JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 11, 751–755 (1998)

1:1 Crystal complex of 2′,6′-dimethoxyflavone and 2,6-dimethoxybenzoic acid. Relationship of pK_a to x-ray hydrogen bond data

J.-C. Wallet,[1]* E. Molins[2] and C. Miravitlles[2]

[1]Laboratoire de Phytochimie, Case 412, Faculté des Sciences et Techniques de Saint-Jérôme, 13397 Marseille Cedex 20, France
[2]Institut de Ciència de Materials de Barcelona, CSIC, Campus Universitat de Bellaterra, 08193 Cerdanyola, Spain

Received 15 July 1997; revised 18 October 1997; accepted 11 November 1997

ABSTRACT: The crystal structure of the 2′,6′-dimethoxyflavone–2,6-dimethoxybenzoic acid complex was determined. Owing steric hindrance of the methoxy groups, the two H-bonded molecules are twisted. Earlier results were used to establish a relationship between the pK_a values of different acids and their hydrogen bond distances in complexes with 2′,6′-dimethoxyflavone. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: 2′,6′-dimethoxyflavone–2,6-dimethoxybenzoic acid complex; crystal structure; pK_a values; hydrogen bonds

Hydrogen bonds are a type of intermolecular interactions that direct molecular self-assembly. Carboxylic acids are good proton donors and form well known types of hydrogen bond patterns involving both carboxyl–carbonyl and carboxyl–hydroxyl groups, each hydroxyl group binding the carbonyl group of a neighbouring molecule.[1] It is accepted that the best proton donor will form a first hydrogen bond with the best proton acceptor.[2] Therefore, if a group more basic than the carbonyl group is present, the hydroxyl group should form preferentially a hydrogen bond with it. Triphenylphosphine (TPPO)[3] is a good example. Numerous TPPO complexes have been described and, among acidic guests, oxalic,[4] trichloroacetic,[5] dimethylmalonic[6] and chloro-substituted phenoxyacetic[7] acids have been considered. Moreover, taking the same base as a reference, it should be possible to compare the strengths of acids.

The general proton transfer process can be represented by the equation

$$A{-}H + B \rightleftharpoons A \cdots H \cdots B \rightleftharpoons A^- + H{-}B^+.$$

With carboxylic acids, the proton will remain attached to the acid molecule but with strong acids proton transfer will occur and the base will be protonated.

Flavones are weak Brönsted bases, and only a few dissociation constants have been measured.[8] Moreover, flavones form isolable salts with strong acids. For example, a bioflavone, meliternatin, gives salts with hydrochloric, perchloric, picric and picrolinic acid.[9]

**Correspondence to:* J.-C. Wallet, Laboratoire de Phytochimie, Case 412, Faculté des Sciences et Techniques de Saint-Jérôme, 13397 Marseille Cedex 20, France.
E-mail: jean-claude.wallet@iut-chimie.u-3mrs.fr

During our studies of the recrystallization of flavones,[10] we encountered difficulties in growing monocrystals of 2′,6′-dimethoxyflavone (**Ia**). Crystals of **Ia** obtained from ethanol, acetonitrile and chloroform quickly became efflorescent and were not usable for x-ray structure determinations. Air-stable crystals of **Ia**

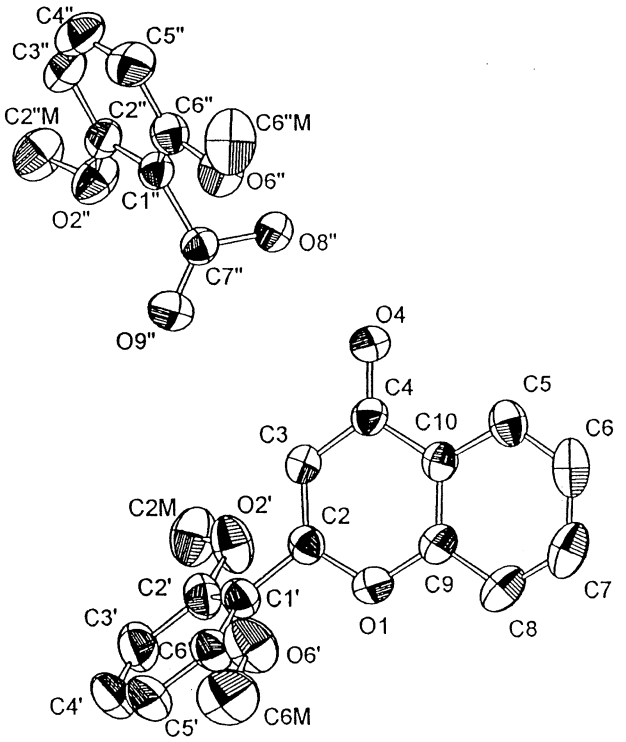


Figure 1. Structure of the complex with atom numbering. The thermal ellipsoids are drawn at 50% probability

CCC 0894–3230/98/100751–05 $17.50

Table 1. Crystal data, summary of intensity data collection and structure refinement

Crystal data:	
Compound	$C_{17}H_{14}O_4.C_9H_{10}O_4$
Colour/shape	Colourless/parallelepiped
Formula weight	464.45
Space group	$P2_1/c$
$F(000)$	976
Cell constants:	
a (Å)	7.250(2)
b (Å)	13.179(1)
c (Å)	24.463(7)
β (°)	96.46(1)
V (Å^3)	2322.5(9)
Z	4
D_c (g cm^{-3})	1.328
μ (cm^{-1})	0.99
Crystal dimensions (mm)	$0.75 \times 0.49 \times 0.37$
Intensity measurements:	
Diffractometer/scan	Enraf-Nonius CAD-4/$\omega - 2\theta$
Radiation, λ	Mo Kα (0.71069 Å)
Temperature (K)	294
Reflections measured	7174
Range of 2θ (°)	3–60
Range of hkl	−10 to 10, 0 to 18 0 to 34
No. of standard reflections	3
Interval between the standards	60 min
Intensity instability	0.4%
Structure refinement:	
No. of reflections included	7015 with $I > 2\ \sigma(I)$
No. of refined parameters	309
Weights	$w = 1/[\sigma^2(F_o^2) + (0.0106P)^2]$ with $P = [\max(0,F_o^2) + 2F_c^2]/3$
Goodness of fit	1.075
$R(F)$	0.0617
$wR(F^2)$	0.1586
Final $\Delta\rho_{max}/\Delta\rho_{min}$/(e$^-$ Å^{-3})	0.229/−0.335

were grown from a 1:1 mixture of ethanol and acetic anhydride. The x-ray crystal determination revealed that molecules of acetic acid were present in the ratio AcOH:**Ia** = 1:1. This was also observed by ^{1}H NMR spectroscopy. The same crystals were obtained by dissolving **Ia** in acetic acid and then allowing the solution to evaporate at room temperature. Using similar methods, complexes of **Ia** with formic and propionic acid[11] were characterized. With strong inorganic acids, **Ia** was dissolved in an anhydrous solvent (diethyl ether or absolute ethanol) and concentrated acid was poured into the solution to precipitate the complex. Recrystallization from absolute ethanol afforded suitable crystals for x-ray determination. With orthophosphoric acid,[12] one molecule of acid is present as a solvate molecule of crystallization and the other is ionized and protonates the carbonyl oxygen of **Ia**. With perchloric acid[13] the stoichiometry is flavone : perchloric acid : water = 1:1:1.

A third method was used to prepare the title complex. Equimolar amounts of acid and **Ia** were dissolved in ethanol and the solution allowed to evaporate at room temperature. Colourless crystals were removed from the solution and air dried. They were initially characterized by ^{1}H NMR spectroscopy and the structure was determined by x-ray crystallography (Fig. 1). The structure was determined by direct methods and refined by full-matrix least-squares on F^2.[14] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were introduced in calculated positions and refined riding on their bonded atom with a global isotropic temperature factor. PLUTON-93 was used for structure drawings.[15]

In 2′,6′-dimethoxyflavone (**Ia**) the bond lengths and bond angles are comparable to those found in similar complexes.[10–12] The torsion angle O(1)—C(2)—C(1′)—C(6′) = 60.8(2)° is in the range expected for these complexes. Variations of the heterocycle double bonds C(4)=O(4) and C(2)=C(3), the single bond C(3)—C(4) and the C(2)—C(1′) bond linking the heterocycle to the dimethoxyphenyl group are consistant with previous results.[13]

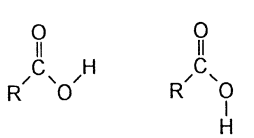
In 2,6-dimethoxybenzoic acid (**Ib**), the bond distances in the phenyl ring are similar to those found in the crystal structure of pure 2,6-dimethoxybenzoic acid (**IIb**).[16] The main difference arises with the carboxyl group. Its plane is more inclined [75.70(7)° to that of the phenyl ring]. The C(1″)—C(7″) bond is lengthened to 1.502(3) Å

Table 2. Fractional atomic coordinates and equivalent isotropic displacement parameters U_{eq} of the non-hydrogen atoms in the complex[a]

Atom	*x*	*y*	*z*	U_{eq} (Å^2)
O(1)	0.8620 (2)	−0.1506 (1)	0.5711 (1)	0.048 (1)
C(2)	0.8594 (3)	−0.2332 (1)	0.5379 (1)	0.043 (1)
C(3)	0.8171 (3)	−0.2265 (2)	0.4830 (1)	0.046 (1)
C(4)	0.7699 (2)	−0.1321 (1)	0.4563 (1)	0.041 (1)
O(4)	0.7336 (2)	−0.1223 (1)	0.4058 (1)	0.057 (1)
C(5)	0.7074 (3)	0.0512 (2)	0.4733 (1)	0.051 (1)
C(6)	0.6986 (3)	0.1300 (2)	0.5091 (1)	0.063 (1)
C(7)	0.7451 (3)	0.1156 (2)	0.5649 (1)	0.067 (1)
C(8)	0.7998 (3)	0.0219 (2)	0.5853 (1)	0.058 (1)
C(9)	0.8084 (2)	−0.0583 (1)	0.5487 (1)	0.042 (1)
C(10)	0.7639 (2)	−0.0450 (1)	0.4928 (1)	0.039 (1)
C(1′)	0.9031 (3)	−0.3275 (2)	0.5691 (1)	0.049 (1)
C(2′)	1.0519 (3)	−0.3896 (2)	0.5593 (1)	0.055 (1)
O(2′)	1.1569 (2)	−0.3561 (1)	0.5202 (1)	0.069 (1)
C(2M)	1.3058 (4)	−0.4183 (2)	0.5064 (1)	0.077 (1)
C(3′)	1.0860 (4)	−0.4792 (2)	0.5888 (1)	0.070 (1)
C(4′)	0.9668 (5)	−0.5061 (2)	0.6264 (1)	0.084 (1)
C(5′)	0.8192 (4)	−0.4474 (2)	0.6370 (1)	0.077 (1)
C(6′)	0.7866 (3)	−0.3580 (2)	0.6085 (1)	0.061 (1)
O(6′)	0.6414 (3)	−0.2951 (2)	0.6138 (1)	0.081 (1)
C(6M)	0.5199 (4)	−0.3183 (3)	0.6538 (1)	0.098 (1)
C(1″)	0.3819 (3)	−0.3543 (1)	0.2830 (1)	0.042 (1)
C(2″)	0.4660 (3)	−0.4267 (2)	0.2526 (1)	0.048 (1)
O(2″)	0.6384 (2)	−0.4558 (1)	0.2747 (1)	0.065 (1)
C(2″M)	0.7260 (4)	−0.5360 (2)	0.2488 (1)	0.075 (1)
C(3″)	0.3755 (3)	−0.4624 (2)	0.2034 (1)	0.062 (1)
C(4″)	0.2027 (4)	−0.4251 (2)	0.1853 (1)	0.071 (1)
C(5″)	0.1157 (3)	−0.3540 (2)	0.2147 (1)	0.064 (1)
C(6″)	0.2067 (3)	−0.3187 (2)	0.2642 (1)	0.049 (1)
O(6″)	0.1362 (2)	−0.2494 (1)	0.2976 (1)	0.063 (1)
O(6″M)	−0.0509 (3)	−0.2186 (2)	0.2849 (1)	0.086 (1)
C(7″)	0.4848 (3)	−0.3137 (2)	0.3351 (1)	0.043 (1)
O(8″)	0.5498 (2)	−0.2227 (1)	0.3276 (1)	0.057 (1)
O(9″)	0.5078 (3)	−0.3581 (1)	0.3778 (1)	0.082 (1)

[a] Numbers in parentheses are estimated standard deviations in the least significant digits.

[1.485(4) Å in **IIb**], presumably owing to the carboxyl group being more twisted. In the complex, the acid is bound through its hydroxyl group to the carbonyl of the flavone and does not form chains which involve participation of both oxygen atoms of the carboxyl group. The carboxyl group in **Ib** is found in the *Z* conformation, unlike the carboxyl group in **IIb**, which exists in the *E* conformation.[16,17]



Z rotamer E rotamer

According to theoretical calculations on formic and acetic acid,[18] *Z* rotamers are more stable than *E* rotamers. Single C—O and double C=O bond distances are longer

Table 3. Bond lengths (Å) and angles (°)

O(1)—C(2)	1.358 (2)
O(1)—C(9)	1.373 (2)
C(2)—C(3)	1.345 (3)
C(2)—C(1′)	1.474 (3)
C(3)—C(4)	1.429 (3)
C(4)—O(4)	1.239 (2)
C(4)—C(10)	1.458 (3)
C(5)—C(6)	1.366 (3)
C(5)—C(10)	1.399 (3)
C(6)—C(7)	1.382 (4)
C(7)—C(8)	1.373 (3)
C(8)—C(9)	1.392 (3)
C(9)—C(10)	1.381 (3)
C(1′)—C(2′)	1.396 (3)
C(1′)—C(6′)	1.409 (3)
C(2′)—O(2′)	1.361 (3)
C(2′)—C(3′)	1.392 (3)
O(2′)—C(2M)	1.426 (3)
C(3′)—C(4′)	1.378 (4)
C(4′)—C(5′)	1.369 (4)
C(5′)—C(6′)	1.376 (3)
C(6′)—O(6′)	1.358 (3)
O(6′)—C(6M)	1.422 (3)
C(1″)—C(6″)	1.384 (3)
C(1″)—C(2″)	1.391 (3)
C(1″)—C(7″)	1.502 (3)
C(2″)—O(2″)	1.359 (3)
C(2″)—C(3″)	1.387 (3)
O(2″)—C(2″M)	1.418 (3)
C(3″)—C(4″)	1.372 (3)
C(4″)—C(5″)	1.376 (3)
C(5″)—C(6″)	1.392 (3)
C(6″)—O(6″)	1.363 (2)
O(6″)—C(6″M)	1.417 (3)
C(7″)—O(9″)	1.193 (2)
C(7″)—O(8″)	1.309 (2)
C(2)—O(1)—C(9)	119.07 (14)
C(3)—C(2)—O(1)	122.1 (2)
C(3)—C(2)—C(1′)	125.7 (2)
O(1)—C(2)—C(1′)	112.2 (2)
C(2)—C(3)—C(4)	122.0 (2)
O(4)—C(4)—C(3)	124.1 (2)
O(4)—C(4)—C(10)	120.7 (2)
C(3)—C(4)—C(10)	115.3 (2)
C(6)—C(5)—C(10)	120.2 (2)
C(5)—C(6)—C(7)	120.4 (2)
C(8)—C(7)—C(6)	120.7 (2)
C(7)—C(8)—C(9)	118.8 (2)
O(1)—C(9)—C(10)	122.2 (2)
O(1)—C(9)—C(8)	116.6 (2)
C(10)—C(9)—C(8)	121.2 (2)
C(9)—C(10)—C(5)	118.7 (2)
C(9)—C(10)—C(4)	119.1 (2)
C(5)—C(10)—C(4)	122.2 (2)
C(2′)—C(1′)—C(6′)	118.9 (2)
C(2′)—C(1′)—C(2)	122.1 (2)
C(6′)—C(1′)—C(2)	118.9 (2)
O(2′)—C(2′)—C(3′)	124.0 (2)
O(2′)—C(2′)—C(1′)	115.7 (2)
C(3′)—C(2′)—C(1′)	120.3 (2)
C(2′)—O(2′)—C(2M)	118.6 (2)
C(4′)—C(3′)—C(2′)	118.4 (3)
C(5′)—C(4′)—C(3′)	122.9 (2)
C(4′)—C(5′)—C(6′)	118.8 (2)

continued

Table 3. continued

O(6′)—C(6′)—C(5′)	124.4 (2)
O(6′)—C(6′)—C(1′)	115.0 (2)
C(5′)—C(6′)—C(1′)	120.6 (2)
C(6′)—O(6′)—C(6M)	118.8 (2)
C(6″)—C(1″)—C(2″)	119.8 (2)
C(6″)—C(1″)—C(7″)	120.7 (2)
C(2″)—C(1″)—C(7″)	119.5 (2)
O(2″)—C(2″)—C(3″)	124.9 (2)
O(2″)—C(2″)—C(1″)	114.9 (2)
C(3″)—C(2″)—C(1″)	120.2 (2)
C(2″)—O(2″)—C(2″M)	118.1 (2)
C(4″)—C(3″)—C(2″)	118.9 (2)
C(3″)—C(4″)—C(5″)	122.1 (2)
C(4″)—C(5″)—C(6″)	118.8 (2)
O(6″)—C(6″)—C(1″)	114.8 (2)
O(6″)—C(6″)—C(5″)	125.0 (2)
C(1″)—C(6″)—C(5″)	120.2 (2)
C(6″)—O(6″)—C(6″M)	118.3 (2)
O(9″)—C(7″)—O(8″)	123.8 (2)
O(9″)—C(7″)—C(1″)	125.2 (2)
O(8″)—C(7″)—C(1″)	111.0 (2)

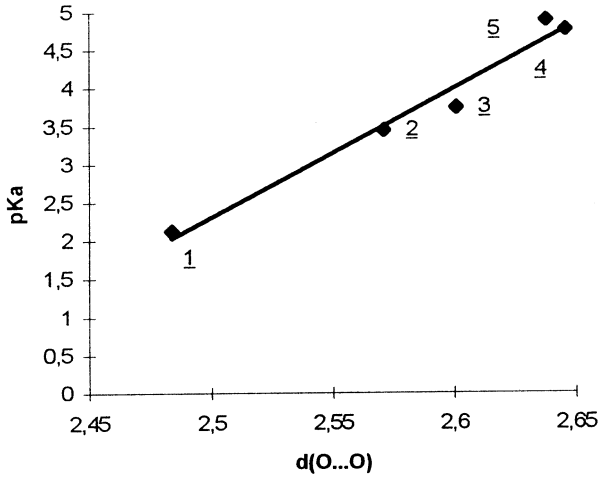


Figure 2. Dependence of pK_a on hydrogen bond distance. For acid numbering, see Table 4

in pure acid crystals because O—H or C=O groups interact with the C=O and O—H (and C—H in acetic acid) of neighbouring molecules.[19–21] The corresponding bond distances in the complexes are shorter, involving larger O—C=O bond angles due to stronger repulsion between oxygen atoms (Table 3).

Since in a series of carboxylic acids (plus orthophosphoric acid) (see above) the acid OH group was bound to the carbonyl of **Ia** through a single hydrogen bond involving acid–flavone pairs of molecules, a favourable situation was available to examine the hydrogen bonding. We correlated the pK_a of these acids with the hydrogen bond distance in crystals of the acid–flavone complexes. Figure 2 shows a plot of the data obtained for the different complexes. This plot exhibits a satisfactory linear correlation ($r = 0.986$) given by the equation $pK_a = (16.8 \pm 1.6)d(O—O) - (39.8 \pm 4.2)$.

Flavones are also weak Lewis bases. We have recently reported the structure of the 2′,6′-dimethoxyflavone–chlorotriphenyltin adduct.[24] Using the chlorotriphenyltin as a Lewis acid, it seems possible to compare the strengths of Lewis bases (the stronger the base, the shorter the Sn—O distance). Conversely, using the title flavone as a Lewis base, it should be possible to compare the strengths of similar Lewis acids and establish a quantitative acidity ladder.

Hence it appears that x-ray analysis of hydrogen bond lengths in all these complexes with the title flavone allow one to obtain pK_a values of suitable carboxylic acids. This method could be valuable when the experimental pK_a determination is difficult or impossible. Work is in progress to analyse other complexes with 2,6-substituted benzoic acids used in the preparation of inhibitors of various enzymes[25] and other carboxylic acids to increase the data and improve the correlation.

A scale correlating carbon acidities to C—H···O distances in crystal structures is known.[26] Results were obtained from large samplings of crystallographic data from the Cambridge Structural Database. However, carbon acids C—H were related to different O atom basicities.

Table 4. pK_a values, bond angles, bond distances and hydrogen bond distances

Acid[a]	pK_a[b]	O—C=O (°)		C—O (Å)		C=O (Å)		O—H—O (Å)	
		A	C	A	C	A	C	A	C
1	2.12	–	–	–	–	–	–	–	2.484 (3)
2	3.44	118.6 (3)	123.8 (2)	1.317 (4)	1.309 (2)	1.224 (4)	1.193 (2)	2.673 ([c])	2.571 (2)
3	3.75	123.9 (2)	126.1 (9)	1.308 (2)	1.282 (9)	1.222 (2)	1.196 (9)	2.624 (2)	2.601 (6)
4	4.75	122.0 (6)	121.4 (5)	1.318 (7)	1.280 (5)	1.220 (6)	1.215 (5)	2.626 (6)	2.646 (6)
5	4.87	122.0 ([c])	123.2 (3)	1.32 (1)	1.310 (4)	1.22 (1)	1.186 (4)	2.644 ([c])	2.638 (4)

[a] **1**, Orthophosphoric acid, Ref. 12; **2**, dimethoxybenzoic acid, A Ref. 16, C this work; **3**, formic acid, A Ref. 21, C Ref. 11; **4**, acetic acid, A Ref. 20, C Ref. 10; **5**, propionic acid, A Ref. 19, C Ref. 11. A Crystal structure of the pure acid; C, crystal structure of the acid–flavone complex.
[b] pK_a values are from Ref. 22, except for acid **2** (Ref. 23).
[c] Estimated standard deviation not given in the reference.

REFERENCES

1. G. R. Desiraju. *Angew. Chem., Int. Ed. Engl.* **34,** 2311–2327 (1995).
2. M. C. Etter. *Acc. Chem. Res.* **23,** 120–126 (1990).
3. M. C. Etter and P. W. Baures. *J. Am. Chem. Soc.* **110,** 639–640 (1988).
4. D. Thierbach and F. Huber. *Z. Anorg. Allg. Chem.* **477,** 101–107 (1981).
5. L. Golic and V. Kaucic. *Cryst. Struct. Commun.* **5,** 319–324 (1976).
6. J. P. Declercq, G. Germain, J. P. Putzeys, J. Rona and M. Van Meerssche. *Cryst. Struct. Commun.* **3,** 579–582 (1974).
7. D. E. Lynch, G. Smith, K. A. Byriel and C. H. L. Kennard. *Aust. J. Chem.* **45,** 835–844 (1992); *Z. Kristallogr.* **200,** 73–82 (1992); *Acta Crystallogr., Sect. C* **49,** 285–288 (1993).
8. C. T. Davis and T. A. Geissman. *J. Am. Chem. Soc.* **76,** 3507–3511 (1954).
9. L. H. Briggs and R. H. Locker. *J. Chem. Soc.* 2157–2162 (1949).
10. J.-C. Wallet, E. M. Gaydou and A. Baldy. *Acta Crystallogr., Sect. C* **45,** 512–515 (1989).
11. B. Tinant, J. P. Declercq, J.-C. Wallet, E. M. Gaydou and A. Baldy. *Bull. Soc. Chim. Belg.* **100,** 329–337 (1991).
12. J.-C. Wallet, V. Cody, A. Wojtczak and R. H. Blessing. *Anti-Cancer Drug Des.* **8,** 325–332 (1993).
13. J.-C. Wallet, V. Cody and A. Wojtczak. *Struct. Chem.* **5,** 361–366 (1994).
14. G. M. Sheldrick. *SHELXL93, A Program for Refining Crystal Structures.* University of Göttingen, Göttingen (1993).
15. A. L. Spek. *PLUTON-93, Program for Display and Analysis of Crystal and Molecular Structures.* University of Utrecht, Utrecht (1993).
16. R. F. Bryan and D. H. White. *Acta Crystallogr., Sect. B* **38,** 1014–1016 (1982).
17. G. M. Frankenbach, D. Britton and M. C. Etter. *Acta Crystallogr., Sect. C* **47,** 553–555 (1991).
18. K. B. Wiberg and K. E. Laidig. *J. Am. Chem. Soc.* **109,** 5935–5943 (1987).
19. J. L. Derissen. *J. Mol. Struct.* **7,** 81–88 (1971).
20. I. Nahringbauer. *Acta Chem. Scand.* **24,** 453–462 (1970).
21. I. Nahringbauer. *Acta Crystallogr., Sect. B* **34,** 315–318 (1978).
22. R. C. Weast (Ed.). *Handbook of Chemistry and Physics*, 67th ed., p. 161D. CRC Press, Boca Raton, FL (1986).
23. M. M. Davis and H. B. Hetzer. *J. Phys. Chem.* **61,** 125–126 (1957).
24. W. Maniukiewicz, E. Molins, C. Miravitlles, J. -C. Wallet and E. M. Gaydou. *J. Chem. Cryst.* **26,** 691–694 (1996).
25. C. Subramanyam, M. R. Bell, P. Carabateas, J. J. Court, J. A. Dority, Jr, E. Ferguson, R. Gordon, D. J. Hlasta, V. Kumar, M. Saindane, R. P. Dunlap, C. A. Franke and A. J. Mura. *J. Med. Chem.* **37,** 2623–2626 (1994).
26. V. R. Pedireddi and G. R. Desiraju. *J. Chem. Soc., Chem. Commun.* 988–990 (1992).

