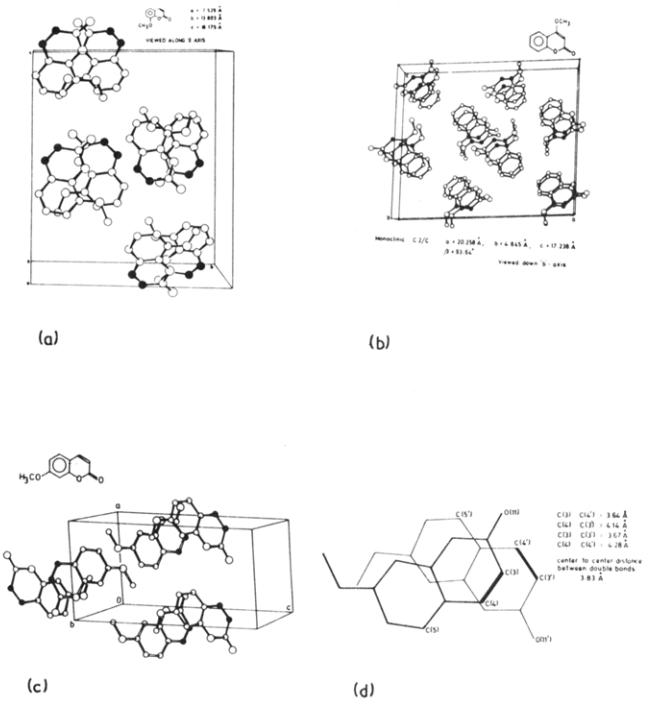

Figure 4. Packing Arrangement of (a) 8-methoxycoumarin, (b) 4-methoxycoumarin, (c) 7-methoxycoumarin, and (d) disposition of the reactive double bonds C(3)–C(4) and C(3′)–C(4′) of 7-methoxycoumarin. Darkened circles corresponds to reactive double bond.

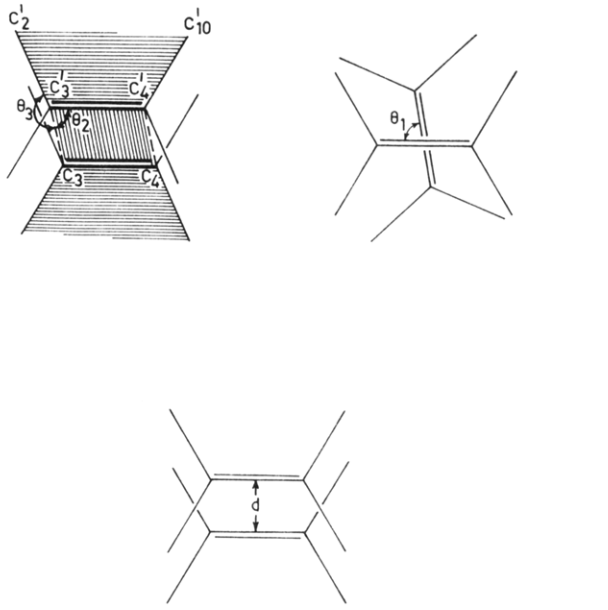

Figure 5. Geometrical parameters used in the relative representation of reactive double bonds.

whereas those of anti isomers resonate below 3.90. This shielding is caused by the diamagnetic anisotropic effects of a carbonyl or phenyl nucleus in the anti configuration. Cyclobutyl protons of the dimers of 6-chloro-, 7-chloro-, 7-methyl-, 6-methoxy-, 6-acetoxy-, and 7-acetoxycoumarins exhibited patterns identical with the syn head–head dimer of coumarin. Further, they all possess two sets of protons (2 H) corresponding to four protons above δ 4.00 and are centered at δ ~4.10 and 4.20. Therefore, these dimers are assumed to have syn configuration. The dimer derived from 7-methoxycoumarin is confirmed by X-ray crystallographic studies to have syn head–tail configuration. In this isomer, the aromatic protons H_5, H_6, and H_8 appear as an AMX system. In comparison with the same protons

Table II. X-ray Crystallographic Structural Data for Coumarins

no.	compound	space group; no. of molecules/ unit cell	unit cell parameters, Å; deg	suitable orientation for topochemical dimerization and expected dimer
1	4-chlorocoumarin	monoclinic $P2_{1/n}$; $Z = 4$	$a = 7.271$, $b = 12.816$, $c = 9.078$; $\beta = 111.82$	no
2	7-chlorocoumarin	monoclinic $P2_{1/n}$; $Z = 4$	$a = 4.454$, $b = 30.488$, $c = 5.684$; $\beta = 91.21$	yes, syn HH (pair I) anti HT (pair II)
3	6-chlorocoumarin	monoclinic $P2_{1/c}$; $Z = 4$	$a = 4.039$, $b = 5.848$, $c = 32.471$; $\beta = 92.64$	yes, syn HH
4	4-methyl-7-chlorocoumarin	monoclinic $P2_1$; $Z = 2$	$a = 4.083$, $b = 9.728$, $c = 10.870$; $\beta = 90.91$	yes, syn HH
5	4-methyl-6-chlorocoumarin	monoclinic $P2_{1/c}$; $Z = 4$	$a = 7.161$, $b = 8.903$, $c = 13.775$; $\beta = 104.04$	no
6	4-methoxycoumarin	monoclinic $C_{2/c}$; $Z = 8$	$a = 20.258$, $b = 4.645$, $c = 17.238$; $\beta = 93.64$	no
7	7-methoxycoumarin	triclinic $P\bar{1}$; $Z = 4$	$a = 6.834$, $b = 10.672$, $c = 12.60$; $\alpha = 108.19$, $\beta = 95.23$, $\gamma = 95.22$	
8	8-methoxycoumarin	monoclinic $P2_{1/a}$; $Z = 8$	$a = 7.529$, $b = 13.803$, $c = 16.176$; $\beta = 102.07$	yes, anti HT
9	6-methoxycoumarin	orthorhombic P_{ca2_1}; $Z = 4$	$a = 6.73$, $b = 7.17$, $c = 21.26$; $\alpha = \beta = \gamma = 90$	data not available
10	7-acetoxycoumarin	monoclinic $P2_{1/c}$; $Z = 4$	$a = 3.833$, $b = 22.665$, $c = 10.975$; $\beta = 96.27$	yes, syn HH
11	7-methylcoumarin	orthorhombic P_{bca}; $Z = 8$	$a = 13.13$, $b = 18.60$, $c = 6.587$; $\alpha = \beta = \gamma = 90$	no
12	4,7-dimethylcoumarin	triclinic $P\bar{1}$; $Z = 2$	$a = 7.002$, $b = 7.375$, $c = 10.377$; $\alpha = 70.5$, $\beta = 66.2$, $\gamma = 69.5$	no
13	4-hydroxycoumarin[a]	orthorhombic $P2_12_12_1$; $Z = 4$	$a = 10.11$, $b = 12.18$, $c = 6.95$; $\alpha = \beta = \gamma = 90$	no
14	4-methyl-7-hydroxycoumarin[b]	orthorhombic $P2_12_12_1$; $Z = 4$	$a = 11.90$, $b = 13.17$, $c = 5.243$; $\alpha = \beta = \gamma = 90$	no
15	coumarin[c]	orthorhombic P_{ca2_1}; $Z = 4$	$a = 15.466$, $b = 5.676$, $c = 7.917$; $\alpha = \beta = \gamma = 90$	no

[a] Gaultier, J.; Hauw, C. *Acta Crystallogr.* **1966**, *20*, 646. [b] Schmizu, S.; Kashino, S.; Haisa, M. *Acta Crystallogr., Sect. B* **1975**, *31*, 1285. [c] Gavuzzo, E.; Mazza, F.; Giglio, E. *Acta Crystallogr., Sect. B* **1974**, *30*, 1351.

of the monomer, H_5 and H_6 are shifted slightly upfield while H_8 is shifted to a higher field by over 0.6 ppm. This strong shielding effect on H_8 caused by diamagnetic anisotropy of a phenyl nucleus situated in front of the proton is possible only in the syn head–tail configuration. This upfield shift of H_8 is characteristic of syn head–tail dimers.[3c,d] The dimers derived from 6-chloro-, 7-chloro-, 7-methyl-, 6-methoxy-, 6-acetoxy-, and 7-acetoxycoumarins did not have any aromatic upfield shifted protons and these appear in the normal region δ ~6.60–7.00. Therefore, they all are believed to be syn head–head dimers. Indeed it is satisfying to note that these are the expected dimers on the basis of their β-type packing in many of these cases. The dimer of 8-methoxycoumarin is assigned to have anti head–tail configuration based on the following observations. Based on the δ values of cyclobutyl protons it was quite obvious that it is not the syn isomer. Comparison of ^{1}H NMR spectra of the above dimer with anti head–head dimers of coumarin and 7-acetoxycoumarin readily revealed that it is not a head–head isomer. In these anti head–head dimers cyclobutyl protons appear as a complex multiplet centered at δ 3.90. The dimer of 8-methoxycoumarin has two quartets (J = 7 and 5 cps) at δ 4.20 and 3.65 corresponding to four protons. The above coupling constants correspond to the expected cis and trans couplings in cyclobutyl systems.[9] The pattern of cyclobutyl signals is very much similar to the anti head–tail dimer of 7-alkoxycoumarin.[7]

Dimers of 4-methyl-7-acetoxy-, 4-methyl-7-chloro-, and 4-methyl-6-chlorocoumarins show closely similar ^{1}H NMR spectra. 4-Methyl and cyclobutyl proton signals of these three have almost identical δ values, 4-methyl, 1.65, 1.64, and 1.66, respectively, and cyclobutyl protons 3.71, 3.71, and 3.69, respectively. This suggest that the dimers from all the three coumarins probably have identical configurations. From our solution studies,[8a] we find that anti dimers have their 4-methyl and cyclobutyl protons in the region ~1.20 and 3.40, respectively, whereas syn dimers have theirs in the region ~1.70 and ~3.60. The upfield shift of 4-methyl and cyclobutyl protons is expected in the anti dimers due to the diamagnetic anisotropic effect of a carbonyl or phenyl nucleus situated in front of them. Based on this comparison, the dimers from 4-methyl-7-acetoxy-, 4-methyl-7-chloro-, and 4-methyl-6-chlorocoumarins are believed to have syn configuration. Distinguishing syn head–head from syn head–tail dimers was fairly straight forward as the H_8 proton was shifted upfield as discussed above in syn head–tail dimers. Absence of any upfield shifted aromatic protons in the above three dimers suggested that they were syn head–head dimers. Dimers derived from 4-chlorocoumarin are assigned syn head–tail and anti head–tail on the basis of a shift reagent study and by comparison with solution dimers.

(b) General Considerations. Of the 28 coumarins investigated 12 showed photoreactivity in the solid state. This is remarkable considering the fact that coumarin itself does not dimerize in the solid state. With the exception of 4-chlorocoumarin, all others gave a single dimer in each case (Table I). 6-Methoxy-, 4-methyl-6-chloro-, and 7-methylcoumarins yield syn head–head dimers, expected from the β-type packing. It is obvious from the packing arrangements however (Figures 2c and 3c) that the reactive double bonds of 7-methyl- and 4-methyl-6-chlorocoumarins are not suitably disposed for dimerization. From the preliminary cell parameters of 6-methoxycoumarin (Table II) it is clear that the molecules are not packed according to β-type packing. In 4-chlorocoumarin, the center–center distance between the reactive double bonds is 4.47 Å which is well above the accepted limit although the perpendicular distance between the parallel planes is 3.47 Å. Further, the reactive double bonds (Figure 3) exhibit no π overlap and therefore the dimerization would require substantial movement of atoms. Thus, formation of syn head–tail dimer can not be rationalized on the basis of the packing diagram. Therefore, the observed reactivity in the above four coumarins must be due to defects in the crystal. Time of irradiation vs. yield plots (Figure 1) were also indicative that the reactivity of 4-chloro-, 6-methoxy-, 4-methyl-6-chloro-, and 7-methylcoumarins was nontopochemical in nature. No further experiments such as electron microscopic studies were carried out to establish the exact nature of the defects which may be responsible for the nontopochemical nature of dimerization.

Photodimerization of the remaining coumarins showed no induction time (Figure 1a). Packing arrangements (Figure 2 and 3) reveal that β-type packing is present in

(9) Fleming, I.; Williams, D. H. *Tetrahedron* **1967**, *23*, 2747. Dilling, W. L.; Tabor, T. E.; Boev, F. P.; North, P. P. *J. Am. Chem. Soc.* **1970**, *92*, 1398.

7-acetoxy-, 7-chloro-, and 4-methyl-7-chlorocoumarins, the repeat distance being 3.83, 4.45, and 4.08 Å, respectively, along the *a* axis. Preliminary cell dimensions (Table II) suggest that 6-chlorocoumarin also possesses a similar packing with 4.04 Å repeat along the *a* axis. Syn head-head dimers obtained are the direct consequence of the above packing arrangement. Packing arrangements for 8-methoxycoumarin (Figure 4a) indicate that there are two centrosymmetrically related pairs in the unit cell, the center–center distance between the reactive double bonds in these two independent pairs being 4.07 and 3.86 Å. Consistent with the packing mode, anti head–tail dimer is formed. The mechanism of photodimerization of 7-methoxycoumarin is discussed in detail in the next section.

Structural data obtained by us for 4-methoxy- and 4,7-dimethylcoumarins and the data taken from the literature for 4-hydroxy- and 4-methyl-7-hydroxycoumarins suggest that they should not dimerize and this is consistent with their solid-state photochemical behavior. In 4-methoxycoumarin the shortest repeat distance is 4.65 Å (Figure 4b). It is noteworthy that while 7-chlorocoumarin with a repeat length of 4.45 Å undergoes dimerization, 4-methoxycoumarin (4.65 Å) shows no reactivity. While the results of the present study on coumarins are along the lines expected from the topochemical postulates of Schmidt,[1] a critical analysis of our results provides valuable information on certain important specific questions concerning the flexibility that may be permissible in the topochemical criteria as originally proposed by Schmidt.[1]

(c) Parallelism Criteria for Dimerization. In the crystal of methyl *m*-bromocinnamate, one of the potentially reactant double bonds makes an angle of 28° with the other when projected along the line joining the centers of the two bonds; the centers of the bonds are 3.93 Å apart.[10] Schmidt has cited this example where nonparallelism of double bonds prevents reactions. Since then a few examples have been reported in support of this requirement.[11,12] On the other hand, a few cases have also been reported where exact parallelism between reactant double bonds has not been adhered to and yet photodimerization occurs.[12-16] It is clear that a reexamination into the parallelism criterian for double bond dimerization in the solid state is essential. In this connection solid-state photobehavior of 7-methoxycoumarin is particularly relevant.

The dimer yield within 24 h of irradiation of the crystalline 7-methoxycoumarin was ~90% as monitored by NMR integration. The structure of the dimer as established by X-ray crystallography corresponds to syn head–tail. X-ray crystal structure analysis shows that the potentially reactive double bonds of the monomer molecules within the assymmetric unit are rotated by 65° with respect to each other with the center–center distance between the double bonds of 3.83 Å (Figure 4d). Thus it appears that the double bonds are not topochemically (Schmidt's criteria) preformed in the crystal. From Figure 1 it is seen that 7-methoxycoumarin behaves very much like the ones in which the dimerization takes place clearly in a topochemical fashion. Thus the presence of a certain degree of inherent orientational flexibility of the molecules in the crystal lattice has to be invoked to explain the topochemical dimerization.

It is quite likely that the UV irradiation absorbed by the reacting molecules is sufficient to allow the molecules to undergo the required rotation (syn head–tail dimer, 65°; anti head–head dimer, 115°) provided the motion is cooperative and extends through the crystal. Therefore, in order to estimate the inherent orientational flexibility of the molecules in the crystal lattice, lattice energy calculations were carried out with a computer program WMIN developed by Busing.[17] The calculation performed in the present case allows for the relaxation of the surrounding molecules. Much to our surprise the energy calculations revealed the presence of orientational flexibility in the ground state for both the molecules present in the assymmetric unit.[6] Indeed a total rotation of about 20° in the direction to generate syn head–tail dimer in the ground state is possible without much increase in the lattice energy from the minimum energy position as determined by X-ray crystallography ($\Delta E \sim 9.8$ kcal/mol). In most crystals, electronic excitation is known to increase the attractive forces so that the excited molecule interacts more strongly with its neighbors.[18] With the increase in attractive forces between the reactive molecules upon excitation, one may expect that the motion of the molecules so as to achieve a maximum π overlap will become possible. We propose that additional rotation (in addition to that is available in the ground state as indicated by the lattice energy calculations) to generate the syn head–tail dimer is achieved due to the interaction of the excited- and ground-state molecules. Thus the mechanism of photochemical dimerization of 7-methoxycoumarin involves a total rotation of 65° within the crystal lattice.

Although the radiation energy absorbed by the reactive molecules would be large enough to allow the molecules to undergo rotation it seems essential to postulate an inherent flexibility within the crystal lattice for these molecules to undergo rotation as this would allow us to understand the large yield of dimers. It would be interesting to investigate such orientational flexibility for a few of the systems reported in the literature[12-16] wherein the double bonds are nonparallel with respect to each other. However these molecules are conformationally not as rigid as 7-methoxycoumarin and hence detailed calculations could not be performed as easily.

(d) Distance Criteria for Dimerization. From the X-ray studies of a large number of derivatives of *trans*-cinnamic acids, it has become clear that unless potentially reactive groups are separated by less than 4.2 Å no photodimerization will occur in the solid state.[1] However, the upper limit of the critical distance for photodimerization in the solid state is not inexpungably established; the limit of 4.2 Å is set by the absence of experimental data in the range of 4.2–4.7 Å, above which photodimerization does not occur. Results of 7-chlorocoumarin are of interest in this context. Irradiation of crystalline 7-chlorocoumarin yielded a single dimer (syn head–head), without induction period, in ~70% yield within 30 h. The packing arrangement (Figure 3b) reveals that the two potentially reactive 7-chlorocoumarin molecules are separated by 4.45 Å, this being the repeat along the *a* axis. Interestingly, the centrosymmetrically related double bonds are closer, the

(10) Leiserowitz, L.; Schmidt, G. M. J. *Acta Crystallogr.* **1965**, *18*, 1058.
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center–center distance between them being 4.12 Å. As the only dimer obtained corresponds to syn head–head, it is clear that the reaction is between the pairs translated along the *a* axis. It is noteworthy that the distance of 4.45 Å lies outside the so far accepted limit of 3.5–4.2 Å for photodimerization in the solid state. 7-Chlorocoumarin is the first example wherein photodimerization occurs between the double bonds separated by more than 4.2 Å.

It is important to understand the reasons for the absence of reaction between centrosymmetrically related monomers which are at a closer distance. We attribute this to the poor overlap of the π orbitals of these potentially reactive double bonds. This becomes evident when one compares the lateral displacement and angle between least square planes through relevant atoms in these two pairs of molecules. The angle between the least square plane through the centrosymmetrically related atoms of the reactive bonds C_3, C_4, C_3'', and C_4'' and that passing through C_2, C_3, C_4, and C_{10} is 107.0°, whereas the angle between the planes formed by translated atoms C_3, C_4, C_3', and C_4' and C_2, C_3, C_4, and C_{10} is 85.3°. From the ideal value of 90°, deviation is more in the case of centrosymmetrically related pair. Further, the lateral displacement of the centrosymmetrically related pair is 0.9 Å whereas the same for translated atoms is as small as 0.3 Å. These values indicate that the π orbitals of the translated atoms overlap relatively better than the centrosymmetrically related ones. Further, it is expected from the larger lateral displacement of the centrosymmetrically related double bonds, the energy requirements for the displacement of the molecule would be larger for the formation of the centric dimer.

Therefore, it appears now that a short distance between the reactive double bonds is not necessarily the most important factor in allowing photodimerization in the solid state. Orientation and overlap of participating orbitals play a determining role.

(e) Minimum Translational Movement in the Crystal Lattice. Topochemical postulates imply that for the formation of a cyclobutane ring with C–C length of 1.56 Å the double bonds can undergo a total displacement of about 2.64 Å toward each other from the original maximum distance of 4.2 Å. It would be expected that in some cases molecular motions such as (i) rotation of double bonds with respect to each other (to bring about parallelism from nonparallel arrangement), (ii) a rotation about its own C=C axis (to achieve a maximum overlap of the π orbitals), (iii) translation of double bonds in the plane of the molecule, and (iv) movement along the C–C double bond axis may become necessary before dimerization can take place. It may be pointed out that the reduction in the number of parameters namely, four instead of six, results from the implicit assumption of symmetry elements ($\bar{1}$ or 2 or *m*) relating the reacting partners. Based on the photodimerization of coumarins, observations on such translational movement of molecules in the crystal are discussed. Geometrical parameters that are useful, in addition to center–center distance, are θ_1, θ_2, θ_3, and the displacement of double bonds with respect to each other (Figure 5). θ_1 corresponds to the rotational angle of one double bond with respect to the other, θ_2 corresponds to the obtuse angle of the parallelogram formed by double bond carbons C_3, C_4, C_3', and C_4', whereas θ_3 measures the angle between the least square plane through the reactive bonds C_3, C_4, C_3', and C_4' and that passing through C_2, C_3, C_4, and C_{10}. The ideal values (for the best overlap of π orbitals of the reactive double bonds) for θ_1, θ_2, and θ_3 are 0, 90, and 90°, respectively. While θ_2 reflects the displacement along the double bond axis, θ_3 measures it in the molecular plane. Perusal of Table III reveals that in all the four coumarins the reactive double bonds are not ideally placed. Although they are coplanar and parallel to each other, the two double bonds are displaced with respect to each other both in the molecular plane as well as along the double bond axis. In all the four cases the configuration of the dimers obtained in high yield corresponds to the one that is expected based on molecular packing in the crystal (Figures 2–4). This suggests that motions of molecules in molecular plane and along double bond axis, in addition to toward each other, are required and indeed occur. It may be added that although motions of molecules in the solid state of the types described above have not been explicity discussed in the literature, some examples requiring such type of motion have been reported.[19-21] We infer that minimum motion of various types are possible in the monomer crystal upon excitation.

(f) Studies on Crystal Engineering. As mentioned earlier hydroxyl, methyl, methoxy, acetoxy, and chloro were examined as steering agents and were substituted at 4-, 6-, 7-, and 8-positions of the coumarin framework. In each case a minimum of five substrates were investigated. Valuable conclusions are drawn from the photobehavior of the acetoxy and chlorocoumarins. Of the five acetoxycoumarins, three underwent topochemical dimerization (Figure 1) in fairly high yield to the corresponding syn head–head dimers. The packing diagram (Figure 2b) for 7-acetoxycoumarin showed that it possess β-type packing (3.833 Å along the *a* axis). Similar packing arrangement (β-type) must be present in photodimerizable crystals of 6-acetoxy- and 4-methyl-7-acetoxycoumarins in view of the syn head–head dimers obtained. Thus it is clear that the acetyl group plays a strategic role in steering coumarin rings to pack themselves into a β-type stacked structure. Packing similar to 7-acetoxycoumarin has been reported[22] with 4-(2-carboxyvinyl)-α-cyanocinnamic acid dimethyl ester. A parallel plane-to-plane stack is found along the short c axis (3.956) in which the molecules overlap completely. Earlier, interaction involving overlap of an ester group of one molecule with the benzene ring of another had been utilized to steer acrylic acids into packing arrangements suitable for solid-state polymerization.[23] In these examples the ester oxygen atom with lone pair electrons approaches the benzene ring. It has been reported recently[24] that a methylenedioxy substituent in a planar aromatic molecule tends to bring molecules to overlap. Lahav and co-workers have utilized the ester functionality as a steering group during the asymmetric synthesis of chiral dimers and polymers from benzene-1,4-diacrylates.[25] In these cases an attractive interaction between carbonyl and phenyls of adjacent molecules has been implicated. However, such interactions are neither present in 7-acetoxycoumarin nor expected in the other two reactive acetoxycoumarins. An extensive analysis which is underway is therefore warranted to comprehend the mode of packing of molecules bearing acetoxy functionality.

All the chloro-substituted coumarins underwent photodimerization in the solid state (Table I). It is noteworthy

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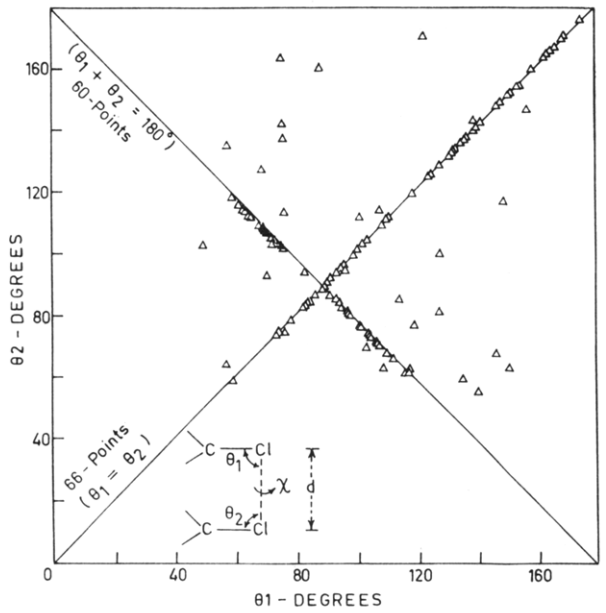

Figure 6. Mode of packing in chloro-substituted aromatic organic crystals within 4.2 Å.

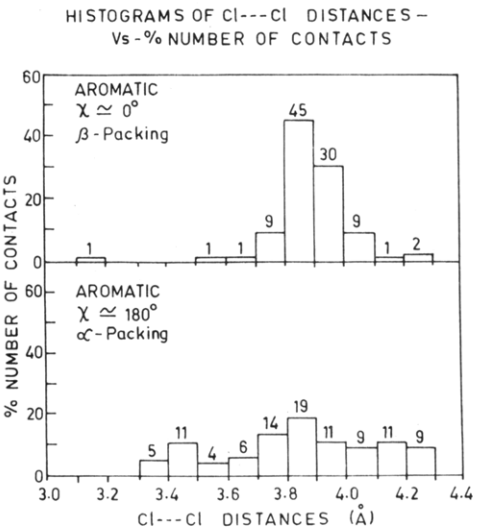

Figure 7. Histograms of Cl···Cl interactions vs. number of contacts.

that whereas coumarin does not undergo dimerization in the solid state, all the five chlorocoumarins underwent photodimerization. However, only three of them have β-type packing (Figure 3). Syn head–head dimers obtained in 6-chloro-, 7-chloro-, and 4-methyl-7-chlorocoumarins are the direct consequence of their β-type packing arrangements. It is significant that in these three cases the perpendicular distance between the closest neighbors varies from 3.45 to 4.45, while in coumarin crystals it is as large as 5.67 Å.

Monochloro substitution and especially dichloro substitution in aromatic and related molecules are reported to be very effective steering devices.[25] The use of 2,6-dichlorophenyl substituent drives the molecule containing a photoreactive group into a mode of crystal packing which is favorable for topochemical (2 + 2) photocycloaddition. Present results on coumarins further establish the use of "chloro" as a steering agent during the solid-state photodimerization.

Regarding "chloro" as a steering group, it was felt that the systematics in the mode of packing in crystal structures containing a chloro group attached to the aromatic rings are worthy of investigation.[26] The experimental information for our analysis was taken from the Cambridge Crystallographic Data Base (version Dec, 1981). Metal complexes and molecules carrying charges were eliminated from the analysis. For detailed analysis only structures which contained Cl···Cl distances <4.2 Å were considered. Out of a total of 132 structures, only 22 did not contain any Cl···Cl interaction within the above limit. In the 110 structures, there were 341 interactions. The geometrical parameters used in the analysis are shown in Figure 6; d is the distance between two chlorines and χ is the dihedral angle about $Cl_1 \cdots Cl_2$ (C_1–$Cl_1 \cdots Cl_2$–C_2). When $\chi = 0.0°$, the atoms C_1 and C_2 are in cis configuration, whereas χ = 180.0° corresponds to trans configuration. Figure 6 shows a plot of of the angles θ_1 vs. θ_2. 60 points lie on the line with $\theta_1 + \theta_2 = 180°$ and in these cases ($\chi = 0°$) the arrangement of the molecules is similar to β-type packing. 66 points are on the line with $\theta_1 = \theta_2$ and this condition simulates the packing similar to α-type arrangement. It may be added that the packing modes corresponding to $\chi = 0°$ and 180° are similar but not identical with the β and α type packing arrangement observed in photoreactive crystalline compounds. It is noteworthy from Figure 7 which portrays the plot of N (number of interactions) vs. d (Cl···Cl distance) that when $\chi = 0°$ most of the Cl···Cl distance lie within a narrow range of 3.8–4.0 Å whereas the range is broad (3.5–4.2 Å) when $\chi = 180°$. The observed smaller width for $\chi = 0°$ may be attributed to the additional intermolecular interactions between the close neighbors. One may conclude from the results discussed above that when there is chloro substitution, the chlorine atoms of the neighboring molecules in the crystal lattice tend to come closer to one another within a distance of about 4.2 Å and this propensity of the chlorine atoms to come closer would be of practical value in crystal engineering. Additional interactions arising from the other groups may be expected to steer the molecule toward either an α- or β-type of packing arrangement.

One of the strategies that has been useful in crystal engineering operations is the replacement of groups of equal volume. In this connection, the interchangeability of chloro (19.9 Å^3) and methyl (23.5 Å^3) groups has been mentioned in the literature. Methyl derivatives frequently crystallize in structures isomorphous with those of the correspondingly substituted chloro compounds.[27] A remarkable observation with respect to interchangeability of chloro and methyl substituents has been made in 2-benzyl-5-benzylidenecyclopentanone series.[28] However, use of this observation in crystal engineering has not been conclusively established. For example, Schmidt has reported that crystal structures of *o*- and *p*-methylcinnamic acids are not related in an obvious manner to the corresponding chloro acids.[1] Results of the present study on coumarins support the conclusion that the interchangeability solely based on the size of methyl and chloro substituents can not be taken to be valid under all circumstances. The crystallographic and photochemical properties of the methyl coumarins turned out to be different from those of the corresponding chlorocoumarins. Whereas three of the five chlorocoumarins undergo topochemical dimerization and pack in a β-type arrangement

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Table III. Relative Orientation of Reactive Double Bonds[a]

no.	coumarin	center to center distance between the reactive double bonds, Å	θ_1, deg	θ_2, deg	θ_3, deg	displacement of double bonds upon projection, Å
1	7-chlorocoumarin					
	pair I (translation)	4.45	0	131.4	85.3	0.287
	pair II (centrosymmetric)	4.12	0	127.9	107.0	0.936
2	4-methyl-7-chlorocoumarin	4.08	0	121.4	88.53	0.011
3	7-acetoxycoumarin	3.83	0	106.4	125.45	1.329
4	8-methoxycoumarin					
	pair I	4.07	0	122.4	63.77	1.565
	pair II	3.86	0	117.4	112.88	1.333
5	7-methoxycoumarin	3.83	65			
6	ideal values	4.2	0	90°	90°	0.0

[a] For definition of geometrical parameters see Figure 5.

Table IV. Spectral Data of Dimers

no.	dimer of	nature, mp, °C	IR (nujol) C=O, cm^{-1}	^1H NMR δ ($CDCl_3$–Me_2SO-d_6)	mass spectra, m/e
1	6-chlorocoumarin	syn head–head, 280–282	1750	4.18–4.21 (2 H, m), 4.26–4.29 (2 H, m), 6.90 (2 H, d, J = 10 cps), 7.04 (2 H, d, J = 3 cps), 7.26 (2 H, dd, J = 10 cps)	(70 eV) 360 (M^+), 289, 268, 252, 239
2	7-chlorocoumarin	syn head–head, 235–236	1765	4.08–4.11 (2 H, m), 4.16–4.23 (2 H, m), 6.76 (2 H, d, J = 8.1 cps), 6.92 (2 H, d, J = 1.9 cps), 6.98 (2 H, dd, J = 8.1 and 1.9 cps)	(CI, NH_3) 378 ($M + NH_4^+$), 361 ($M + 1$), 180, 152
3	4-methyl-6-chlorocoumarin	syn head–head	1770	1.66 (6 H, s), 3.69 (2 H, s), 6.77 (2 H, d, J = 2.6 cps), 6.83 (2 H, d, J = 8.9 cps), 7.18 (2 H, dd, J = 8.9 and 2.6 cps)	(70 eV) 388 (M^+), 371, 353, 331, 291, 196, 166
4	4-methyl-7-chlorocoumarin	syn head–head	1760	1.64 (6 H, s), 3.71 (2 H, s), 6.74 (2 H, d, J = 8.55 cps), 6.88 (2 H, d, J = 1.9 cps), 6.95 (24 H, dd, J = 8.5 and 2.2 cps)	(30 eV) 320, 310, 295, 270, 247, 194
5	4-chlorocoumarin	anti head–tail	1755	3.92 (2 H, s), 7.18 (2 H, dd, J = 9 and 2 cps), 7.34 (2 H, dt, J = 9 and 2 cps), 7.51 (2 H, dt, J = 9 and 2 cps), 7.63 (2 H, dt, J = 9 and 2 cps)	(70 eV) 324, 296, 289, 261, 182
6	4-chlorocoumarin	syn head–tail		4.40 (2 H, s), 6.90 (2 H, dd, J = 9 and 2 cps), 7.04 (2 H, dt, J = 9 and 2 cps), 7.17 (2 H, dt, J = 9 and 2 cps), 7.88 (2 H, dt, J = 9 and 2 cps)	
7	7-methylcoumarin	syn head–head, 220–222	1750	2.27 (6 H, s), 3.99–4.02 (2 H, m), 4.12–4.15 (2 H, m), 6.65 (2 H, d, J = 8 cps), 6.67 (2 H, s), 6.73 (2 H, d, J = 8 cps)	(30 eV) 320 (M^+), 279, 223, 205, 160
8	6-methoxycoumarin	syn head–head		3.53 (6 H, s), 4.69–4.13 (2 H, m), 4.19–4.23 (2 H, m), 6.52 (2 H, s), 6.77 (4 H, s)	
9	7-methoxycoumarin	syn head–tail, 207–209	1750	3.71 (6 H, s), 4.15–4.19 (2 H, m), 4.23–4.27 (2 H, m), 6.20 (2 H, d, J = 2.4 Hz), 6.67 (2 H, dd, J = 2.4, 8,4 Hz), 7.04 (2 H, d, J = 8.4 Hz)	(70 eV) 352 (M^+), 176, 148
10	8-methoxycoumarin	anti head–tail	1760	3.65 (2 H, q), 3.86 (6 H, s), 4.20 (2 H, q), 6.81 (2 H, dd, J = 1.5, 8.1 Hz), 7.05 (2 H, dd, J = 1.5, 8.1 Hz), 7.13 (2 H, d, J = 8.1 Hz)	(70 eV) 352 (M^+), 176, 161, 148
11	6-acetoxycoumarin	syn head–head, 250–252	1750	2.23 (6 H, s), 4.06–4.08 (2 H, m), 4.19–4.21 (2 H, m), 6.60 (2 H, s), 6.93 (2 H, s), 6.94 (2 H, s)	(70 eV) 408 (M^+), 366, 324, 247, 204, 162
12	7-acetoxycoumarin	syn head–head, 215–217	1750	2.21 (6 H, s), 4.15–4.19 (2 H, m), 4.24–4.28 (2 H, m), 6.66 (2 H, d, J = 2.2 Hz), 6.73 (2 H, dd, J = 2.2, 8.5 Hz), 6.92 (2 H, d, J = 8.5 Hz)	(I, NH_3) 426 ($M + NH_4^+$), 222, 205, 180, 163
13	4-methyl-7-acetoxycoumarin	syn head–head, 180–182	1760	1.65 (6 H, s), 2.26 (6 H, s), 3.71 (2 H, s), 6.62 (2 H, d, J = 2.2 Hz), 6.72 (2 H, dd, J = 2.2, 8.6 Hz), 6.79 (2 H, d, J = 8.5 Hz)	(70 eV) 436 (M^+), 410, 382, 365, 351, 261, 219, 218

none of the corresponding methylcoumarins show topochemical behavior and arrange in a packing similar to that of chlorocoumarins.

Based on the photoreactivity of five hydroxycoumarins (Table I), we conclude that the hydroxyl group is not a good steering agent. Reported X-ray crystallographic structures of 4-hydroxy- and 4-methyl-7-hydroxycoumarins support our conclusion.[29] Similar conclusions could be drawn on the use of a methyl group as a steering device. Both 7-methyl- and 4,7-dimethylcoumarins whose structures were investigated do not have suitable packing arrangement for photodimerization (Figure 2 parts c and d). As discussed earlier, the reactivity of 7-methylcoumarin inspite of unfavorable geometry must be attributed to defects. Other methylcoumarins are inert upon photolysis.

Methoxycoumarins were investigated in detail. Of the eight methoxy-substituted coumarins studied, only three showed reactivity in the solid state. Unlike chloro- and acetoxycoumarins wherein syn head–head dimers were obtained uniformally, the configuration of the dimers obtained from the three methoxycoumarins are different (8-methoxy, anti head–tail; 7-methoxy, syn head–tail; 6-methoxy, syn head–head). This indicated that the packing arrangement must be different for each one of these. Indeed the packing arrangements for these and the nonreactive 4-methoxycoumarins are different (Figure 4). Therefore, no generality in the mode of packing of methoxycoumarins is to be observed. This probably implies that the interactions resulting from the methoxy group must be too weak to control the mode of packing.

Conclusion

Since the pioneering studies by Schmidt and Cohen on cinnamic acids, the present photochemical and crystallographic studies on coumarins appear to be systematic and exhaustive ones. Present results, although to a large extent support the original observations of Schmidt on cinnamic acids, have provided an opportunity to gain an insight into the subtler aspects of topochemical postulates on photodimerization. It appears that the short distance (<4.2 Å) between the reactive double bonds is not necessarily the only limiting factor of photodimerization in the solid state. Further, orientation and overlap of participating π orbitals play a distinct role. An example has been provided in the instance of 7-methoxycoumarin which suggests that the dimerization between nonparallel double bonds can occur provided there is an inherent orientational flexibility within the crystal lattice. 7-Chlorocoumarin is an example wherein photodimerization occurs between the double bonds separated by more than 4.2 Å. It remains to be established whether the dimerization can occur in general with double bonds separated upto 4.5 Å. It is observed that the acetoxy and chloro groups are valuable steering groups. However it is premature to come to a general conclusion that these groups may be useful for other molecular systems.

Experimental Section

Spectral Data. UV–visible absorption spectra were recorded on a Shimadzu UV-180 double beam spectrophotometer. IR data were obtained with a Perkin Elmer Model 730 infrared spectrometer. Varian T-60 and Bruker HW-270 FT NMR spectrometers were used for recording ^{1}H NMR. Mass spectral data were kindly provided by Profs. M. Mirbach, J. R. Scheffer, and S. Chandrasekar. Intensity measurements for crystal structure analysis were carried out with an ENRAF-nonius CAD-4 dif-

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Table V. Crystal and Refinement Data of Coumarins

	4-chlorocoumarin	7-chlorocoumarin	4-methyl-6-chlorocoumarin	4-methyl-7-chlorocoumarin	4-methoxycoumarin	7-methoxycoumarin	8-methoxycoumarin	dimer of 7-methoxycoumarin	7-methylcoumarin	7-acetoxycoumarin
temperature, K	293	293	293	293	293	293	293	293	293	293
crystallization solvent	ethanol	ethanol	$CHCl_3$–CCl_4	$CHCl_3$–CCl_4	benzene	benzene	benzene	$CHCl_3$–Me_2SO	$CHCl_3$–CCl_4	$CHCl_3$
crystal dimension (mm^3)	0.5 × 0.3 × 0.3	0.6 × 0.4 × 0.1	0.20 × 0.35 × 0.65	0.7 × 0.1 × 0.5	0.7 × 0.3 × 0.2	0.5 × 0.4 × 0.2	0.8 × 0.4 × 0.1	0.4 × 0.3 × 0.3	0.15 × 0.05 × 0.35	0.75 × 0.30 × 0.05
M_r	180.60	180.60	194.62	194.62	176.20	176.20	176.20	352.40	160.20	204.20
D_{obsd}, M g^{-1} (aqueous KI flotation)	1.48	1.56	1.51	1.49	1.51	1.36	1.40	1.28	1.31	1.44
D_{calcd}	1.484	1.554	1.517	1.497	1.522	1.377	1.422	1.280	1.314	1.429
radiation used (λ, Å)	Mo K_α (0.7107)	Cu K_α (1.5418)	Mo K_α (0.7107)	Mo K_α (0.7107)	Cu K_α (1.5418)	Mo K_α (0.7107)	Cu K_α (1.5418)	Mo K_α (0.7107)	Mo K_α (0.7107)	Cu K_α (1.5418)
μ, mm^{-1}	0.18	3.81	0.35	0.35	0.80	0.14	0.80	0.13	0.05	0.44
mode of data collection	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$
θ_{max}, deg	22.5	60	25	60	60	23	60	23	27.5	60
$N(M)^a$	1088	1476	1736	963	1235	2397	2697	3354	2144	1278
$N(S)^b$	843	874	847	637	1063	1395	2055	2338	740	1016
weighting scheme	$[\sigma^2(F) + 0.021F^2]^{-1}$	0.7141/ $[\sigma^2(F) + 0.002F^2]$	unit weights	1.8850/ $[\sigma^2(F) + 0.002F^2]$	unit weights	0.1400/ $[\sigma^2(F) + 0.0098F^2]$	$[\sigma^2(F) + 0.0068F^2]^{-1}$	unit weights	0.4654/ $[\sigma^2(F) + 0.002F^2]$	10.9836/ $\sigma^2(F)$
R^c	0.043	0.085	0.142	0.058	0.148	0.056	0.050	0.050	0.069	0.056
R	0.087	0.105	0.142	0.068	0.148	0.091	0.081	0.050	0.077	0.069

[a] $N(M)$ is the number of independent reflections measured. [b] $N(S)$ is the number with measured intensity significantly above the background at the three level. [c] Function minimized was $\Sigma w(|F_o| - |F_c|)^2$ and the program used for refinement was SHELX-76.

fractometer. X-ray powder photographs were taken with a Philips powder X-ray diffractometer. All melting points were recorded with a hot plate device attached to a thermometer and are uncorrected.

Materials. Coumarin and 4-hydroxycoumarin from Aldrich were used after recrystallizing from hot water several times. With the exception of 4-acetoxycoumarin the other four acetoxycoumarins were prepared from the corresponding hydroxycoumarins by refluxing a mixture of the hydroxycoumarin and acetic anhydride for about 4 h and then adding the mixture to crushed ice. Extraction with ether gave the acetoxycoumarins. The rest of the coumarins including 4-acetoxycoumarin listed in Table I were prepared by following the literature methods.[30] These samples were recrystallized from the solvents indicated in Table II several times and were used for photolysis and X-ray work.

Irradiation Techniques. Powdered single crystals of coumarins kept in a petri dish were irradiated with a Hanovia 450-W medium-pressure mercury arc lamp from a distance of about 2 ft. Samples were turned around periodically to provide uniform exposure. Progress of the irradiation was monitored by the variation in melting point and ^{1}H NMR and IR spectra. After complete conversion, the time of which was dependent on the nature of the coumarin, the dimer was separated from the monomer by TLC (silica gel, hexane/benzene). Dimers were identified by their spectral properties (Table IV). The method of identification is discussed in detail in the Discussion.

No change was observed in some of the coumarins (Table I) even after 200 h of irradiation. In the reactive coumarins the yield reached a saturation limit after a particular duration of irradiation. Yield of the dimer with respect to the time of irradiation was measured by taking the ^{1}H NMR of about 10-mg quantities (out of 500-mg) from the irradiated material at various time intervals. As illustrated in Figure 1 in some of the coumarins the induction period was noticed and in the others the dimerization initiated immediately after UV exposure.

Crystal Structure Analyses. Crystallization conditions, analytical results, and salient crystallographic data are provided in Tables II and V. Intensity measurements were carried out with an ENRAF-Nonius CAD-4 diffractometer. Crystals of 4-methoxycoumarin and 4-methyl-6-chlorocoumarin were not of good quality for accurate work. However interests in the work being mainly in the packing of the molecules rather than details of molecular geometry, these crystals were used in their structure determinations. All the structures were solved (7-methoxycoumarin not without difficulty) with the help of direct methods (Multan Program) and refined[31] by full-matrix least-squares analysis by using the program SHELX-76.[32] The positional and anisotropic thermal parameters of all non-hydrogen atoms were refined. Hydrogen atoms were refined with their positional and isotropic parameters only.

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Supplementary Material Available: Tables of atomic coordinates, anisotropic thermal parameters, bond length, and bond angles for the structures discussed in the paper (54 pages). Ordering information is given on any current masthead page.

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Stereospecific Synthesis of Difunctionalized 2,5-Disubstituted *cis*-2,5-Dimethylpyrrolidine (Azethoxyl) Nitroxides by Oxidative Cleavage of Protected 8-Azabicyclo[3.2.1]octane Precursors

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Dimethylnortropinone nitroxide **6** was converted into bicyclic ketones **8–10**. Rearrangement of the corresponding oxime derivatives **14** and **16** led, respectively, to lactams **18** and **19**. Hydrolysis of **19** with concomitant oxidation gave the *cis*-azethoxyl nitroxide amino acid **20**. Alternatively, reaction of **8** and **10** with BuLi followed by dehydration and ozonolysis of the resulting alkene mixture gave, respectively, cis-substituted pyrrolidines **26** and **29**. From **29** the (somewhat unstable) *cis*-azethoxyl nitroxide diols **32** were prepared. A third method of cleavage of the bicyclic ring system was established by the route **10** → **35** → **36** → **37**. From **37** difunctionalized *cis*-azethoxyl nitroxides **40** and **41** were prepared.

Stereochemically homogeneous difunctionalized azethoxyl nitroxide spin labels[1] are of interest as potential cross-linking agents, as spin labels for saturation transfer electron paramagnetic resonance (STEPR) studies of macromolecular motion,[2] and as possible contrast enhancing agents for whole-body nuclear magnetic resonance imaging applications.[3] We have recently described the stereoselective synthesis of a series of trans 2,5-difunctionalized pyrrolidine (azethoxyl) nitroxides.[4] The key reaction was the addition of a Grignard reagent to a 2,5,5-trisubstituted pyrroline nitrone followed by oxidation (**1** → **2**). We now report a novel synthetic entry into the cis series of azethoxyl nitroxides through oxidative cleavage of N-oxygenated 8-azabicyclo[3.2.1]octane precursors, as shown systematically by **3** → **4**.

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