Intramolecular Michael-type Addition in the Solid State

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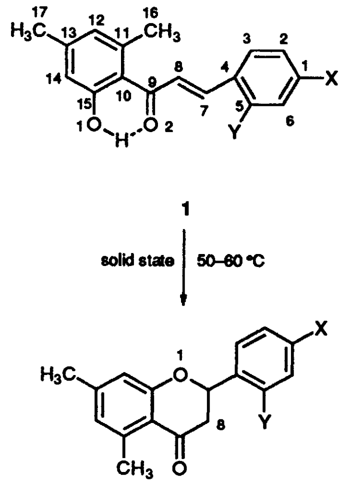
Several substituted 2'-hydroxy-4',6'-dimethylchalcones undergo a solid state intramolecular Michael-type addition reaction to yield the corresponding flavanones, at temperatures significantly below the melting points of the reactants or products. Single crystal X-ray diffraction studies of the reactant and product phases have been carried out and indicate that these solid state reactions most likely proceed in a non-topochemical fashion. A similar conclusion is deduced from X-ray powder diffraction, differential scanning calorimetry and packing energy calculations. Reaction in the defect regions is probably important because considerable relaxation in the molecular conformation of the chalcone is required in the crystal before intramolecular ring-closure to the flavanone can occur.

While solid state photochemical reactions have been extensively researched,[1-3] the systematic study of thermal reactions in the solid state is more recent. Transformations as varied as the Baeyer–Villiger oxidation, $NaBH_4$ reduction, the pinacol–pinacolone rearrangement, the Reformatsky reaction and the Wittig–Horner reaction have been described by Toda and co-workers.[4] However, the crystallographic, mechanistic and topochemical aspects of most of these reactions are largely unknown. Such details have been outlined previously in, for example, the dimerisation of butatrienetetracarboxylic esters,[5] and Chapman rearrangement,[6] Diels–Alder reactions of phenylpropiolic acids[7] and in the rearrangement of α-phenylazo-β-benzoyloxystilbene.[8] Other unusual stereospecific thermal reactions have been reported.[9,10] In this paper, we describe a solid state intramolecular Michael-type addition where crystallographic data, X-ray powder diffraction studies and packing energy calculations suggest a possible reaction pathway. This study originated from the observation that chalcones **1a–d** derived from 2-hydroxy-4,6-dimethylacetophenone underwent colour changes upon mild heating below their 'melting points'.



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a; X = H; Y = H
b; X = Cl; Y = H
c; X = Br; Y = H
d; X = H; Y = Cl

Experimental

3,5-Dimethylphenyl Acetate.—A mixture of 3,5-dimethylphenol (5 g) and acetic anhydride (24 cm^3) upon treatment with 10% NaOH (24 cm^3) for 1 h at 0 °C yielded 4 g (66%) of 3,5-dimethylphenyl acetate, b.p. 118–120 °C.

2-Hydroxy-4,6-dimethylphenylacetophenone.—Anhydrous $AlCl_3$ (6.5 g) was carefully added to the above acetate (4 g) at 0 °C and the mixture warmed for 10 h on the steam bath and then decomposed by steam distillation. The product was isolated as a light yellow solid from the distillate (3.4 g; 88%), m.p. 78 °C; ν_{max}(KBr)/cm^{-1} 3000–3100, 1620, 1200, 1100, 820 and 780; δ_H($CDCl_3$) 12.38 (1 H, s, OH), 7.1–7.3 (2 H, d, ArH), 2.2 (3 H, s, CH_3), 2.4 (3 H, s, CH_3) and 2.6 (3 H, s, OCH_3).

2'-Hydroxy-4',6'-dimethyl Chalcones (**1a–d**).—These chalcones were prepared by the standard method of condensation of the acetophenone obtained above with the corresponding benzaldehydes in a 1:1 molar ratio.[11] When the reaction was conducted for a limited time period, the product obtained contained both chalcone and flavanone. However, as the chalcones could not be purified successfully by recrystallisation, we found it best to extend the reaction time so that the only product was the flavanone and then convert the flavanone back to the corresponding chalcone. The general method was as follows: to a saturated EtOH solution of the above acetophenone (1 equiv.) was added 50% aqueous NaOH (1.5 equiv.). The mixture was stirred vigorously while the appropriate benzaldehyde (1 equiv.) was added. The resulting mixture was kept for 2 h at 20 °C and a white precipitate of the flavanone was obtained. The flavanone was filtered off, redissolved in a minimum quantity of EtOH and 5 volumes of 10% aqueous NaOH were added. Finally the clear solution was acidified with conc. HCl until the solution was pH 3. The overall yields of chalcone are generally above 70%. It is important to follow the above procedure to get the pure chalcone. Other procedures for work-up invariably led to material contaminated with the flavanone. (**1a**) ν_{max}(KBr)/cm^{-1} 3550–3200, 1675, 1620, 1050, 700 and 800; δ_H($CDCl_3$) 11.28 (1 H, s, OH), 8.3–7.0 (5 H, m, ArH), 7.1–7.3 (1 H, d, α, β), 2.2 (3 H, s, CH_3) and 2.5 (3 H, s, CH_3). (**1b**) and (**1c**) ν_{max}(KBr)/cm^{-1} 3500–3100, 1620, 1200, 1100, 800 and 790; δ_H($CDCl_3$) 11.28 (1 H, s, OH), 8.3–7.0 (4 H, q, ArH), 7.1–7.3 (1 H, d, α, β), 2.2 (3 H, s, CH_3) and 2.5 (3 H, s, CH_3). (**1d**) ν_{max}(KBr)/cm^{-1} 3550–3200, 1675, 1620, 1050, 700 and 800; δ_H($CDCl_3$) 11.28 (1 H, s, OH), 8.3–7.0 (4 H, m, ArH), 7.1–7.3 (1 H, d, α, β), 2.2 (3 H, s, CH_3) and 2.5 (3 H, s, CH_3).

Solid State Reactions of Chalcones.—Finely powdered chalcones (100–500 mg) were heated at 50–60 °C with

Table 1 Crystallographic data for compounds **1b–d**, **2a** and **2c**

	1b	**1c**	**1d**	**2a**	**2c**
Formula	$C_{17}H_{15}O_2Cl$	$C_{17}H_{15}O_2Br$	$C_{17}H_{15}O_2Cl$	$C_{17}H_{16}O_2$	$C_{17}H_{15}O_2Br$
Mol. wt.	286.76	331.21	286.76	252.31	331.21
Crystal system	triclinic	orthorhombic	monoclinic	monoclinic	monoclinic
Space group	$P\bar{1}$	$P2_12_12_1$	$P2_1/n$	$P2_1/c$	$P2_1$
a/Å	9.391(3)	15.428(2)	7.699(2)	11.842(4)	4.194(1)
b/Å	10.004(3)	16.008(2)	12.486(2)	5.002(1)	13.149(4)
c/Å	8.074(2)	11.958(2)	14.5820(3)	23.472(6)	12.993(2)
α/°	106.14(2)	90	90	90	90
β/°	93.48(3)	90	95.87(2)	97.60(2)	91.67(3)
γ/°	88.27(3)	90	90	90	90
Cell volume/Å	727.2(4)	2953.3(9)	1394.4(4)	1378.2(6)	716.3(4)
Z	2	8	4	4	2
F(000)	300.0	1344.0	600.0	536.0	336.0
D_{calc}/g cm^{-3}	1.309	1.490	1.366	1.316	1.536
λ/Å	0.7107	0.7107	0.7107	0.7107	0.7107
μ/cm^{-1}	2.16	27.00	2.7	0.44	27.84
Diffractometer	CAD-4	CAD-4	CAD-4	CAD-4	CAD-4
T/K	293	293	293	293	293
X-Radiation	Mo-Kα	Mo-Kα	Mo-Kα	Mo-Kα	Mo-Lα
2θ/°	50	55	55	50	50
h	−10 to 10	0 to 17	−9 to 9	−13 to 13	−4 to 4
k	−11 to 11	0 to 17	0 to 16	0 to 6	0 to 16
l	0 to 9	0 to 15	0 to 18	0 to 28	0 to 16
Total reflections	2556	3782	3291	3174	1733
σ-Level	3	3	3	3	3
R	0.060	0.044	0.043	0.066	0.094
R_w	0.058	0.039	0.047	0.077	0.104
Max. e/Å^{-3}	0.26	0.46	0.22	0.50	0.65

Table 2 O–H···O Intramolecular hydrogen bonds for chalcones **1b–d**

	O(1)···O(2)/Å	H(1)···O(2)/Å	O(1)–H(1)···O(2)/°
1b	2.481(5)	1.55(6)	149(5)
1c A	2.573(15)	2.08(5)	114(3)
B	2.549(15)	1.52(5)	151(3)
1d	2.472(3)	1.76(4)	149(4)

occasional stirring for 7–20 days. Chalcones **1a–c** were found to gradually change their colour during heating but chalcone **1d** remained stable. The flavanones **2a–c** were separated from the reaction mixtures by column chromatography (silica gel, hexane–5% EtOAc) in nearly 70% isolated yield. All products were characterised by NMR and IR spectroscopy and also compared with the authentic samples. (**2a**) ν_{max}(KBr)/cm^{-1} 1720, 1625, 1050, 800 and 700; δ_H($CDCl_3$) 7.8–7.2 (5 H, m, ArH), 6.8–6.5 (1 H, dd), 3.1–3.3 (2 H, m); 2.2 (3 H, s, CH_3) and 2.5 (3 H, s, CH_3). (**2b**) and (**2c**) ν_{max}(KBr)/cm^{-1} 1720, 1625, 1050, 800 and 790; δ_H($CDCl_3$) 7.8–7.2 (4 H, q, ArH), 6.8–6.5 (1 H, dd), 3.1-3.3 (2 H, m), 2.2 (3 H, s, CH_3), 2.5 (3 H, s, CH_3).

X-Ray Crystallographic Studies of **1b–d**, **2a** *and* **2c**.—Crystals of **1b–d** suitable for X-ray work were obtained from petroleum ether, whereas the **2a** and **2c** crystals were obtained from MeOH. Crystals of **1a**, **2b** and **2d** were heavily striated and opaque and were found to be unsuitable for X-ray work. Intensity data were collected for all compounds on an Enraf–Nonius CAD4 diffractometer. The crystal structures were solved by the Heavy Atom method for all compounds except **2a**. The crystal structure of **2a** was solved by Direct Methods using the SHELXS-86 program[12] and the refinement was carried out using full-matrix least squares methods using the SHELX-76 program.[13] Most of the H-atoms of **1b–d** and **2c** were located from difference Fourier maps but the H-atoms of **2a** were fixed geometrically. All non-H atoms were refined anisotropically and the H-atoms were refined isotropically. In **2c**, the Br atom is disordered and was refined with partial occupancies of 0.57 and 0.43. This might in part account for the high R-factor. For **1c** and **2c**, the enantiomorph was determined. Crystallographic information pertaining to **1b–d**, **2a** and **2c** are presented in Table 1. Details of the hydrogen bond geometry are given in Table 2. The positional and thermal parameters for these structures have been deposited.

Differential Scanning Calorimetry (*DSC*).—These traces were recorded for chalcones **1b** and **c** on a Perkin-Elmer DSC-4 Differential Scanning Calorimeter with a scanning rate of 5 deg min^{-1} from 40–115 °C.

Geometry-Energy Calculations.—The feasibility of solid state reactivity in these crystalline chalcones was examined with packing energy calculations using the program OPEC.[14] For the solid state reaction to occur, bonds C(8)–C(9) and C(9)–C(10) in the chalcone molecules should have rotational freedom because this is the only way to bring the potentially reactive atoms O(1) and C(7) closer. So the two bonds C(8)–C(9), C(9)–C(10) in the chalcone molecules were rotated with 5° intervals from 0–20°. These rotations were chosen arbitrarily. The energies required are given in Table 3.

We also performed packing energy calculations using the concept of the 'reaction cavity'. For this purpose, we created cavities in the lattice of chalcones **1b**, **1c** and flavanone **2a** by removing a single molecule. In these created cavities, we introduced the guest molecule, that is the corresponding flavanone in the chalcone lattice or the chalcone in the flavanone lattice. The guest molecule was then rotated 360° around the inertial axes and the surrounding molecules were also relaxed (a range of 9.0 Å was chosen for the surrounding molecules). Because the crystal structures of **1a** and **2b** could not be determined, we used the geometries of **1b** and **2a** for **1a** and **2b**, respectively, in these calculations by replacing a H atom by the Cl atom and Cl atom by the H atom. Details of these calculations are given in Table 4.

Table 3 Energy (kcal mol^{-1}) for simultaneous rotations about bonds C(8)–C(9) and C(8)–C(10) in the crystalline chalcones **1b–d**

	Energy before rotation 0°,0°/kcal mol^{-1}	Energy after rotation 20°,20°/kcal mol^{-1}	Total energy required for rotation/kcal mol^{-1}	Distance after rotation C(7) ··· O(1)	Nature of reactivity
1b	−55	−5	50	4.88	reactive
1c A	−113	−53	60	4.91	reactive
B	−113	−60	53	4.98	
1d	−59	4	63	4.62	unreactive

Table 4 Packing energy (kcal mol^{-1}) determined using the reaction cavity method (flavanone in the chalcone cavity)

	Initial crystal energy of chalcone (OPEC)	Final crystal energy of flavanone in chalcone (OPEC)	Total crystal energy of flavanone as guest (Final–Initial)	Molecular stabilisation energy of flavanone with respect to chalcone (MMX)	Total energy associated with solid state reaction
1b	−55	11	66	−96	−30
1c A	−108	−28	80	−31	49
B	−108	−40	68	50	118

Results and Discussion

Solid State Thermal Reactivity of **1a–d**.—This study began with the observation that orange crystals of chalcone **1a** (m.p. 47 °C) transformed quantitatively (25 °C, 1 week) into the pale-yellow coloured flavanone **2a** (m.p. 78 °C). Further work on this compound was difficult because of the low temperature of the solid state reaction. Therefore, to study this reaction more conveniently we prepared crystalline **1b** (m.p. 79 °C) and **1c** (m.p. 80 °C). These compounds were found to react at temperatures between 50–60 °C (**1b**: 1 week; **1c**: 2 weeks) to give flavanones **2b** (m.p. 93 °C) and **2c** (m.p. 115 °C) in good yields. Conversions **1b** ⟶ **2b** and **1c** ⟶ **2c** could be followed easily by the orange ⟶ pale yellow colour change. Chalcone **1d** is, however, not reactive. For the reactive chalcones, there was no sign of premelting and the solid remained free-flowing throughout the heating period. In fact, it was noticed that physical 1:1 mixtures of the chalcones **1a–c** with their corresponding flavanones **2a–c** melt at 57, 83 and 90 °C respectively. These melting temperatures are significantly greater than the reaction temperatures and this shows that these transformations can be termed genuine solid-state reactions.[15]

This cyclisation reaction of 2′-hydroxy chalcones to flavanones is catalysed in plants by the chalcone–flavanone isomerase enzyme.[16] In solution, the reaction is base-catalysed and proceeds *via* a Michael-type[†] 1,4-addition to the α,β-unsaturated carbonyl system.[17] Clearly the flavanones can be formed only if the phenolic oxygen atom somehow approaches the β-carbon atom because these atoms are covalently bonded in the product. Further discussion on how this could occur in the solid state would have been speculative in the absence of crystallographic data. Hence, the crystal structures of chalcones **1b–d** and flavanones **2a** and **c** were carried out. Crystals of flavanone **2b** were unsuitable for X-ray work (see Table 1).

Crystal Structures of Thermally Reactive **1b** *and* **c** *and Thermally Stable* **1d**.—Varying the substitution on the styryl phenyl ring, we synthesised compounds **1a–d** to study their solid state reactivity. The crystal structures of chalcones **1b–d** are shown in Figs. 1, 2 and 3. In all these molecular structures, the chalcones exist in a *trans* conformation with the alkenic double bond C(7)–C(8) and the carbonyl group C(9)–O(2) in a *cisoid* geometry. Further, all these molecules have intramolecular O–H ··· O hydrogen bonds (Table 2). The general molecular structures of **1b–d** are similar but for the presence of two symmetry-independent molecules, designated hereinafter **A** and **B** for chalcone **1c**. There is neither intermolecular O–H ··· O hydrogen bonding nor any halogen ··· halogen interactions in these crystal structures. Intermolecular forces, are in general, weak and we believe this Michael-type addition to be intramolecular.

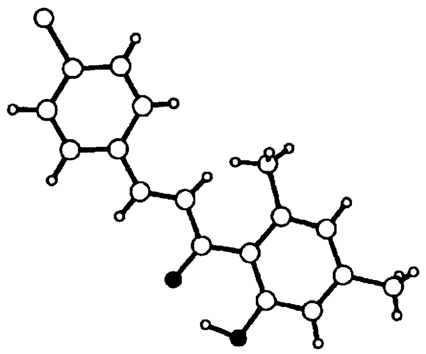
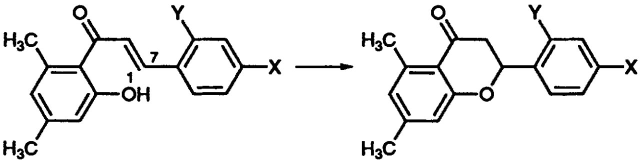


Fig. 1 Molecular structure of chlorochalcone (**1b**). O-Atoms are shaded.



Crystal Structures of Flavanones **2a** *and* **c**.—The flavanones **2a** and **c** are the products of the solid state reactions of **1a** and **c**. The packing of the former molecules are shown in Figs. 4 and 5. In the molecular structure of **2a**, the six-membered heterocyclic ring is a distorted boat and the substituted phenyl ring is twisted out of the mean heterocyclic ring plane. But in the case of **2c**, the heterocyclic ring is a distorted chair and the phenyl group is

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[†] We use the term 'Michael-type' here because the nucleophilic species is not a C atom.

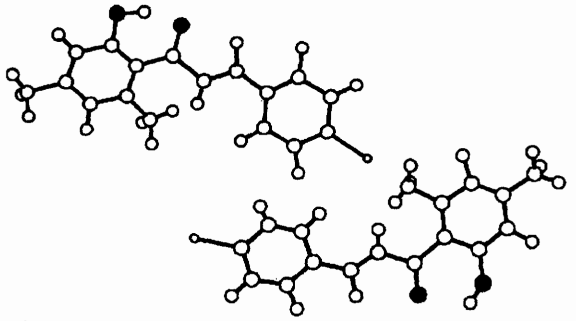

Fig. 2 Molecular structure of bromochalcone (**1c**). The two symmetry-independent molecules are shown. O-Atoms are shaded.

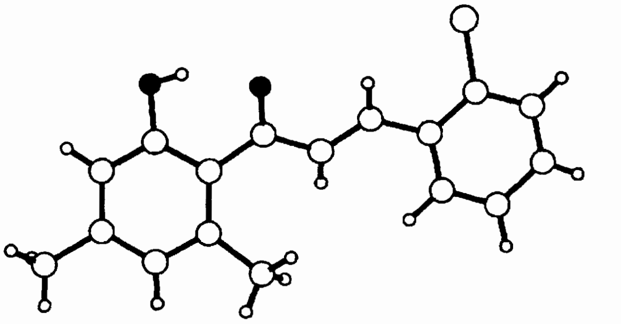

Fig. 3 Molecular structure of chlorochalcone (**1d**). O-Atoms are shaded.

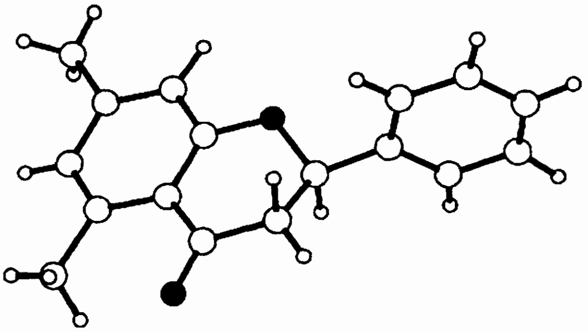

Fig. 4 Molecular structure of flavanone (**2a**). O-Atoms are shaded.

nearly in the same plane. Weak Br ••• Br contacts of 4.194 and 4.483 Å are found.‡ The crystal structures of **2a** and **c** are stabilised by C–H ••• O hydrogen bonds.

Packing Energy Calculations—Correlation with Reactivity.—The distance between the phenolic oxygen O(1) and the β-carbon C(7) atoms, is 5.06 Å in **1b**, 5.11(A) and 5.17(B) Å in **1c** and 4.91 Å in **1d**. These distances are too great for a topochemical reaction to occur. Calculations with the program OPEC[12] give an estimate of the rotation and energy required to effect a shortening of the intramolecular O(1) ••• C(7) distance in the crystal. We performed rotations simultaneously around C(8)–C(9) and C(9)–C(10) and the resultant packing energies and respective distances are given in Table 3. In this event, both reactive and unreactive chalcones showed almost the same energies for a similar shortening of the C(7) ••• O(1) non-bonded distance. There is no apparent correlation between the energy required for the rotation and the presence/absence of reactivity. Therefore it may be concluded that this reaction is not governed by topochemical principles.

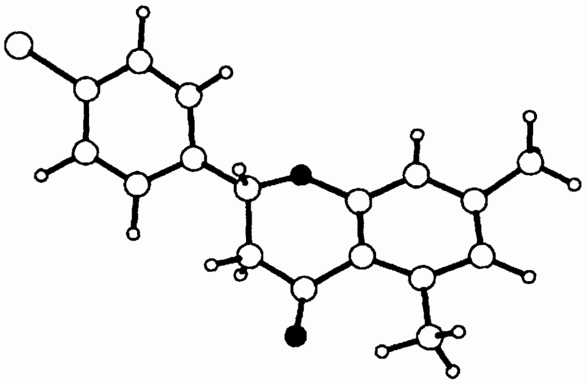

Fig. 5 Molecular structure of bromoflavanone (**2c**). O-Atoms are shaded.

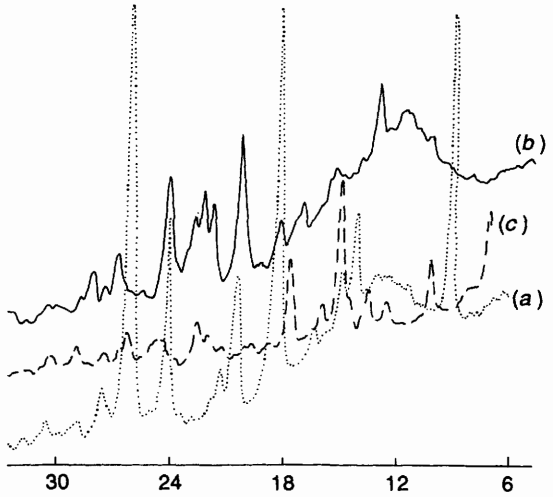

Fig. 6 X-Ray powder diffraction patterns: (*a*) chalcone **1b**; (*b*) chalcone **1b** after 7 days heating; (*c*) flavanone **2a**

In the above discussion it has been implicitly assumed that the topochemical reaction criteria which were developed for photochemical reactions[1,2] are also applicable to thermal reactions. This may or may not be strictly correct. Large separations are present in many thermal processes and it is not clear at this time which of these are 'topochemical' or whether the term itself has the same significance in the broad context of thermal reactions.

Differential Scanning Calorimetry (DSC) and X-Ray Powder Diffraction Experiments.—We tried to asecertain the possibility of phase transitions in crystalline **1b** and **c** before the onset of solid state reactivity. Such an experiment is important because a low temperature (30–50 °C) phase transition could yield a crystalline form of the chalcones which could then undergo topochemical conversion to the flavanones. However, DSC of **1b** showed only two peaks at 88 and 98 °C. It may be noted that the melting point of **1b** is 78 °C. The peak at 88 °C approximates to the melting point of the 1:1 mixture of chalcone and flavanone, whereas the second peak at 98 °C corresponds to the melting point of flavanone **2a**. Similarly, chalcone **1c** gives two DSC peaks at 95 and 103 °C. These results suggest that the DSC experiments are too insensitive to detect the thermal reactions. Accordingly it is difficult to state that the reaction proceeds without any phase transitions on the basis of the DSC experiments.

We also monitored the progress of the solid state reactions of **1b** and **c** with X-ray diffraction. The powder traces taken after about one week of heating showed that both chalcone and product flavanone are present (Fig. 6).

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‡ Two distances are given because of the disorder of the Br atom.

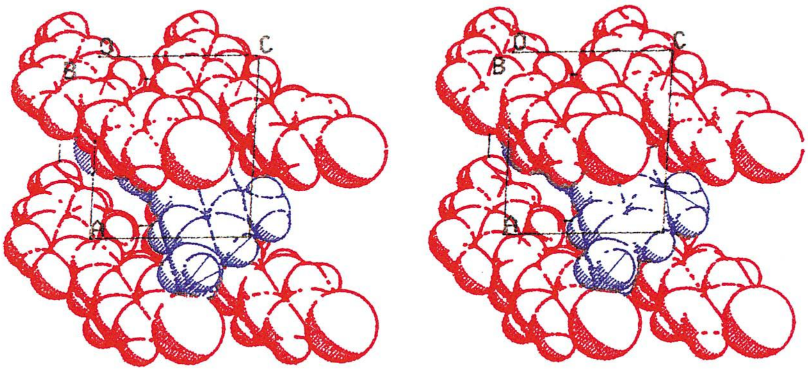


Fig. 7 Space filling stereodrawing of the crystal structure of chalcone (**1b**) down [101] with a molecule of flavanone (**2b**) inserted in the central site. Chalcone molecules are coloured red and the guest flavanone blue.

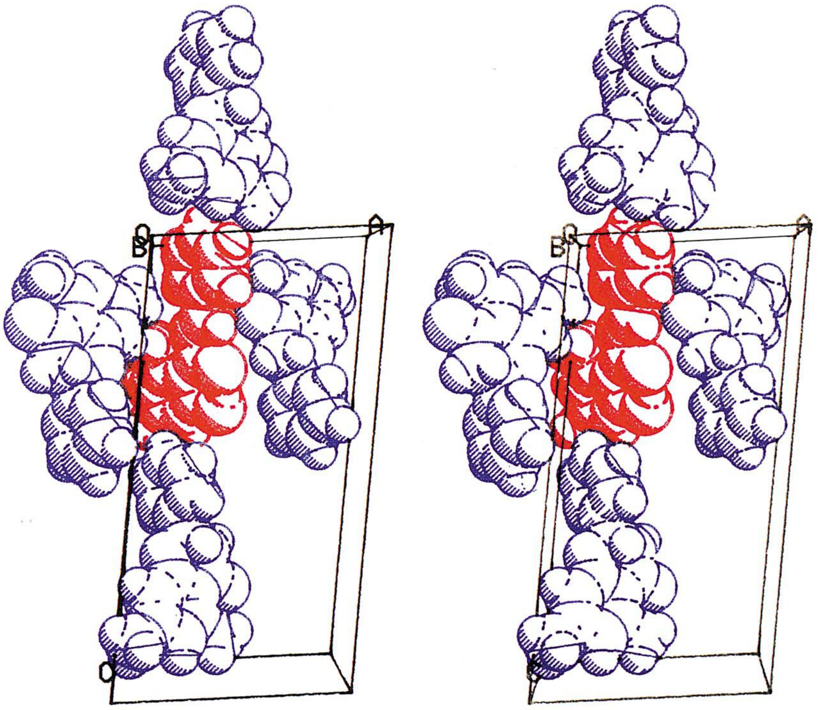
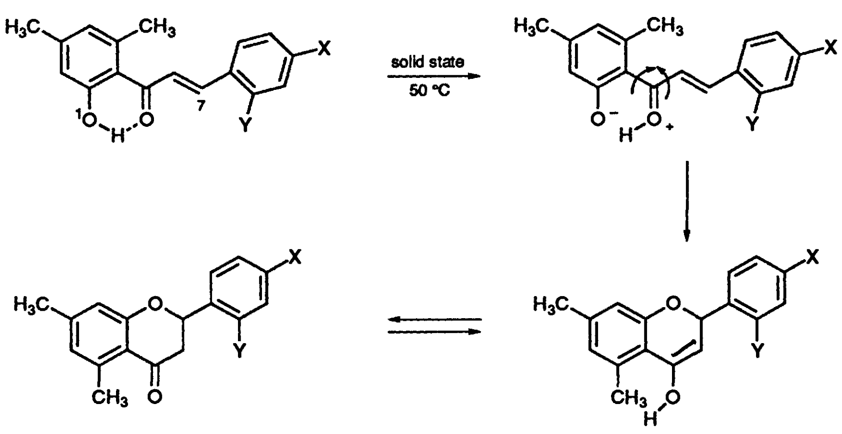


Fig. 8 Space filling stereodrawing of the crystal structure of flavanone (**2a**) down [101] with a molecule of chalcone (**1a**) inserted in the central site. Flavanone molecules are coloured blue and the guest chalcone red.



Scheme 1

From these results, one may conclude that the transformation from chalcone to flavanone may occur first at the surface of crystals (defect regions)[18] where the molecules are more free to rotate. Subsequently, and with an increase in the number of defects caused by the initial reaction, further reaction could take place in the interior of the crystal.[8] In the defect sites there is presumably enough space around the molecules so that they can relax into favourable conformations for the formation of the corresponding flavanones.

Chalcone **1d** which is converted in solution to the corresponding flavanone is unreactive in the solid state. From the crystal structure of **1d**, it is not very clear why it should be unreactive except for the fact that the *ortho*-Cl substituent might somehow hinder the molecular relaxation which is a prerequisite for the formation of flavanone **2d**.

Packing Energy Calculation—Reaction Cavities.—The concept of the reaction cavity[19] has been used to computationally probe the course of a solid state reaction.[20] This procedure is only useful when there is evidence of solid solution formation of the product within the reactant or *vice versa* but this has been postulated as being of general occurrence.[15] We have used this method for the system under study and further calculations were performed with the OPEC program. Firstly we estimated the positioning of the product flavanone molecule in the crystal lattice of the reactant chalcone. For example, a molecule of flavanone **2b** was substituted for a molecule of chalcone **1b** in the crystal structure of the latter. The position and orientation of the guest molecule and its near neighbours were allowed to relax. The final orientation of molecules is shown in Fig. 7. We found that the energy required to place a (**2b**) molecule in the (**1b**) crystal is *ca.* 66 kcal mol^{-1}. However, flavanone (**2b**) is 96 kcal mol^{-1} more stable than chalcone (**1b**).§ In effect, ΔH for the reaction is -30 kcal mol^{-1}, that is 66–96 kcal mol^{-1}. In the bromo crystal (**1c**), the two symmetry-independent sites A and B are distinctive. The final ΔH values are 49 kcal mol^{-1} for site A (80 − 31 kcal mol^{-1}) and 118 kcal mol^{-1} for site B [68 − (−50) kcal mol^{-1}]. In practice, this is corroborated by the more sluggish reaction rate for chalcone (**1c**). These details are provided in Table 4.

Similarly we performed calculations wherein a chalcone **1a** molecule was introduced into the crystal lattitce of the flavanone **2a**. The energy of chalcone **1a** in the flavanone lattice was estimated to be 44 [−6 − (−50)] kcal mol^{-1}. The final orientation of the chalcone guest is shown in Fig. 8.

These computations provide a very approximate energy profile for this solid state reaction. However, as considerable molecular movement is involved, such an analysis may be valid only during the initial stages of the reaction. In any event, the reaction could proceed by a simultaneous or stepwise occurrence of the following events: (*a*) H^+ transfer across the intramolecular hydrogen bond; (*b*) a near-approach of O(1) and C(7) brought about by single bond rotation; (*c*) nucleophilic attack by O^- on C(7); (*d*) tautomerisation to yield the product. A possible pathway is outlined in Scheme 1.

Conclusions

This study of solid state Michael addition reactions of a series of 2′-hydroxy-4′,6′-dimethylchalcones shows that the reactions do not proceed according to topochemical principles. However, the crystal structures of the chalcones and the product flavanones together with DSC and X-ray powder diffraction experiments, indicate that the reactions could occur at the surface of the crystals and other defect regions.

Acknowledgements

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§ This value was obtained from MMX calculations. The (**1b**) conformation was taken from its crystal structure and the (**2b**) conformation as in the crystal structure of (**2a**) with neither conformation optimised.

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