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Packing Modes in Some Mono- and Disubstituted Phenylpropiolic Acids: Repeated Occurrence of the Rare *syn,anti* Catemer

Dinabandhu Das and Gautam R. Desiraju*[a]

Dedicated to Professor L. Leiserowitz

Abstract: The catemer is an infinite one-dimensional pattern formed by the carboxylic acid group in crystals, and is constituted with O–H···O hydrogen bonds. The catemer is uncommon and may be contrasted with the ubiquitous carboxylic acid dimer, the favored mode of association of this functional group. Both catemers and dimers, however, have two O–H···O hydrogen bonds for each carboxy group, so the reasons for the rarity of the catemer must lie elsewhere. In this paper, we describe a group of around 25 phenylpropiolic acids in which the catemer is the default packing mode. Exceptionally, the particular catemer that is found in this family is of the very rare *syn,anti* variety. We show that a necessary ingredient in catemer formation is a supportive C–H···O hydrogen bond from a proximal C–H group, which is located on the phenyl ring, *ortho* to the ethynyl group, and suitably activated by electron withdrawing substituents. When steric factors become noteworthy, alternative patterns are adopted, such as the *syn,syn* catemer and, in one case, a rare *cisoid* dimer. When electron-donating groups, either through inductive effect such as methyl or through resonance such as halogens, are present on the phenyl ring, the dimer is formed in all but one case. Polymorphism seems not to be an issue in these carboxylic acids in that no compound would generally crystallize as both a dimer and a catemer. It may be concluded that a supporting interaction, in this case a C–H···O hydrogen bond, is the essential condition for the formation of any carboxylic acid catemer. Catemers are so rare because it is difficult to set up this type of supporting interaction in most carboxylic acids.

Keywords: carboxylic acids · catemers · crystal engineering · hydrogen bonds · supramolecular chemistry

Introduction

Crystal engineering is the rational design of functional molecular solids.[1,2] This subject includes three distinct activities that form a continuous sequence: 1) the study of intermolecular interactions;[3] 2) the study of packing modes as a function of molecular structure and intermolecular interactions in the context of design strategy;[4] 3) The study of crystal properties and their fine-tuning with respect to crystal packing.[5] In effect, these three stages represent the "what", "how", and "why" of the subject. This paper is concerned with the second of these activities, and attempts to correlate the crystal structures of a family of mono- and disubstituted phenylpropiolic acids, Ar–C≡C–CO_2H, with the nature and position of the substituent groups on the aromatic ring.

Why are the packing modes of organic molecular solids, especially carboxylic acids, which are one of the most heavily studied systems in crystal engineering, still being studied? It is exactly 30 years since Leiserowitz wrote his seminal review on this topic,[6] and while many of the principles laid down in that review are still valid, the vast numbers of crystal structures determined today have also led to novel and unexpected packing modes. These newer structures demand a modification of our earlier understanding or at least a re-evaluation of older ideas. The cornerstone of qualitative, heuristic, or synthon-based crystal engineering is that experimental crystal structures are available in sufficiently large and representative numbers.[7] The more comprehensive our knowledge of the overall packing landscape,[8] the greater will be the reliability with which we predict an unknown crystal structure.[9] More recently, quantitative crystal engi-

[a] D. Das, G. R. Desiraju
School of Chemistry, University of Hyderabad
Hyderabad 500 046 (India)
Fax: (+91) 40-2301-0567
E-mail: gautam_desiraju@yahoo.com

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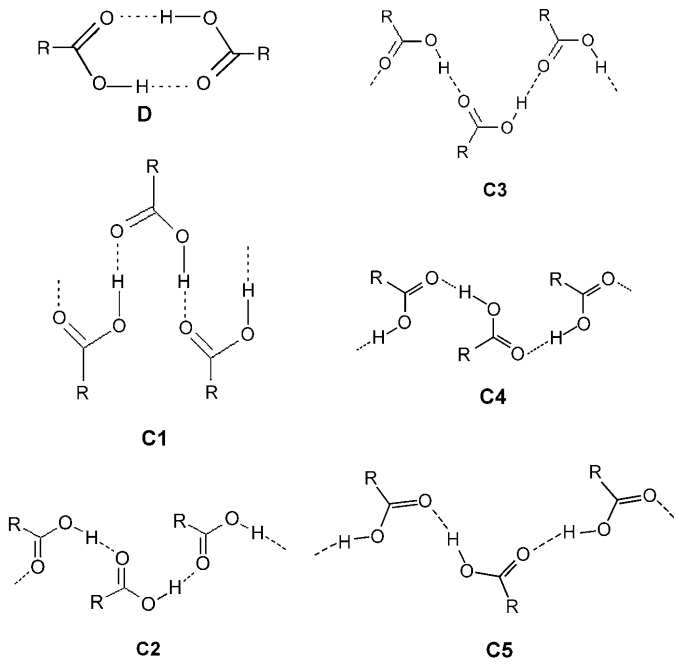
neering, or (computer-based) crystal-structure prediction, has come to the forefront.[10] Here too, an understanding of packing modes is vital, either to validate or benchmark the results, or as an input in knowledge-based strategies that attempt to circumvent the difficulties inherent in the fact that crystallization is a kinetically controlled process.[11] In the end, we really do not know if any set of available experimental crystal structures is truly representative of a particular family of compounds at any given point in time. A new structure will always be discovered, and the nature of the packing in this structure may either strengthen or weaken currently held views.[12] The analysis of packing modes is, therefore, a continuous and ongoing activity in crystal engineering, and we do not expect this situation to change in the immediate future.

Results and Discussion

Dimers and Catemers

Monocarboxylic acids, RCO_2H, can exist in one of two conformations, *syn* and *anti*, and there are two broad modes of association of these molecules in crystals.[6] The cyclic dimer is formed by the *syn* conformation and is zero-dimensional (**D**). A number of catemers, or open chains of various types (**C1**–**C5**), exist. In **C1**, **C2** and **C3**, all the molecules are *syn*; **C4** is obtained by switching the H atoms in **C2** and is *anti* throughout,[19,20] whereas **C5** contains alternating *syn* and *anti* molecules. All these catemers are 1D patterns. For both dimers and catemers, the number of O–H···O hydrogen bonds per carboxy group is two. Therefore, there is no reason, at least at the gross level, for a preference for either the dimer or the catemer arrangement. However, the frequencies of occurrence of dimers and catemers are very different.[21,22] The dimer is a common pattern seen in around a third of all carboxylic acids in the Cambridge Structural Da-



Abstract in Telugu:

కార్బాక్సిలిక్ ఆమ్ల సమూహంలోని O-H...O హైడ్రోజన్ బంధాలు ఏకదిశలో (one-dimensional) అనంతంగా ఏర్పడటాన్ని "బహు అణుకం" (catemer) అంటారు. కార్బాక్సిలిక్ ఆమ్లాలలో ద్వి అణుకం (dimer) ఏర్పడటం సర్వసాధారణంగానూ బహు అణుకం ఏర్పడటం చాలా అరుదుగానూ జరుగుతుంది. ద్వి అణుక మరియు బహు అణుకాలలో ప్రతి కార్బాక్సిలిక్ ఆమ్ల సమూహం రెండేసి O-H...O హైడ్రోజన్ బంధాలను ఏర్పరుస్తుంది. కావున బహు అణుకం ఏర్పడటంలో O-H...O సమూహ ప్రమేయం కాక ఇతర కారణాలు ఉండవచ్చును. ఈ వ్యాసంలో బహు అణుకం ద్వారా సంపుటీకరణ (packing) జరిగిన 25 ఫినైల్‌ప్రోపియోలిక్ (phenylpropiolic) ఆమ్లాల గురించి వివరించడం జరిగింది. ఈ కూటమిలో అసాధారణమైన O-H...O బహు అణుకం గుర్తించబడింది. ఎలక్ట్రాన్ ఉపసంహరణశక్తిగల (withdrawing) ఇథైనైల్ సమూహానికి ఆర్థో-స్థానంలోని (ortho-position) ఉత్తేజిత ఫినైల్ C-H ల ద్వారా ఏర్పడిన C-H...O బంధం, బహు అణుకం ఏర్పడటానికి మూలకారణంగా గుర్తించబడింది. కాని త్రిమితీయ గుణకం (steric factor) అధికమైనప్పుడు ప్రత్యమ్నాయ ఆకృతులైన సిస్-సిస్ (syn-syn) లేదా అసాధారణమైన సిసోయిడ్ (cisoid) ద్వి అణుకం కాని ఏర్పడుతుంది. స్వతహాగా ఎలక్ట్రాన్ దాత అయినటువంటి మిథైల్ కాని లేదా అనునాదం (resonance) ద్వారా ఎలక్ట్రాన్ దాత అయినటువంటి హాలోజన్ (halogen) కాని ఫినైల్‌రింగ్‌పై ఉన్న పక్షంలో ఒక్క పదార్థంలో మినహా అన్ని పదార్థాలలో ద్వి అణుకం ఏర్పడుతుంది. ఈ కార్బాక్సిలిక్ ఆమ్లాలలో ఏ ఒక్కటి కూడా ద్వి అణుక బహు అణుకాల రెండింటి ద్వారా స్ఫటీకీకరణం (crystallization) జరగటం గుర్తించబడలేదు. కావున, ఈ సంపుటిలో బహురూపకతకు (polymorphism) స్థానంలేదు. బహు అణుకం ఏర్పడటానికి C-H...O బంధాల సహకారం తప్పనిసరి. ఈ విధమైన C-H...O బంధాలు ఏర్పడటం అన్ని రకాల కార్బాక్సిలిక్ ఆమ్లాలలో సాధ్యం కాదు, కావున బహు అణుకం (catemer) చాలా అరుదుగా ఏర్పడుతుంది.

International Advisory Board Member

Gautam R. Desiraju *has been at the Univ. of Hyderabad since 1979 and has contributed greatly to crystal engineering, in particular, the properties of the weak hydrogen bond and supramolecular synthons in logic-based retrosynthesis. He has published 2 definitive books and over 275 papers. He received the 2000 Alexander von Humboldt Forschungspreis and was a Visiting Professor/Fellow at the Weizmann Institute of Science, the JSPS, and the Univ. of Bologna. He is on the Executive Committee of the International Union of Crystallography.*

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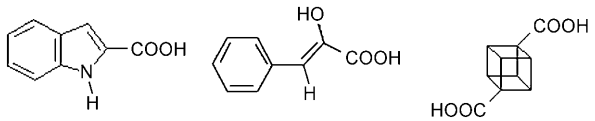
tabase (CSD) (1350 dimers from around 4000 carboxylic acids).[23] Catemers occur far less frequently, with only around 110 reported structures; the 98 *syn,syn* variants (**C1**, **C2**, **C3**) dominate in this group. Most of these facts are well-known and it is not our intent to review them here. Rather, we prefer to list some information that is pertinent to our discussion on the *syn,anti* catemer, **C5**, which is the theme of this paper.

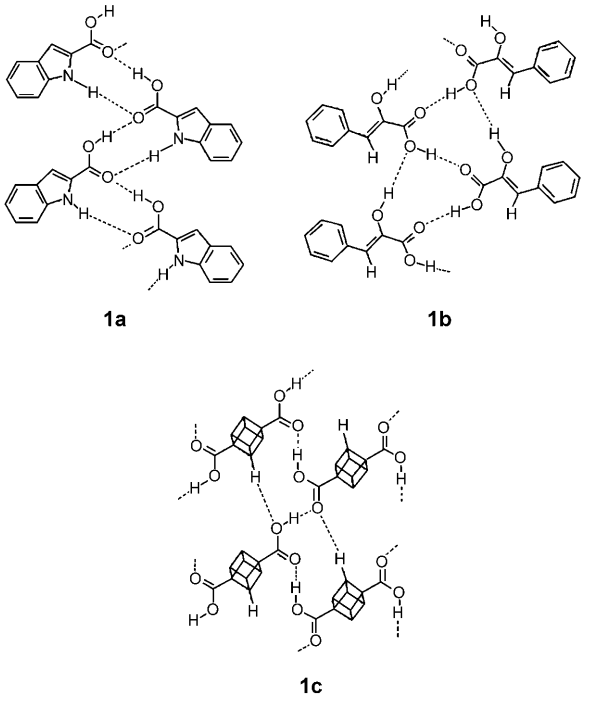
The relative infrequency of catemers was ascribed by Leiserowitz to the fact that these patterns are more sensitive to the steric effects of the R group (**C2**, **C3**) or to the presence of repulsive O···O lone-pair interactions (**C1**).[6] The infrequency of the *anti* relative to the *syn* catemers was attributed to the higher energy ($\approx$6 kcal mol^{-1}) of the *anti* conformation. Conversely, the ubiquity of the dimer was ascribed to the fact that its formation is largely independent of the nature of the R group; the carboxy and hydrocarbon regions are effectively insulated in the crystal. These ideas are generally well-accepted. However, subsequent work showed that dimers and catemers may be more equiprobable than previously thought if energy considerations alone were important;[24–27] computations showed the catemer to be generally just as stable as the dimer. A distorted catemer of benzoic acid was found at an energy of 1.5 kcal mol^{-1} above the dimer.[28] What does this mean? Can one infer that the steric argument for catemer formation is of only limited applicability? Calculations showed the dimer and catemer to be evenly matched in acetic acid, in which experimental efforts have failed to uncover the dimer.[29–31] Does this reflect a kinetic factor? Again, some categories of acids, for example, 2,6-disubstituted benzoic acids, give catemers (11 out of 50 in the CSD). This last example is interesting: does it indicate that dimer formation, at least in aromatic acids, is driven by a planar conformation in which the carboxy group is in conjugation with the ring, this conjugation more than compensating for the inherently lower stability of the dimer? According to such an argument, if a planar conformation is precluded by, say, 2,6-disubstitution, the molecule adopts the catemer.[32] This sort of reasoning is similar to that used by Leiserowitz for enantiomeric acids. He held that since an inversion centre is impossible in an ordered structure in these cases, a catemer is formed.[33]

We argued previously that the presence of an auxiliary hydrogen bond is a major factor that directs catemer formation, whether *syn* or *anti*.[34–36] Consider, for example, the cases of indole-2-carboxylic acid (**1a**) and phenylpyruvic acid (**1b**), both of which form *syn,syn* catemers. These cat-



1a **1b** **1c**

emers are clearly stabilized by the additional N–H···O and O–H···O hydrogen bonds, respectively, to the carboxy groups (Figure 1).[37] Analogously, one may suggest that the



1a **1b** **1c**

Figure 1. O–H···O catemer in carboxylic acids. The catemers are stabilized by supporting interactions in each case: N–H···O in **1a**, O–H···O in **1b**, and C–H···O in **1c**.

very rare *syn,anti* catemer in cubane-1,4-dicarboxylic acid (**1c**)[38] arises because of the supportive C–H···O bond donated by the (activated) cubyl C–H group (Figure 1).[34] Indeed, the existence of such interaction mimicry is taken as good evidence of the C–H···O interaction being a genuine hydrogen bond.[36] Catemer formation in acetic acid has also been rationalized with a similar argument involving a C–H···O bond.[6] The rarity of catemers relative to dimers is nicely accounted for by this hypothesis of a supporting interaction because most carboxylic acids would not be able to form such an additional suitably located interaction. In general, the role of C–H···O bonds in establishing O–H···O patterns in carboxylic acid crystal structures is well-accepted.[39] Herein, we assess the hypothesis that a supportive C–H···O interaction is necessary for catemer formation.

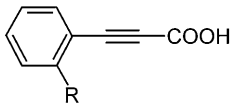
The higher energy of the gas-phase *anti* conformation of the carboxy group with respect to the *syn* conformation seems not to pose as insuperable a barrier to its existence in crystals as is stated by the energy difference of 6 kcal mol^{-1}. Li and Houk suggested that the *anti* conformation in crystals is stabilized by O–H···O hydrogen bonding so that it is only around 1–2 kcal mol^{-1} less stable than the *syn* conformation.[24,40] What is true is that the *syn,anti* catemer (**C5**) is very rare for carboxylic acids. The first reported instance of this pattern was by Ermer and Lex on **1c**.[38] We later published the second case, which occurred in 4-chlorophenylpropiolic acid (**4b**).[41] Further studies by us[34] showed that this phenomenon occurs in around 10 other 4-substituted cubanecarboxylic and phenylpropiolic acids, so the first two occurrences of the *syn,anti* catemer were not freak observa-

tions on unstable polymorphs. Whether **C5** will be seen in other classes of acid is a difficult question to answer, and the only other example we found is 3-(ferrocenylcarbonyl)-propionic acid.[42] We discuss herein the reasons for adoption of the *syn,anti* catemer with respect to the dimer in some mono- and disubstituted phenylpropiolic acids, and report a large number of these catemers. The *syn,anti* catemers reported in this paper represent the overwhelming majority for this packing mode in the literature.

Two final points need to be mentioned before we describe the crystal structures themselves. The first concerns polymorphism and whether carboxylic acids can crystallize as both the dimer and the catemer in polymorphic structures; if they did, the arguments in this paper, which rely on stereoelectronic effects of substituent groups, would be compromised. This, happily, is not the case: no simple carboxylic acid,[43] except oxalic acid[44,45] and tetrolic acid,[46] is known to form both the dimer and the catemer. Therefore, issues of polymorphism were not expected to pose problems in the present study.[47] Even then, as a matter of caution, we subjected each compound in this study to a standard polymorph screen of recrystallization from 10 solvents or solvent mixtures. In all cases save one, no polymorphs were obtained. The second point pertains to disorder of the carboxy group. This is a well-known phenomenon and is monitored by the difference between the two C–O distances in the carboxy group. If this distance is large ($\approx$0.1 Å), the carboxy group is ordered; if it is small (tending to zero), the carboxy group is disordered. Intermediate degrees of disorder have intermediate differences in C–O distance.[48] Both dimers and *syn,anti* catemers can be disordered, but the basic packing arrangement is independent of this disorder.

2-Substituted Phenylpropiolic Acids

The acids discussed here are the fluoro (**2a**), chloro (**2b**), bromo (**2c**), iodo (**2d**), methyl (**2e**), methoxy (**2f**, **2f′**), and trifluoromethyl (**2g**) derivatives. Relevant crystallographic details are given in Table 1 for all compounds in this study. All acids with a *syn,anti* catemer are characterized by a crystal axis of around 7.5 Å, which is the translational repeat along the direction of hydrogen bonding. The first three halogenated derivatives **2a–c** take the *syn,anti* catemer (Figure 2), and whereas the carboxy groups in **2a** and **2c** are disordered, they are ordered in **2b**. The disordered catemers are generated with distinct inversion centers, and the ordered catemer is obtained with symmetry-independent molecules (*syn* and *anti*). All three catemers are stabilized by proximal C–H···O interactions.



2a: R = F **2e**: R = CH_3
2b: R = Cl **2f**: R = OMe
2c: R = Br **2g**: R = CF_3
2d: R = I

Table 2 gives the (supportive) C–H···O geometrical details for all the catemers in this study.[49] These interactions occur over distances of 2.45–2.67 Å and at angles of 132–145°. The catemer geometry is almost identical in **2a–c** and in all the other **C5** catemers in Table 2. This is an indirect indication that the C–H···O bonds are important. Notably, this *syn,anti* catemer motif is quite flat and forms a tape which is able to stack with a crystallographic short axis of $\approx$4.0 Å to allow maximum π–π stabilization.[50] The stacks are further assembled in **2a** with C–H···F interactions (between 2_1-related molecules) and in **2b** with long and bifurcated C–H···Cl bridges. In **2c**, the C–H···Br interactions are within the tape,

Table 1. Crystallographic details of the phenylpropiolic acids in this study.[a]

	2a	**2b**	**2c**	**2d**	**2e**	**2f**	**2f′**	**2g**
Emp.formula	$C_9H_5FO_2$	$C_9H_5ClO_2$	$C_9H_5BrO_2$	$C_9H_5IO_2$	$C_{10}H_8O_2$	$C_{10}H_8O_3$	$C_{10}H_8O_3$	$C_{10}H_5F_3O_2$
M_r	164.13	180.58	225.04	272.03	160.16	176.16	176.16	214.14
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
T [K]	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)	298(2)
Space group	$P2_1/n$	$P2_1$	$C2/c$	$P2_1/c$	$P2_1/n$	$P2_1/c$	$P2_1/c$	$P2_1/c$
a [Å]	3.8056(6)	3.7640(5)	14.7837(11)	4.8561(6)	7.5699(14)	7.5666(9)	8.7511(4)	13.750(3)
b [Å]	6.3411(9)	27.884(4)	3.8430(3)	28.943(3)	21.518(4)	17.373(2)	5.0628(3)	7.8640(16)
c [Å]	30.843(5)	7.5259(9)	28.983(2)	12.5658(14)	14.985(3)	7.1160(8)	19.1804(9)	8.3060(17)
α [°]	90	90	90	90	90	90	90	90
β [°]	92.520(2)	100.602(2)	103.9390(10)	99.6320(10)	92.258(3)	116.541(2)	96.490(3)	94.48(3)
γ (°)	90	90	90	90	90	90	90	90
Z	4	4	8	8	12	4	4	4
V [Å^3]	743.57(19)	776.39(17)	1598.2(2)	1741.2(4)	2439.0(8)	836.83(17)	844.34(7)	895.4(3)
D_{calcd} [g cm^{-3}]	1.466	1.545	1.871	2.075	1.309	1.398	1.386	1.589
R_1	0.0483	0.0438	0.0272	0.0362	0.0800	0.0431	0.0403	0.0374
wR_2	0.1062	0.0925	0.0569	0.0735	0.1623	0.1023	0.1064	0.0749
GOF	1.205	1.098	1.216	0.972	1.058	1.081	1.032	1.104
N total	6584	4042	8206	14683	20815	5241	8545	1747
N independent	1519	2119	1645	3403	4808	1663	2103	1569
N observed	1485	2004	1514	2605	3293	1431	1593	1206
Parameters	117	218	117	223	337	127	121	141
Structure type[b]	catemer	catemer	catemer	dimer	catemer	catemer	dimer	*syn,syn* catemer
Carboxylic group	disordered	ordered	disordered	ordered	disordered	disordered	ordered	ordered
CCDC no.	299754	299753	299752	299755	299756	299757	299758	299759

Table 1. (Continued)

	3a	**3b**	**3c**	**3d**	**3e**	**5a**	**5b**	**5c**
Emp.formula	$C_9H_5FO_2$	$C_9H_5ClO_2$	$C_9H_5BrO_2$	$C_9H_5IO_2$	$C_{10}H_8O_2$	$C_9H_4F_2O_2$	$C_9H_4F_2O_2$	$C_9H_4F_2O_2$
M_r	164.13	180.58	225.04	272.03	160.16	182.12	182.12	182.12
Crystal system	triclinic	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic	triclinic
T [K]	100(2)	223(2)	100(2)	223(2)	298(2)	298(2)	100(2)	293(2)
Space group	$P\bar{1}$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/n$	$P2_1/n$	$P2_1/n$	$P\bar{1}$
a [Å]	3.8378(6)	4.891(4)	4.7185(10)	10.2226(7)	9.611(2)	3.8159(8)	3.7382(9)	3.8186(12)
b [Å]	6.1078(9)	9.862(8)	10.078(2)	4.7960(3)	5.0139(12)	6.3305(13)	6.3729(15)	11.043(3)
c [Å]	15.695(2)	16.881(15)	10.039 (4)	18.4340(12)	17.987(4)	32.311(7)	31.479(7)	19.776(6)
α [°]	89.897(2)	90	90	90	90	90	90	81.295(5)
β [°]	85.809(2)	96.29(2)	94.373(4)	105.6790(10)	104.678(4)	91.80(3)	93.399(4)	88.697(5)
γ [°]	85.225(2)	90	90	90	90	90	90	83.603(5)
Z	2	4	4	4	4	4	4	4
V [Å^3]	365.63(10)	809.4(12)	807.9(3)	870.15(10)	838.5(3)	780.1(3)	748.6(3)	819.2(4)
D_{calcd} [g cm^{-3}]	1.491	1.482	1.850	2.077	1.269	1.551	1.616	1.477
R_1	0.0686	0.0834	0.0498	0.0444	0.0515	0.0763	0.0724	0.0699
wR_2	0.1338	0.1880	0.1224	0.1193	0.1222	0.2228	0.1524	0.1760
GOF	1.314	1.171	1.118	1.062	1.027	1.064	1.227	1.063
N total	4024	3081	4267	7217	8065	1581	4447	8347
N independent	1450	1013	1639	2171	1631	1380	1523	3208
N observed	1376	766	1482	1750	1109	852	1270	1806
Parameters	115	109	113	109	115	119	126	243
Structure type[b]	catemer	dimer	dimer	dimer	dimer	catemer	catemer	dimer
Carboxylic group	disordered	ordered	ordered	ordered	disordered	disordered	disordered	ordered
CCDC no.	299765	299764	299763	299766	299767	299745	299747	299749

	5d	**5e**	**5f**	**6b**	**6c**	**6d**	**6f**
Emp.formula	$C_9H_4F_2O_2$	$C_9H_4F_2O_2$	$C_9H_4F_2O_2$	$C_9H_4Cl_2O_2$	$C_9H_4Cl_2O_2$	$C_9H_4Cl_2O_2$	$C_9H_4Cl_2O_2$
M_r	182.12	182.12	182.12	215.02	215.02	215.02	215.02
Crystal system	monoclinic	triclinic	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
T [K]	100(2)	100(2)	298(2)	100(2)	298(2)	100(2)	100(2)
Space group	$C2/c$	$P\bar{1}$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/n$
a [Å]	12.4524(15)	3.7264(4)	6.83(2)	3.813(3)	3.875(6)	3.7809(9)	3.7901(6)
b [Å]	8.0516(10)	7.4178(9)	16.02(6)	7.405(6)	17.75(2)	6.2252(15)	15.425(2)
c [Å]	31.015(4)	14.0071(16)	17.85(6)	31.94(2)	13.627(19)	36.625(9)	15.483(2)
α [°]	90	91.260(2)	90	90	90	90	90
β [°]	101.362(2)	97.152(2)	90.11(8)	91.762(13)	90.14(2)	92.344(4)	92.098(2)
γ [°]	90	98.075(2)	90	90	90	90	90
Z	16	2	10	4	4	4	4
V [Å^3]	3048.7(7)	380.05(8)	1954(12)	901.4(12)	937(2)	861.3(3)	904.6(2)
D_{calcd} [g cm^{-3}]	1.587	1.591	1.548	1.584	1.524	1.658	1.579
R_1	0.0474	0.0410	0.1546	0.0619	0.0711	0.0396	0.0614
wR_2	0.1149	0.1043	0.3968	0.1053	0.1374	0.0907	0.1497
GOF	1.033	1.055	0.907	1.022	1.119	1.148	1.319
N total	13792	3513	11555	4809	8600	5683	8852
N independent	3119	1511	3963	1775	1789	1682	1773
N observed	2765	1295	574	1119	1300	1552	1711
Parameters	263	136	235	121	122	124	121
Structure type[b]	catemer	catemer	dimer	*syn*,*syn* catemer	dimer	catemer	dimer
Carboxylic group	disordered	disordered	disordered	ordered	ordered	disordered	ordered
CCDC no.	299761	299762	299751	299746	299749	299760	299750

[a] The data for **4a–f**, which are discussed herein, have been published previously.[35],[41] [b] Catemer here means *syn*,*anti* catemer unless otherwise stated.

and the stacks are held with weak C–H···π interactions (Figure 2). In effect, all these three acids adopt the so-called 4.0 Å short axis corrugated-sheet structure.[51]

We move now to the four other 2-substituted acids **2d–g**, which are extremely interesting, each in a different way. Let us consider the iodo acid **2d** first (Figure 3). This acid crystallizes as the dimer, but the dimer does not lie on an inversion center. Indeed, it has the very rare *cisoid* configuration, which is generally disfavored when compared to the *transoid* configuration on energetic and packing grounds. The possibility of a *cisoid* configuration for dimers of unsymmetrically substituted aromatic acids was first raised by Patil et al., who wrote that "in spite of the seeming rarity of the *cisoid* configuration, it is likely that *m*-substituted benzoic acids, under suitable conditions, may be induced to crystallize in polymorphic forms composed of acid dimers in the *cisoid* arrangement."[52] For example, *m*-nitrobenzoic acid is dimorphic with a stable *transoid* and an unstable *cisoid* form. Two features of the crystal structure of acid **2d** are then notable: 1) it is the first example of an *ortho*-substituted acid to show

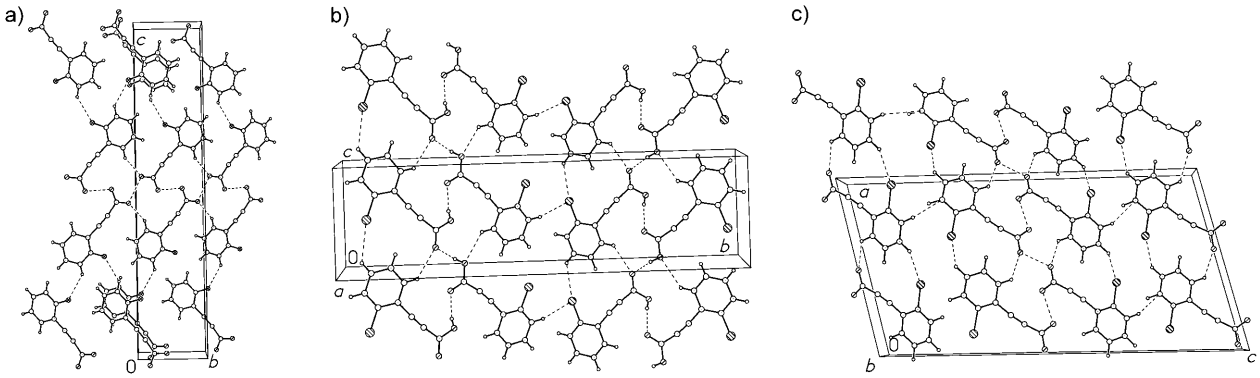
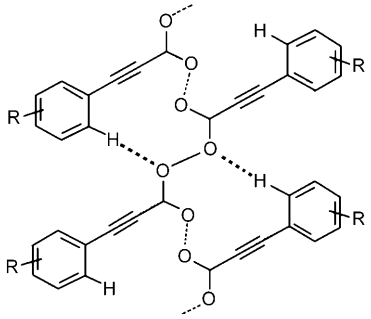


Figure 2. Catemers in a) **2a**, b) **2b**, and c) **2c**.

Table 2. Geometrical properties of the supportive C–H···O interactions (shown in bold) in acids that display the catemer motif.[a]



Acid	*d* [Å]	*D* [Å]	θ [°]
2a	2.45	3.372(2)	142
2b	2.52	3.371(4)	135.0
	2.63	3.475(4)	134.9
2c	2.66	3.483(4)	132
2e	2.62	3.489(4)	136.3
	2.64	3.603(4)	147.7
	2.70	3.652(4)	145.9
2f	2.63	3.589(2)	146.8
2g[b]	2.58	3.318(3)	125
3a	2.52	3.394(3)	137
4a	2.47	3.345(8)	136.6
4b[c]	2.53	3.47	144
4c[c]	2.43	3.37	143
4d	2.38	3.36(2)	150
	2.46	3.405(16)	145.3
4f	2.60	3.425(3)	132
5a	2.50	3.431(6)	143
5b	2.44	3.340(5)	139.7
5d	2.51	3.408(2)	139.9
5e	2.59	3.573(2)	149
6b[b]	2.62	3.399(7)	134
6d	2.40	3.327(3)	142.3

[a] Catemer here means *syn*,*anti* catemer unless otherwise stated. For definitions of *d*, *D* and θ, see reference [3a]. [b] *syn*,*syn* Catemer. [c] For esd (σ), see reference [41].

the *cisoid* configuration; 2) the acid is not polymorphic, at least not as far as we were able to conclude after the several attempts we made in this direction. Acid **2d** is centrosymmetric ($P2_1/c$, $Z'=2$), and the carboxy groups are ordered and synplanar in both the symmetry-independent molecules.

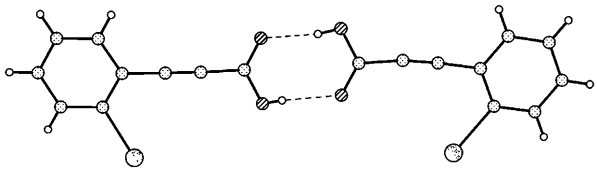
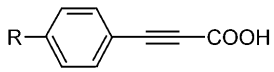


Figure 3. Cisoid dimer in **2d**.

The difference between them is that the I atom is *cis* to the C=O group in one and *trans* in the other. Short I···O interactions (3.302 Å) connect 2_1-related dimers.

In our earlier paper on the 4-substituted phenylpropiolic acids, we correlated catemer formation with the presence of an electron-withdrawing substituent.[35] The idea was that an electron-withdrawing group on the phenyl ring would activate the C–H groups sufficiently to stabilize the supportive C–H···O interactions. Accordingly, we rationalized why all the monohalogenated acids (**4a–d**) give catemers while the 4-methyl derivative **4e** gives the dimer.[53] To test this hypothesis further, we studied acids **2e** and **2f**. To our surprise, the methyl derivative **2e** forms a catemer (Figure 4). The catemers are packed in a very unusual manner. While they form planar tapes and are supported by C–H···O interactions as usual, the stacking is not infinite with a short 4.0 Å or 8.0 Å axis; rather, it takes the form of finite triads which are close-packed in the pyrene sandwich herringbone structure, in this case a triple-decker sandwich.[54] The triad lies on a center of inversion, and whereas the central catemer has carboxy-group disorder, the two outer catemers are ordered. Why this complex crystal structure is formed by a molecule that is so simple remains an unanswered question. Suffice it to say that **2e** did not yield any polymorphs in our hands. We carried out at least 50 crystallization experiments with at least 20 solvents; we never obtained a simple catemer structure of the type seen in **2a–c** or the (expected) dimer. Still, we did not give up the idea that catemer formation is favored by an electron-



4a: R = F **4d**: R = I
4b: R = Cl **4e**: R = CH_3
4c: R = Br **4f**: R = NO_2

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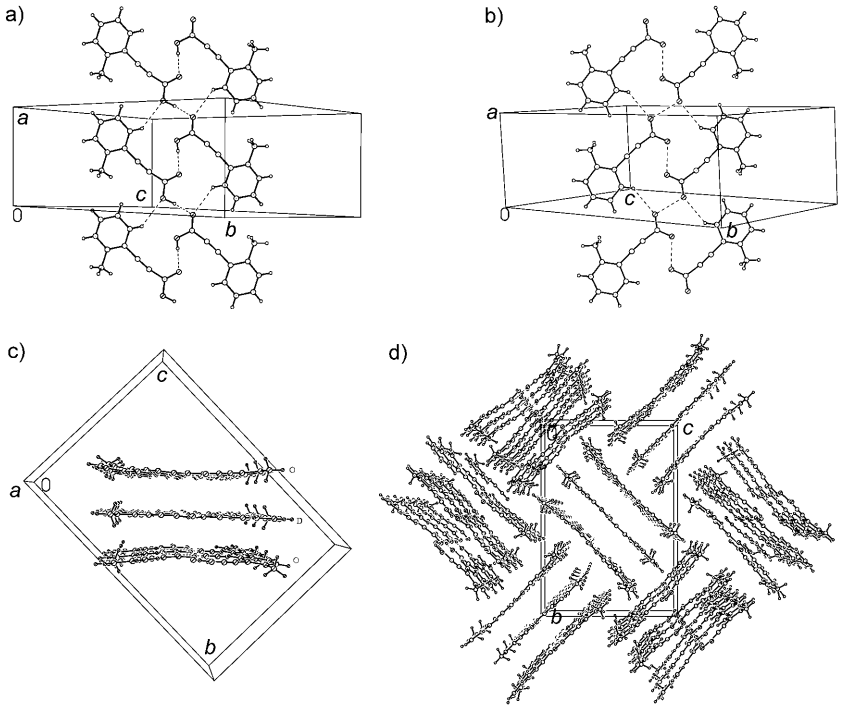


Figure 4. Packing diagram of **2e**: a) ordered catemer; b) disordered catemer; c) construction of triple-decker with two ordered (**O**) and one disordered (**D**) catemer; d) close packing of triple-deckers.

withdrawing substituent, and proceeded to study the methoxy derivative **2f**.

Acid **2f** was crystallized from EtOAc, EtOAc/hexane (1:1), and several other solvent mixtures. In all these cases, the same *syn,anti* catemer structure was routinely obtained. This structure is very similar to those of acids **2a–c** except for the fact that the catemer tapes are offset in the stacks, which in turn are steeply inclined to each other as in the structure of coronene[55] (Figure 5). The catemer was not anticipated, and as with **2e**, we began an exhaustive polymorph screening. Eventually, a dimer **2f′** was obtained, but only from aqueous EtOH. While polymorphism is a common phenomenon in small organic molecules, it is not so common in carboxylic acids, and only 51 functionally unelaborated acids are reported to be polymorphic in the CSD (out of around 3000 compounds). Among these, only two (oxalic acid and tetrolic acid) crystallize as both the dimer and the catemer, and this has been mentioned earlier in this paper. The formation of both the unexpected dimer **2f′** and the expected catemer **2f** for the methoxy acid is, therefore, noteworthy. Calculations (Cerius^2, COMPASS) showed the dimer ($E = -37.50$ kcal mol^{-1}) to be more stable than the catemer ($E = -26.27$ kcal mol^{-1}),[56] yet the catemer was obtained quantitatively in bulk samples from seven solvents in our polymorphism screen.[57] The dimer, on the other hand, was obtained from only one solvent. Is the catemer the kinetic and the dimer the thermodynamic polymorph, thus vindicating the inductive-effect model for C–H···O activation? This question is still open for debate.

Replacement of the electron-donating Me group in **2e** by the electron-withdrawing isosteric CF_3 group gives **2g**, which forms a catemer (Figure 6). However, this catemer is *syn,syn* and of the **C3** variety, resembling formic, acetic, and β-tetrolic acids. The carboxy group is ordered. As in acetic acid, the *syn,syn* catemer is supported by a C–H···O interaction, and the catemer itself is constructed with glides of axial length 7.864 Å. There is an increasing distortion of the hydrogen bond O···O distances (D) as one moves from formic acid (2.58 Å), acetic acid (2.63 Å), β-tetrolic acid (2.66 Å), and finally to **2g** (2.70 Å). This distortion may be because of the increasing bulk around the carboxy group. Adjacent catemer tapes are connected with C–H···F interactions.

Analysis of the crystal structures of **2a–g** indicates that the catemer is the preferred structure but that its formation does not seem to depend exclusively on electronic factors as was suggested in our previous study of the 4-substituted acids. In that study, we stated that the C–H groups in cubanecarboxylic acids are sufficiently

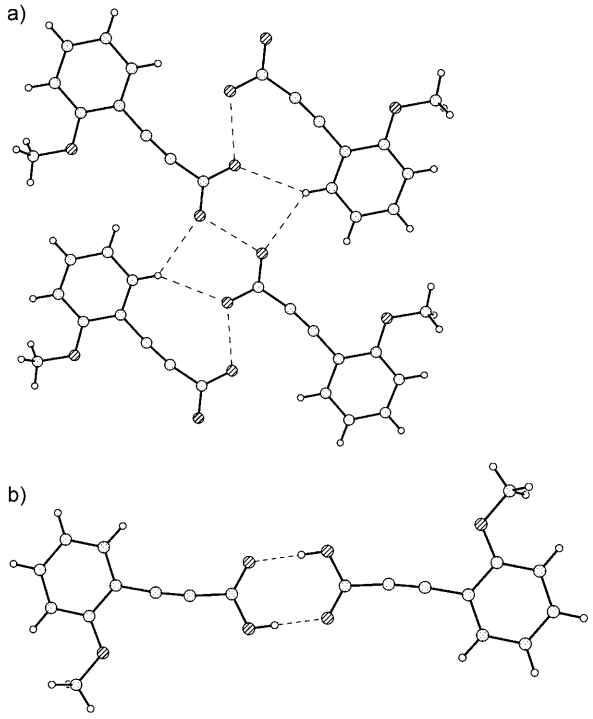


Figure 5. Polymorphism in a carboxylic acid: a) catemer of **2f**; b) dimer of **2f** (**2f′**).

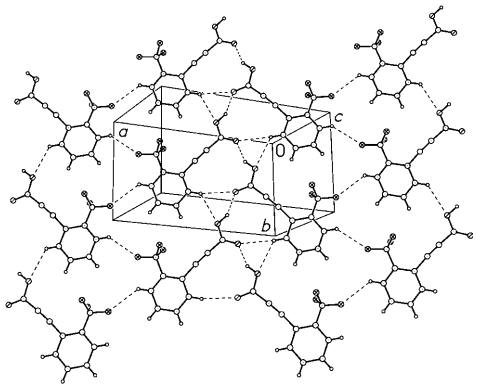


Figure 6. Ordered *syn,syn* catemer in **2g**. Note the C–H···F interactions that link adjacent chains.

activated to form good C–H···O interactions (which are required for catemer stabilization), whereas the *ortho* C–H groups in phenylpropiolic acids need extra activation from the substituents to form these interactions. In the light of the present results, we must conclude that the activation of the C–H groups in any phenylpropiolic acid is sufficient for C–H···O bond formation, possibly on account of the electron-withdrawing ethynyl group. In all the catemers seen here (**2a**–**c**, **2e**–**g**), the catemer is stabilized by a C–H···O bond with lengths of 2.45, 2.57, 2.66, 2.65, 2.63, and 2.58 Å, respectively.[58] It would seem that further activation or deactivation by the substituent (which is in a position *meta* to the pertinent C–H group) is not so crucial for the formation of the C–H···O contact because acids with both electron-withdrawing (F, Cl, Br) and electron-donating groups (Me, OMe) form catemers, although there is a rough inverse correspondence between the length of the C–H···O interaction and the electronegativity of the substituent group. The fact that the iodo derivative **2d** gives a dimer suggests that a steric effect could be involved. Careful observation of the catemer tape (Figure 7) shows that the H atom in the 3-position (*ortho* to the C–H group that forms the structure-defining C–H···O bond and *para* to the substituent group) fills the pocket formed by the substituent group, the triple bond, and the carboxy O atom of the 7.5-Å translated molecule. For all the 2-substituted acids except **2d**, this pocket is large enough to accommodate the *meta* H atom. As a result, these acids can form the catemer. In **2d**, the pocket is so small that catemer formation is impossible (if the catemer is to remain planar[59]), and a dimer results. Why this dimer is *cisoid* rather than the almost universally observed *transoid* configuration is another matter altogether. Does it mean that the dimer is an "uncomfortable" packing for this acid? Did this acid "almost" crystallize as a catemer? These questions are philosophical, and we make no further comment on the matter.

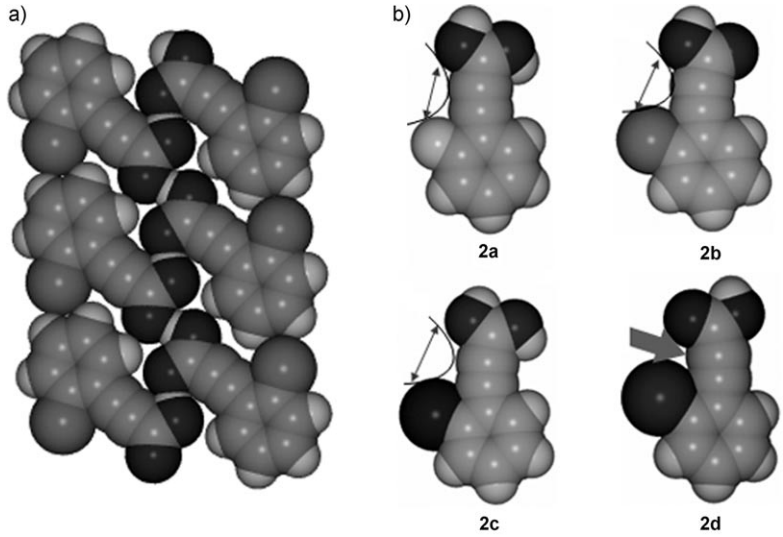
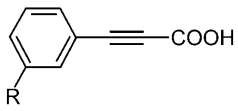


Figure 7. a) Space-filling model of catemer chain in the chloroacid **2b**. Notice the space between the Cl atom and the carboxy oxygen in which a phenyl H atom of a [001] translated molecule must fit in order to maintain the catemer. b) The space between the 2-substituent and the carboxy O atom is sufficient to sustain the catemer in **2**a–**c**, but not in the iodoacid **2d**, which forms a dimer.

3-Substituted Phenylpropiolic Acids



3a: R = F **3d**: R = I
3b: R = Cl **3e**: R = CH_3
3c: R = Br

The fluoro derivative **3a** takes the form of the *syn,anti* catemer. Instead of forming tapes which are then packed with glides and screw axes in an inclined manner as with the 2-substituted catemers, a layered structure is formed (Figure 8). This layer is mediated by a C–H···F pattern of the $R_2^2 8$ type, which is commonly seen in fluoroaromatic compounds.[60,61] The other 3-substituted acids **3b**–**e** form dimer structures that are nearly identical; this is clearly the default packing in the 3-substituted acids. We believe that the 3-substituent is *para* to the C–H group that forms the supportive C–H···O interaction, which is the requirement for the formation of the *syn,anti* catemer. Whereas the F atom can only behave as an electron-withdrawing group through an inductive effect and thereby activate C–H···O bond formation leading in turn to the catemer, the other halogens are ambivalent. Possibly any electron-withdrawing behavior of Cl, Br, and I by an inductive effect is offset by a polarization that leads to marginal transfer of electron density from the halogen atom into the ring, thus deactivating the C–H group with respect to C–H···O bond formation. These effects are seen, for example, in the regiospecificities observed for electrophilic-substi-

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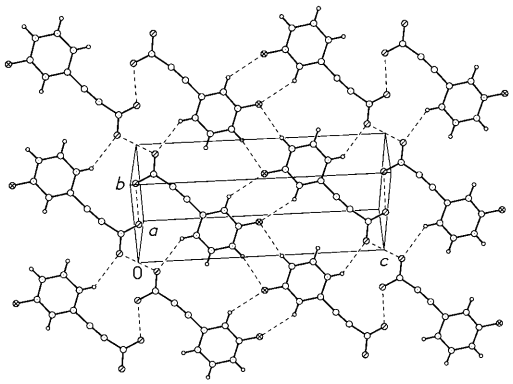


Figure 8. Catemer in **3a** showing the C–H···F (2.48 Å, 3.50 Å, 156°) mediated layer.

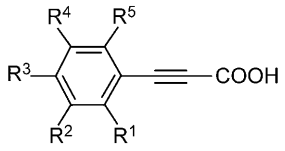
tution reactions on halogenated aromatic rings. In the methyl acid **3e**, there is a full-fledged electron-donating group in the 3-position, and the dimer is the expected structure. A comparison of the 2- and 3-substituted acids shows that the stereoelectronic effects of the substituent groups is also a function of their location in the molecular framework, which is as expected. Electronic effects are, not surprisingly, more pronounced when the substituent groups are *para* to the crucial C–H group, rather than when they are *meta*.

4-Substituted Phenylpropiolic Acids

We will be brief here because the crystal structures of acids **4a–e** have been published by us previously.[34,35] Going by the behaviour of the 2-substituted acids, there seems to be enough activation of the C–H groups in the parent phenylpropiolic acid skeleton, and any electron-withdrawing group in the 4-position (*meta* to the pertinent C–H group) can only increase this activation. Accordingly, the fluoro, chloro, bromo, iodo, and nitro derivatives take the form of the *syn,anti* catemer. An electron-donating group in this position disfavors the catemer marginally, and methyl substitution in **4e** seems to be enough to tip the balance to the dimer. Work from our group showed that 4-methoxy-, 3,4-dimethoxy, and 3,4,5-trimethoxyphenylpropiolic acids all form dimers,[53] and this is in accord with the above hypothesis. However, it is not known why the dimer is not obtained for acid **2e**, in which the Me group is also *meta* to the C–H group.

Disubstituted Acids

All possible difluoro- (**5a–f**) and dichlorophenylpropiolic acids (**6a–f**) were examined. According to our hypothesis of the requirement of a supportive C–H···O interaction for catemer formation, the 2,6-difluoro (**5f**) and 2,6-dichloro (**6f**) derivatives must form dimers because they lack a H atom at the activating position. Indeed, we found that these acids do crystallize as dimers. Furthermore, there was no evidence for a catemer polymorph in our crystallization screens. Let us consider the other difluoro derivatives (**5a–e**) next. The F



5a: $R^1 = R^2 = F$, $R^3 = R^4 = R^5 = H$ **6a**: $R^1 = R^2 = Cl$, $R^3 = R^4 = R^5 = H$
5b: $R^1 = R^3 = F$, $R^2 = R^4 = R^5 = H$ **6b**: $R^1 = R^3 = Cl$, $R^2 = R^4 = R^5 = H$
5c: $R^1 = R^4 = F$, $R^2 = R^3 = R^5 = H$ **6c**: $R^1 = R^4 = Cl$, $R^2 = R^3 = R^5 = H$
5d: $R^2 = R^3 = F$, $R^1 = R^4 = R^5 = H$ **6d**: $R^2 = R^3 = Cl$, $R^1 = R^4 = R^5 = H$
5e: $R^2 = R^4 = F$, $R^1 = R^3 = R^5 = H$ **6e**: $R^2 = R^4 = Cl$, $R^1 = R^3 = R^5 = H$
5f: $R^1 = R^5 = F$, $R^2 = R^3 = R^4 = H$ **6f**: $R^1 = R^5 = Cl$, $R^2 = R^3 = R^4 = H$

atom is small and is nearly the same size as the H atom. The monofluoroacids **2a**, **3a**, and **4a** all form *syn,anti* catemers. Accordingly, one would expect that acids **5a–e** would behave in the same manner. This is borne out in four of these acids **5a**,**b**,**d** and **e**, all of which have very similar catemer structures (Figure 9). Acids **5a** and **5b** are isostructural, and have a unit-cell similarity index parameter (Π) of 0.021.[54] In both cases, the carboxy groups are disordered, and the 2-fluoro substituent does not form any specific interactions.[62] This latter observation is not surprising since organic fluorine is a poor hydrogen-bond acceptor. The other fluoro substituent (3- in **5a** and 4- in **5b**) forms C–H···F interactions with a 2_1-related catemer stack. In the 3,4-derivative **5d** the F atom is equally disordered at the 3- and 5-positions (the carboxy group is ordered), but the packing is essentially similar to that observed in **5a** and **5b**. The 3,5-derivative **5e** forms a sheet structure (like **3a**), and the favored C–H···F dimer synthon is present. But these are all minor differences; what is important is that all these four acids take the *syn,anti* catemer with a supporting C–H···O interaction.

2,5-Difluorophenylpropiolic acid **5c** is distinctive and needs special mention because it forms the dimer. This appears to be the preferred outcome because the molecules are then able to form a layer of unusual compactness. Within this layer, all H and F atoms in the molecule are able to form hydrogen bonds (Figure 10). The carboxy group is ordered, and it is the carbonyl O atom rather than the carboxy one that accepts a C–H···O interaction (3.48 Å, 2.39 Å, 164°) from an activated C–H group, as was stated by Leiserowitz.[6] There is an isolated C–H···F interaction (3.39 Å, 2.41 Å, 150°) as well as the favored C–H···F dimer (3.52 Å, 2.48 Å, 160°). Undoubtedly, a catemer structure that is similar to the one observed in the other difluoroacids could also be envisaged for this compound. Whether this structure could compete energetically, or whether the placement of substituents is so ideal for this layered dimer structure such that no other structure is possible, is a matter for future work. This example indicates that the dimer is an occasional possibility in this family. The catemer is favored; what we are trying to establish are trends rather than certainties.

Let us consider the dichloroacids **6a–f** next. The data is limited but hints that steric factors are important with respect to catemer formation. The 2,3- and 3,5- derivatives, **6a**

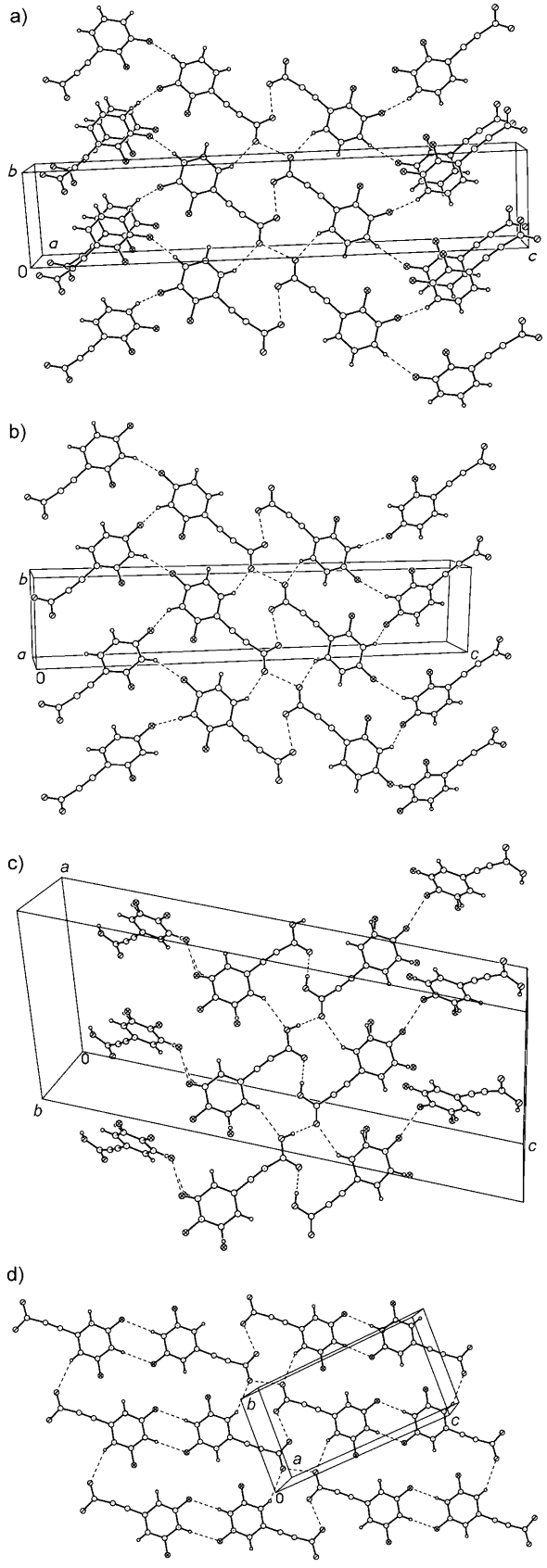


Figure 9. Catemer motif in the difluorophenylpropiolic acids a) **5a**, b) **5b**, c) **5d**, and d) **5e**. The 3-F atom in the 3,4-difluoroacid **5d** is disordered in the 5-position also, thus giving the impression of 3,4,5-trisubstitution.

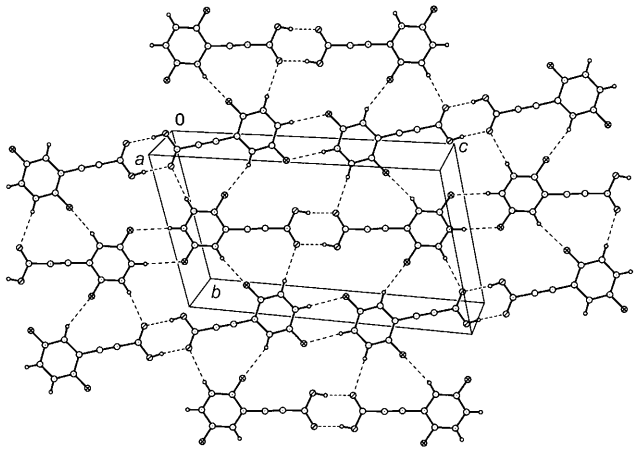


Figure 10. Dimer in **5c** showing the layer structure. Notice the C–H···O and C–H···F hydrogen bonds.

and **6e**, failed to give single crystals of diffraction quality, and the X-ray powder-diffraction spectra were too ill-resolved to permit any analysis. The 2,6-acid has been mentioned earlier. This leaves the 2,4- (**2b**), 2,5- (**2c**) and 3,4- (**2d**) derivatives. Each of these acids behaves differently, but these different outcomes may be satisfactorily rationalized. Acid **2b** forms a *syn,syn* catemer, **2c** gives the dimer, and **2d** gives the *syn,anti* catemer as it is isostructural to the difluoroacids **5a** and **5b**. It appears that chloro substitution nearer the hydrogen-bonding sites results in steric hindrance to the catemer. Therefore the 2,4- derivative gives the *syn,syn* catemer in which more space is available to the substituent group, whereas the less sterically demanding 3,4-acid gives the *syn,anti* catemer. 2,5-Disubstitution proves to be too much of a steric perturbation of the catemer, and the dimer is formed. This behavior is strongly reminiscent of the packing patterns adopted by the dichlorophenols. For the same reasons as those above, we have argued that while 2,3- and 2,4-dichlorophenols take a trigonal space group, the less-encumbered 3,4-derivative is tetragonal and the more-hindered 2,5-compound is monoclinic, all within the boundary condition of O–H···O hydrogen bonding between the phenolic OH groups.[63] We predict accordingly that **6a** will adopt the *syn,syn* catemer, but **6e** will take the form of the dimer. The larger size of the Cl relative to the F atom means that **5a–e** are slightly different from **6a–e**. Nonetheless, certain features are constant in all these disubstituted derivatives. Every catemer is stabilized by a supporting C–H···O interaction of short to moderate length.

Nature of the Supporting C–H···O Interaction

Finally, we investigated the nature of the supporting C–H···O hydrogen bonds in these catemer structures. The evidence presented so far distinctly favors the argument that the O–H···O catemer is supported by an auxiliary C–H···O interaction. Acids with electron-withdrawing substituents generally form the catemer, unless the steric factors are adverse. Except for **2e**, no acid with an electron-donating sub-

stituent forms the catemer. These observations have been rationalized on the basis of activation of the pertinent C–H group with respect to hydrogen-bond donation. However, the C–H···O interactions were also thought to be so weak that they cannot be considered to be always structure-determining.[64,65] These opinions appear to be of a cautionary nature; given the vast, even overwhelming, body of evidence that shows unequivocally the importance of weak hydrogen bonds in organic and biomolecular crystal structures,[3a] the only question must be one of degree: at what point does a "weak" hydrogen bond[66] become so weak (and nondirectional) that its effects on crystal packing are negligible.

We determined the crystal structure of one of the acids in this study at several temperatures between 100 K and room temperature. Acid **5e** was selected for this exercise because the H atom that is *ortho* to the ethynyl group, which offers the supporting C–H···O interaction, is unusually well-activated by the fluoro substituents (Figure 11). If any C–H···O interaction in this study is significant, it is the one in this particular acid. True hydrogen bonds become shorter and more linear as the temperature is decreased, and if the C–H···O contact is electrostatic enough, such behavior would be expected.[67] In contrast, repulsive and destabilizing contacts assume more-distorted geometries at lower temperatures.[68] As a control, we also examined indole-2-carboxylic acid (**1a**) at varying temperatures because there is no doubt in this case that the auxiliary interaction that supports the formation of the catemer is a true hydrogen bond, namely, an N–H···O interaction.

Let us consider **5e** first. Table 3 gives the variation in the lengths and angles of the hydrogen bonds (*D, d, θ*) as a function of temperature. There is not much angular variation, and this is accounted for by the fact that the catemer is a rigid 2D pattern. The O–H···O angles are already close to 180°, and any variation in them would cause too many distortions in the catemer itself. With respect to the hydrogen-bond lengths, all the interactions (O–H···O_{syn}, O–H···O_{anti}, C–H···O, and C–H···F) undergo significant shortening upon cooling. This indicates that all four interactions are of the attractive and stabilizing type. Notably, the difference between the maximum and minimum values for the *D* value in each case is around 17σ for the O–H···O_{syn}, 24σ for the O–H···O_{anti}, 41σ for the C–H···O, and 38σ for the C–H···F.[69] The two softer interactions are clearly more compressible. Notably, the C–H···F interaction behaves similarly to the C–H···O.

Acid **1a** provides a nice confirmation for these effects (Figure 12). Table 4 gives the corresponding geometrical properties at various temperatures. There is only one type of O–H···O bond because this is a *syn,syn* catemer. Furthermore, there is the supporting N–H···O bond and another C–H···O bond to a carboxy O atom, which may be considered as providing secondary support. All three hydrogen bonds shorten upon cooling, and Figure 12 shows that this may take place without imposing serious constraints on the packing. The maximum deformation in hydrogen-bond length is 11σ for the O–H···O, 16σ for the N-H···O, and 27σ for the C–H···O within the temperature range 100–298 K. Once again, the relative shortening increases as the bond strength decreases. In other words, the weaker the interaction, the greater the relative shortening upon cooling, but all three interactions are of the hydrogen-bond variety.

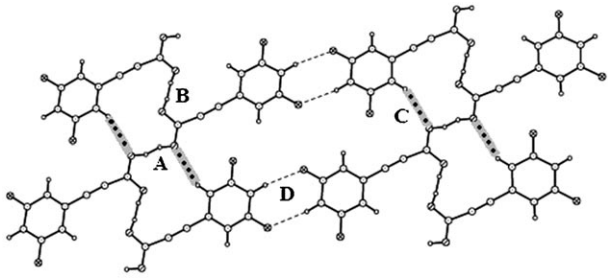


Figure 11. Catemer in 3,5-difluorophenylpropiolic acid (**5e**). Interactions labelled **A**, **B**, **C,** and **D** were monitored as a function of temperature (Table 3).

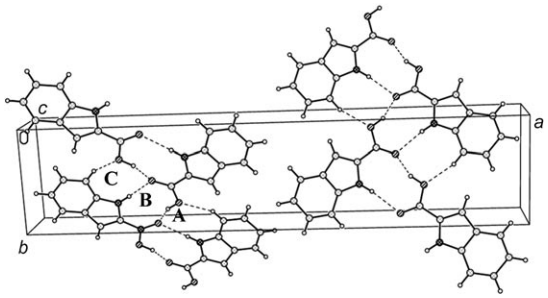


Figure 12. Packing diagram of indole-2-carboxylic acid (**1a**) showing the *syn*,*syn* catemer. Interactions labelled **A**, **B,** and **C** were monitored as a function of temperature (Table 4).

Table 3. Changes in the geometry of the hydrogen bonds with temperature for **5e** (Figure 11).

	O–H···O *syn* (**A**)			O–H···O *anti* (**B**)			C–H···O (**C**)			C–H···F (**D**)		
T [K]	*d* [Å]	*D* [Å]	*θ* [°]	*d* [Å]	*D* [Å]	*θ* [°]	*d* [Å]	*D* [Å]	*θ* [°]	*d* [Å]	*D* [Å]	*θ* [°]
100	1.75(4)	2.6257(17)	167(4)	1.81(4)	2.6112(18)	174(6)	2.71(2)	3.567(2)	150.3(17)	2.55(2)	3.485(2)	159.6(18)
140	1.70(5)	2.6311(17)	163(4)	1.78(4)	2.6112(16)	173(6)	2.69(2)	3.577(2)	150.4(13)	2.59(2)	3.499(2)	160.3(16)
180	1.65(7)	2.631(2)	164(6)	1.77(5)	2.6160(19)	165(8)	2.75(2)	3.592(2)	150.7(17)	2.60(2)	3.513(2)	160.3(19)
220	1.63(10)	2.640(2)	171(9)	1.77(7)	2.618(2)	165(8)	2.77(2)	3.609(3)	149.9(19)	2.65(3)	3.534(3)	160(2)
260	1.83(5)	2.619(3)	173(5)	1.75(7)	2.640(3)	175(8)	2.76(3)	3.619(3)	150(2)	2.66(3)	3.619(3)	150(2)
298	1.84(4)	2.624(2)	164(5)	1.72(7)	2.644(3)	170(6)	2.79(2)	3.634(3)	152.7(19)	2.62(3)	3.546(3)	159(2)

Table 4. Changes in the geometry of the hydrogen bonds with temperature for **1a** (Figure 12).

	O–H···O (**A**)			N-H···O (**B**)			C–H···O (**C**)		
T [K]	d [Å]	D [Å]	θ [°]	d [Å]	D [Å]	θ [°]	d [Å]	D [Å]	θ [°]
100	1.74(2)	2.6351(16)	155.6(18)	2.214(19)	3.0857(17)	166(2)	2.39(4)	3.3129(19)	155.0(16)
160	1.76(2)	2.6416(17)	156(2)	2.20(2)	3.0918(17)	165(2)	2.400(19)	3.323(2)	154.8(16)
220	1.75(2)	2.6471(17)	155(2)	2.20(2)	3.1014(17)	169(2)	2.409(19)	3.337(2)	156.0(16)
260	1.76(3)	2.655(2)	156(2)	2.23(2)	3.109(2)	163(2)	2.44(2)	3.347(2)	155.6(18)
298	1.79(3)	2.658(2)	156(3)	2.22(2)	3.117(2)	166(2)	2.45(2)	3.355(2)	154.7(18)

Conclusions

A number of conclusions may be drawn from this study of substituted phenylpropiolic acids: 1) the O–H···O catemer is a 1D pattern as opposed to the zero-dimensional dimer and could be favored kinetically; 2) a necessary ingredient in catemer formation in this family is a supportive C–H···O hydrogen bond from a proximal C–H group located on the phenyl ring and *ortho* to the ethynyl group. A similar supportive interaction is required in all types of catemers, and is probably the deciding factor for catemer formation in other systems, such as acetic acid; 3) catemers are uncommon because most acids cannot generate this supportive interaction; 4) in the family of acids studied herein, the very rare *syn,anti* catemer is the default packing; 5) this *syn,anti* catemer results when electron-withdrawing substituents are present on the phenyl ring and there are no adverse steric factors present; 6) when steric factors become noteworthy, alternative patterns such as the *syn,syn* catemer and, in one case, the rare *cisoid* dimer are adopted; 7) when electron-donating groups, either through inductive effect (e.g. Me) or resonance (e.g. halogens), are present on the phenyl ring, the dimer is formed in all but one case; 8) polymorphism seems not to be an issue, and we continue to maintain that any given carboxylic acid would not generally crystallize as both a dimer and a catemer.

A few questions for the future arise from this work: 1) if there is sufficient C–H activation in the propiolic acid framework, why does the unsubstituted acid crystallize as the dimer and not the catemer?[70] 2) Why does the 2-methyl derivative **2e** take the catemer structure? At a philosophical level, why is this complex triple-decker catemer structure even formed? 3) Why does the 2,5-difluoro acid **5e** adopt the dimer? 4) Are these anomalies caused by the fact that it is only in these compounds that the kinetic and the thermodynamic crystals are different? 5) Acid **2f** was shown to be polymorphic. Would more acids in the group studied here display dimer/catemer polymorphism if sufficiently intensive efforts were made?

In conclusion, a very rare interaction pattern has been reproduced in more than 15 crystal structures in a particular family of 25 carboxylic acids. This alone would provide enough justification for the detailed analysis of other packing modes in crystal engineering.

Experimental Section

The acids were prepared from the corresponding aldehydes by standard literature procedures or minor variations thereof. The methoxy acid **1f** was prepared from 2-iodoanisole. The acids were purified by column chromatography. All the acids were subjected to a polymorph screen by crystallizing them from each of the following solvents: EtOAc, EtOAc/hexane, MeCN, MeCN/CCl_4, MeCN/$CHCl_3$, MeOH/C_6H_6, $CHCl_3$/C_6H_6, AcOH, HCO_2H, EtOH/H_2O. The solutions were heated slightly and allowed to cool and stand for a day or two until crystals appeared. For each acid, crystals were selected from as many solvents as possible and mounted on the diffractometer. In every case except **2f**, only one crystal form was found. The dimorphs of **2f** are referred to as **2f** and **2f′**. Generally, AcOH and HCO_2H did not yield crystals of diffraction quality.

XRD data of **2a–f, 3a,c,e, 5b–f**, **6b–d**, and **f** were collected with a Bruker SMART APEX CCD[13] diffractometer ($Mo_{K\alpha}$ radiation, λ = 0.71073 Å) and generally at low temperature. The data were reduced by the Bruker AXS SAINTPLUS program[13] (version 6.02 A); a multiscan absorption correction was applied by using the package SADABS.[14] XRD data for **2g** and **5a** were collected with an Enraf–Nonius-MACH-3 diffractometer ($Mo_{K\alpha}$ radiation, λ = 0.71073 Å). Unit-cell parameters were determined by the least-squares fit of 25 reflections. The data were reduced with the program WinGx.[15] No absorption correction was applied. In all these cases, XPREP[16] was used to determine the space group. All the crystal structures were solved by direct methods and refined by full matrix least-squares on F^2 with SHELXTL software[17] (version 6.12 A). The positions of the hydrogen atoms bound to the phenyl ring in all the acids were generated by a riding model on idealized geometries with $U_{iso}(H) = 1.2\ U_{eq}(C)$; the H atoms of the hydroxy groups were located in difference Fourier maps, and these H atoms were also refined as riding, with $U_{iso}(H) = 1.5\ U_{eq}(O)$. The hydrogen atoms of the hydroxy groups in **2a**,**c**,**e**,**f**, **3a**,**b** and **e** were disordered over two sites with occupancies of 0.5 each. In some cases, the U values were somewhat unexpected, and this is because of poor crystal quality. This was especially true for **5f**, which yielded extremely thin (0.03 mm) and poorly diffracting crystals. All the geometry calculations were carried out with PLATON 2002.[18] XRD data of **3c** and **3d** were collected at the Universität Duisburg-Essen, Germany under the supervision of Prof. R. Boese on a SIEMENS SMART diffractometer ($Mo_{K\alpha}$ radiation, λ = 0.71073 Å). Spectroscopic and crystallographic details on all new compounds are given in the Supporting Information.

CCDC-299745–299767 contain the supplementary crystallographic data (excluding structure factors) for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at http://www.ccdc.cam.ac.uk/data_request/cif (see also Table 1).

Acknowledgements

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[58] When there is more than one supporting C–H···O interaction because of bifurcation or symmetry-independent molecules, the average value is given. Note that **2g** forms a *syn*,*syn* catemer and so the C–H···O value cannot be directly compared with the others.
[59] It is likely that planarity of the *syn*,*anti* catemer is nearly compulsory in these phenylpropiolic acids because of the π–π stabilization of tapes that can result. Every *syn*,*anti* catemer structure in this study has crystal axes of around 4.0 or 7.5 Å.
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