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Journal of Molecular Structure 474 (1999) 81–89

Journal of
MOLECULAR
STRUCTURE

Stacking of six-membered aromatic rings in crystals

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Received 6 February 1998; received in revised form 26 May 1998; accepted 26 May 1998

Abstract

Geometrical preferences of stacking and the possibilities and limitations of using stacking in designing crystal structures have been analyzed, based on the crystal structures of benzenes, pyridines and *s*-triazines. It is shown that crystallographic symmetry imposes severe restrictions on stacking parameters and that alteration of the π-electron distribution in the aromatic ring by incorporation of heteroatom(s) significantly increases the possibility of stacking. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Stacking; stacking parameters; crystallographic restrictions on stacking; aromatic hydrocarbons

1. Introduction

Crystal-structure engineering is a fast expanding field of crystallography. It attracts considerable attention due to the possible development of novel materials. The most recognized method of designing structural architecture is the use of molecular motifs capable of hydrogen-bond formation. Other less directional types of intermolecular interactions are generally less effective. However, stacking can display distinct ordering power, especially in structures consisting of aromatic rings. Fig. 1 shows a crystal structure built of aromatic 4-oxocinnoline-3-carboxylate anions, sodium cations and water molecules [1]. In this case both hydrogen bonds and parallel arrangements of aromatic systems are equally important (Fig. 1).

Our interest in stacking was aroused by the observation that *s*-triazine analogs of benzene show different packing. For example 2,4,6-trimethoxy-1,3,5-triazine shows threefold molecular symmetry in the crystal state [2,3] while 1,3,5-trimethoxybenzene crystallizes with asymmetric methoxy group orientations [4–6] (Fig. 2).

Even more interesting was that we could not crystallize the other polymorphic form either for *s*-triazine or for benzene derivative. We suppose that the explanation lies in different stacking preferences for the two aromatic systems (Fig.3). As we show later, *s*-triazines display smaller displacement, which permits the preservation of higher molecular symmetry in crystals, while benzene derivatives display larger displacements; this in turn correlates with a flip of one methoxy group to maintain more compact structures (maximal packing efficiency). Actually, in the case of trimethoxybenzene, the two parallel rings do not overlap but the π system is larger than the ring as it also includes lone electron pairs at oxygen atoms (Fig. 3).

2. What is stacking?

Stacking is a special vertical arrangement of aromatic (π) systems characterized by their parallel

PII: S0022-2860(98)00562-6

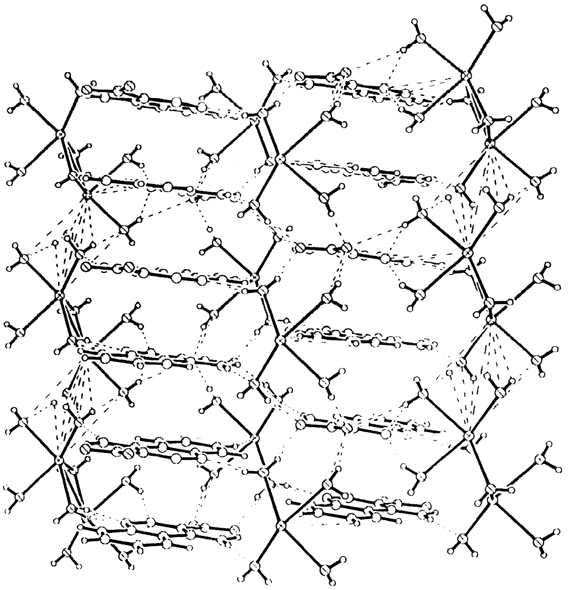

Fig. 1. A crystal structure [1] with packing governed by both hydrogen bonds and stacking. Parallel aromatic cynnoline systems are packed in columns separated by channels filled with heavily hydrated sodium anions. Anionic carboxylate groups make hydrogen bonds with water, occupying hydrophilic channels.

orientation, with a van der Waals distance of about.3.5Å (for the carbon skeleton) and overlapping at least partially (note that parallel arrangement of aromatic rings, which seems to be obviously preferred for planar molecules, is an insufficient requisite for stacking). The best known example of stacking is that observed in nucleic acids. However, geometrical analysis of stacking in nucleic acids is complicated because neighboring bases may differ (heterostacking or heterogenous stacking). Stacking is observed both in solution and in the solid state but further discussion will concern only the crystal state and homostacking. This allows us to utilize for stacking analysis a vast stock of experimental material gathered in the Cambridge Structural Database (CSD) [7] with unequivocal description of the molecular geometry.

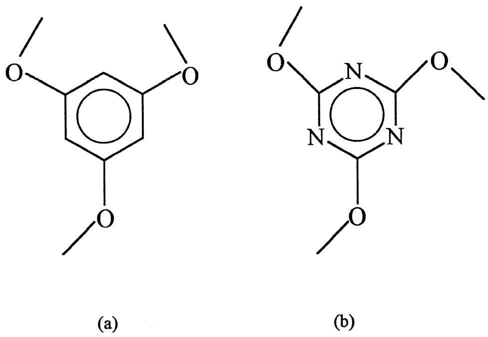

Fig. 2. Conformations of methoxy substituents in 1,3,5-trimethoxybenzene (a) and 2,4,6-trimethoxytriazine (b).

Stacking is quite common in the crystal state. For example, about 30% of benzenes, about 60% of pyridines, and over 70% of *s*-triazines listed in the CSD show stacking.

3. Packing, stacking and intermolecular interactions between parallel aromatic π-systems

Aromatic hydrocarbons are convenient models for analysis and prediction of their crystal structures and intermolecular interactions due to their well-defined and fixed molecular shapes (no conformational freedom). Desiraju and Gavezzotti have shown that packing arrangements of aromatic hydrocarbons depend on the number and positioning of C and H atoms in a molecule [8–11]. The lack of substituents, which strongly affect electron distribution or enable strong hydrogen-bond formation, makes possible the prediction of crystal packing of simple aromatic hydrocarbons but generally it is possible only for selected cases. Besides an obvious ''geometrical'' tendency of aromatic systems to pack in parallel (efficiency of space filling), there are three major interactions types between them, of which only two are related to parallel orientations (and stacking). Unfortunately, all these interactions fall within the same energy ranges and only in selected cases a dominant force may be indicated:

1. π–π electron interation is an important repulsive force, which is roughly proportional to the area of π-overlap. Of course, displacement of π systems diminishes the repulsion.
2. π–σ interaction, between π electrons of one ring and the σ-framework around the inner edge of the cavity of the other ring above is attractive and is maximized in the displaced stacking also.
3. C–H...π, C–H...C etc. Coulombic interactions, which depend on net charge distribution and

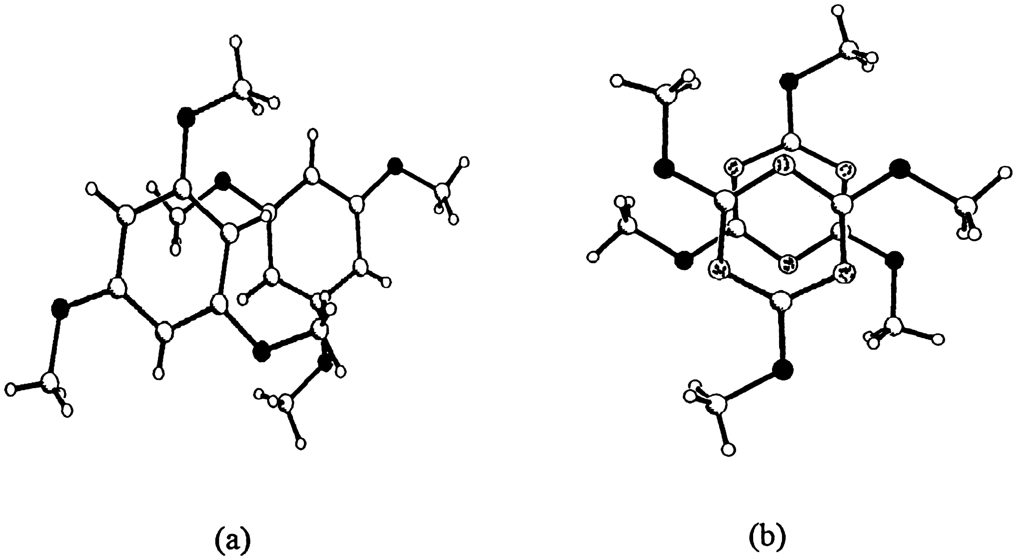

Fig. 3. Stacking of 1,3,5-trimethoxybenze (a) and 2,4,6-trimethoxytriazine (b) shown perpendicularly to the mean planes of the rings.

usually are responsible for the T-shape arrangement (Fig. 4).

This may also explain a lack of structures without displacement (Fig. 11(a)) observed in monosubstituted benzenes.

4. Cambridge Crystallographic Database as a tool for stacking analysis

Although CSD is a vast source of information on molecular and crystal structures, it has several severe limitations when used for stacking analysis [7]. Firstly, most aromatic compounds collected in CSD are not simple hydrocarbons. They merely comprise an aromatic system (ring) and thus prediction of their packing arrangement is extremally difficult. What is worse, in some cases substitution(s) of the aromatic system may exclude stacking completely. Secondly, the crystal state imposes limitations on the packing arrangement, mostly related to crystallographic symmetry. (For example, the twist φ of stacked six-member aromatic rings is restricted to the value of 60° or its multiciplicity). Thirdly, the CSD is not a good statistical representation of chemical categories. Some groups of compounds or substituents are over-populated, some are underpopulated, and many are absent. Importance, fashion, ease of crystallization or synthesis might be the deciding factor of ‘‘popularity’’. Of course, the last remark concerns generally all *analyses* based on CSD data.

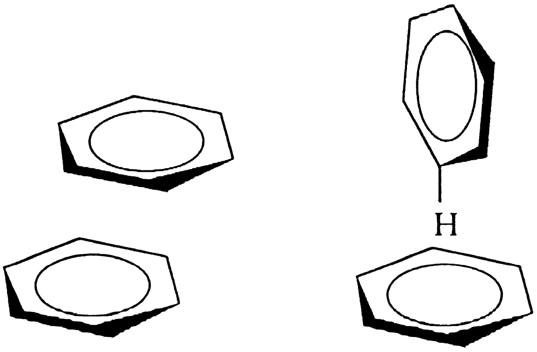

Fig. 4. The two most common arrangements of single aromatic hydrocarbons: parallel displaced and T-shaped.

5. Stacking parameters

Generally, to describe unequivocally the relative orientation of two six-membered rings, six

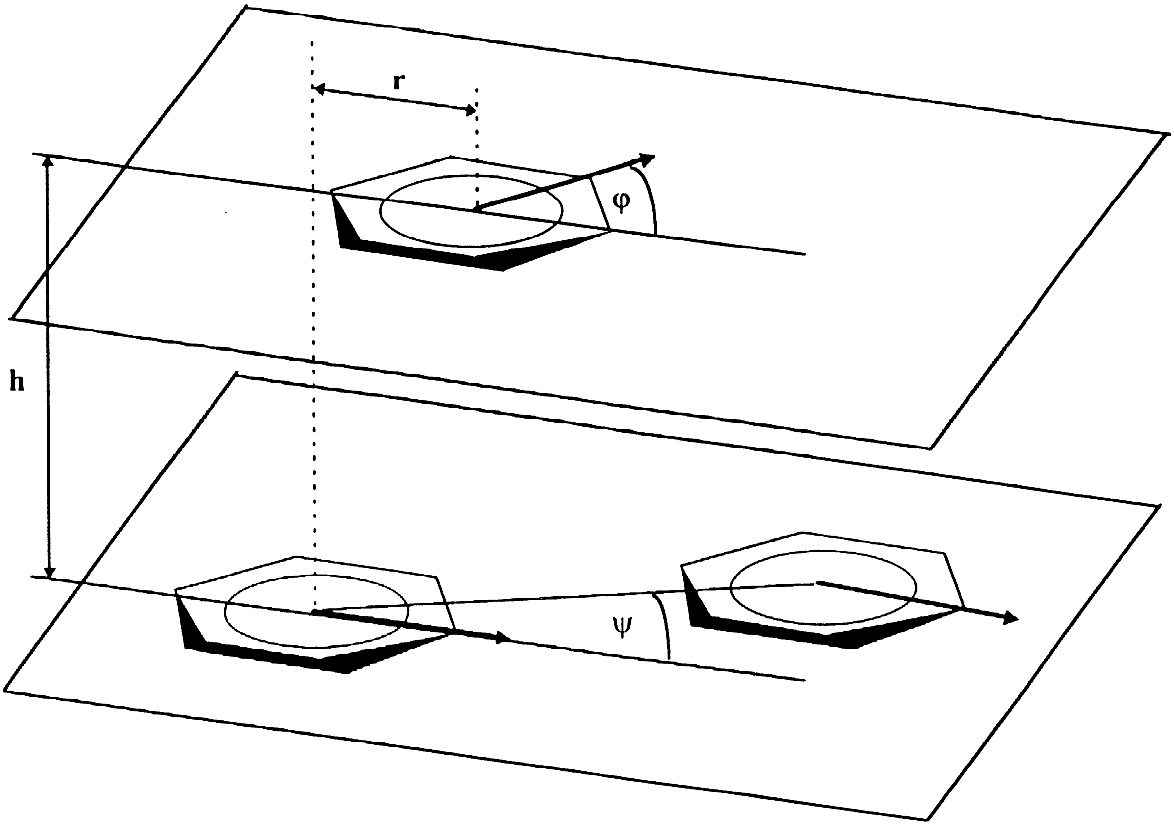

Fig. 5. Stacking parameters.

geometrical parameters are needed (Fig. 5). Practically, the direction of inclination of one ring in relation to the other one is not important, and thus five parameters are sufficient:

1. *Stacking distance h* is the distance between the centre of one ring and a plane defined by the neighboring ring. In the case of parallel rings, this is called the *separation* of rings (planes).
2. *Shift* r (*displacement, offset*) equals the distance between the two centres projected on a plane defined by atoms of one ring.
3. Inclination θ(*tilt*) of one ring plane in relation to the other ring plane.
4. *Twist* ϕ of one ring in relation to the other ring. The reference atom (line) is chosen here arbitrarily (Fig. 6).
5. Direction ψ of the shift r in relation to the chosen, specific direction.

6. Restrictions imposed on stacking parameters

As a result of crystal and molecular symmetry and the chemical properties of atoms, only some (range) of values of stacking parameters are possible or preferred.

h	is the sum of van der Waals radii of ring atoms. In the case of benzene rings, h should be about 3.5 Å as a carbon atom has a van der Waals radius between 1.72–1.80 Å [12]. Resulting from substituents, which may be bulky and/or which affect the π-electron distribution, a wide range of h values were observed (Fig. 7).
r	Stacking requires the two aromatic π systems to overlap and maximal displacement is usually determined by the

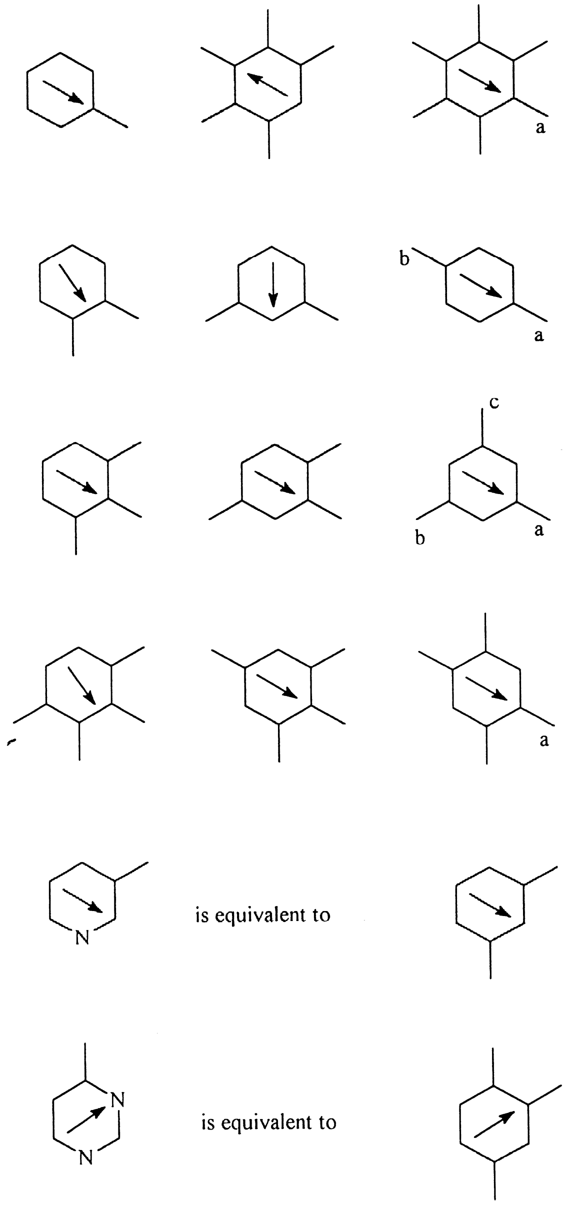

Fig. 6. Calculation of twist φ requires distinction of one atom (or line) called here ''direction''). Our choice of proposed ''directions'' for benzene, pyridine, pyrimidine and *s*-triazine derivatives is shown. Only substituents other than H are shown and aromatic bonds are omitted for clarity. The ''direction'' is indicated by an arrow. In case of different, symmetrically located substituents, Ingold and Prelog rules (a > b > c) of choice are recommended.

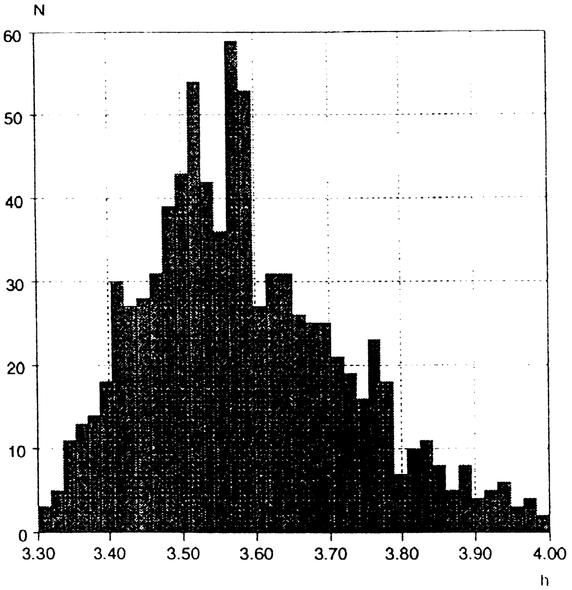

Fig. 7. Distribution (histogram) of *h* value in crystal structures of stacked monosubstituted benzene derivatives.

size of the stacked rings. In the case of six-membered rings, $r_{\max}$ is about 2.8 Å (double the distance between the centre and a ring atom). However, a substituent with lone pair(s), which may conjugate with a π system, will enlarge the limit of possible overlap in the direction of the substituent.

θ In a crystal, stacked molecules should be exactly parallel, to minimize π-system repulsion[1]. Errors in the determination of ring-atom coordinates may result in an apparent non-zero value of θ (Fig. 8). (For example, in the case of $\delta(x,y,z) \backsim 0.03$ Å; $\delta(\theta) \backsim 2°$). Structures in which aromatic systems are not exactly parallel (say less than 10°), form distinct clusters (Fig. 9(a,b)).

ϕ As the stacked rings are usually symmetrically related, only specific values of twist φ

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[1] Slight deviations from $\theta = 0°$ are possible both for symmetrically independent and for symmetrically related rings (not by a centre of symmetry).

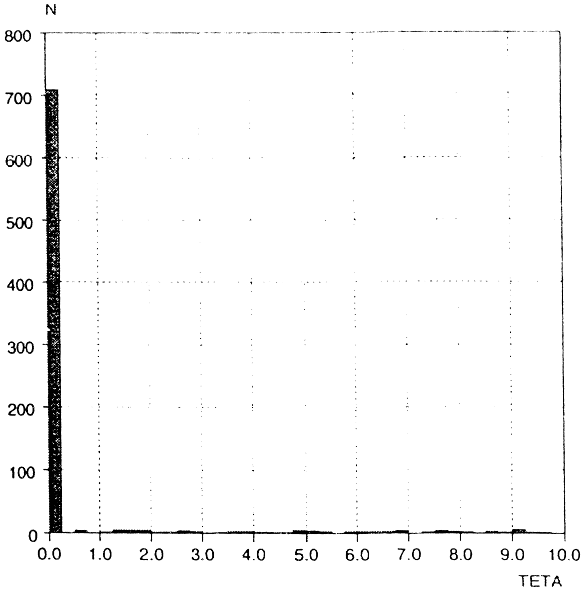


Fig. 8. Distribution (histogram) of θ value in crystal structures of stacked monosubstituted benzene derivatives.

and direction ψ angles are allowed. In 125 crystal structures of 2,4,6-trisubstituted – 1,3,5-triazines, we found 21 examples with $\varphi = 0°$ or 120° (C atoms are over C atoms, N over N), 104 examples with $\varphi = 60°$ or 180° (C over N) (Fig. 10c).[1]

ψ Directions of shift observed in the crystal state are strictly related by crystallographic symmetry (molecular symmetry is less important).

A detailed analysis of φ and ψ parameters will be reported in a separate paper.

Although most of the restrictions on the last two parameters result from crystal symmetry, molecular symmetry of stacked molecules is also important. For example, mono-C(sp^3)-substituted benzene derivatives show very different distribution of φ, as compared with trisubstituted benzenes (Fig.11).

7. Influence of N heteroatoms on stacking of the six-membered aromatic rings

Replacement of the CH group by an N atom in the aromatic six-membered ring visibly affects all stacking-parameter distributions and characteristics. Presence of an N atom in an aromatic system induces differentiation of π (and σ) electrons distributions. It should affect displacement r of stacked rings and may be shown by comparing appropriate analogs. For example, crystal structures of monosubstituted benzenes show a minimum h of 3.31, and an average 3.57 Å. Nitrogen-containing aromatic rings show smaller stacking separation because the van der Waals radius for N is smaller than that for C. As an obvious result, pyridines (unprotonated) have a h minimum 3.17 and average 3.50 Å, and corresponding values for *s*-triazines are 3.31 and 3.51 Å.

Protonation, possible in the case of nitrogen incorporated into an aromatic ring, is also a very important factor affecting stacking (Fig. 12).

Evidently, the number and positions of N atoms in the aromatic ring influence packing preferences for the nearest neighbors. Even so, it is surprising that nearly-parallel arrangements (Fig. 9) are less common for pyrimidine derivatives than for pyridine [Population differences between the two data sets have been taken into account], and are not observed at all for *s*-triazine crystal structures (Fig. 13).

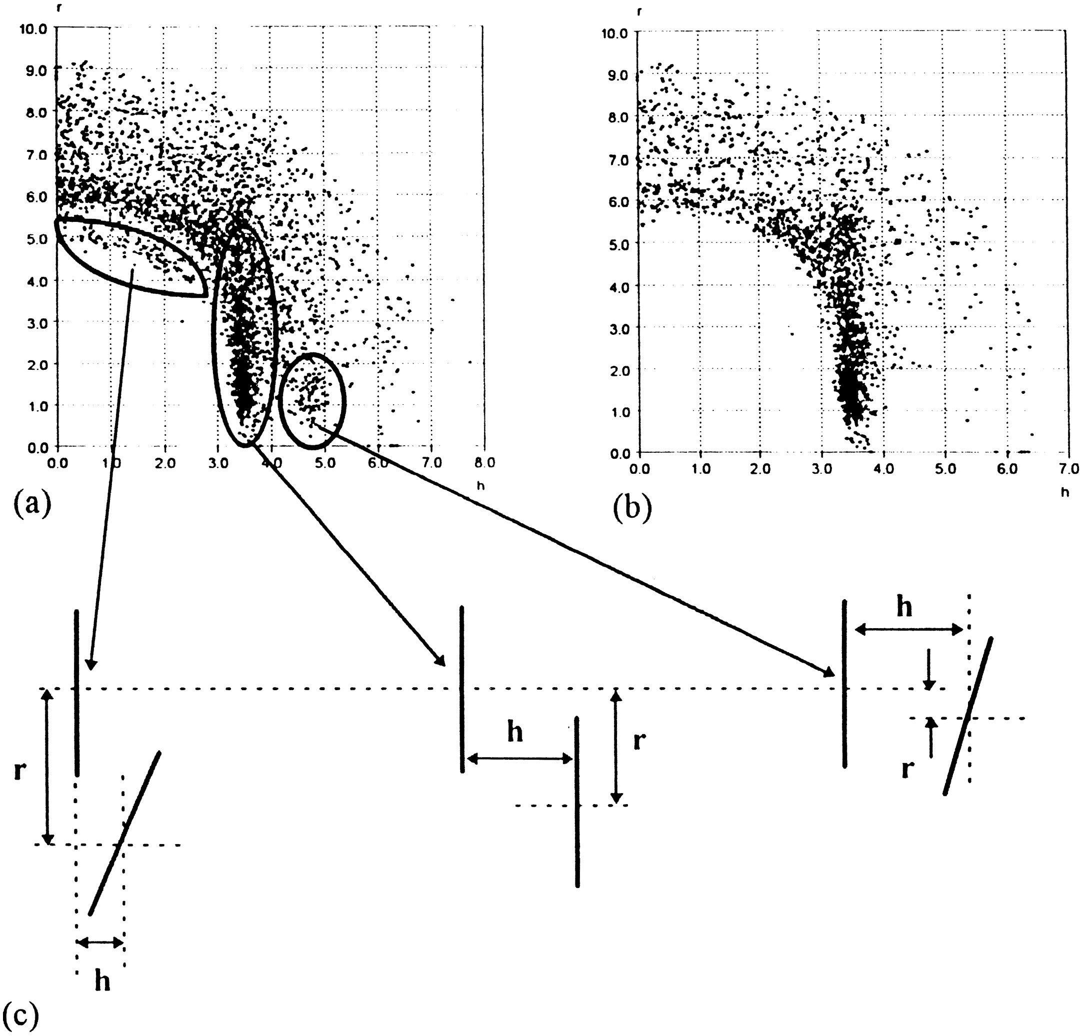


Fig. 9. Packing arrangements in the crystal state of pyridine rings in case of excessive deviation of θ angle from 0°. (a) $\theta \leq 10°$, (b) $\theta \leq 2°$, (c) ring orientations for clusters shown in the scatterogram (a).

8. Conclusions

Stacking of aromatic rings is a common phenomenon in crystals, unless bulky substituents prevent parallel arrangement at a van der Waals distance. The Cambridge Structural Database is a rich but biased source (for the population of a particular class of compounds) of stacking in the crystal state. Molecules containing nitrogen atom(s) in the aromatic rings show a significantly higher population of crystal structures with stacking. Heteroatoms in an aromatic system induce differentiation of (and) electron distributions; thus they influence stacking-type preferences. In parallel, stacked aromatic-system arrangements, displacement of the rings favors minimization of repulsive π–π interaction and maximization of

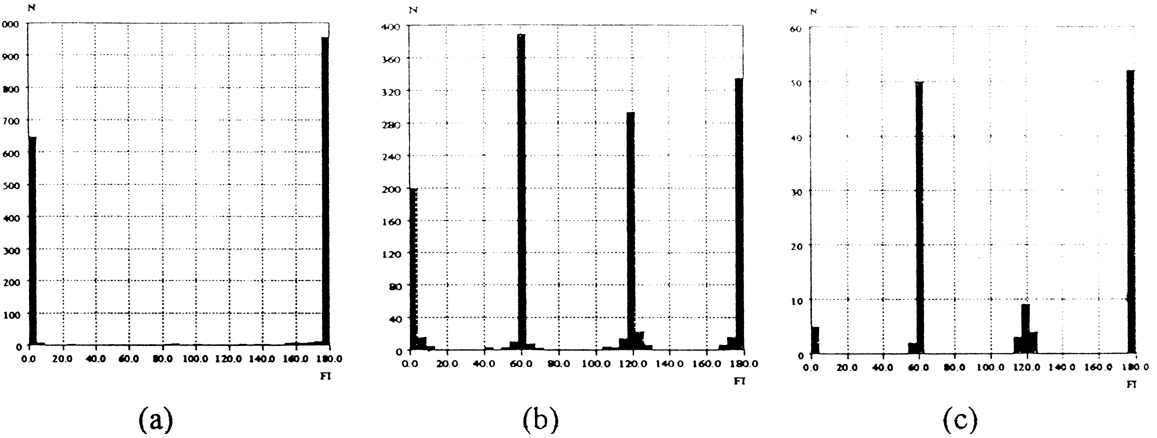


Fig. 10. Distribution (histogram) of φ values in crystal structures of stacked mono-C$(sp)^3$-substituted benzenes (a),1,3,5-tri-C(sp^3)-substituted benzenes (b) and 2,4,6-trisubstituted-1,3,5-triazines (c).

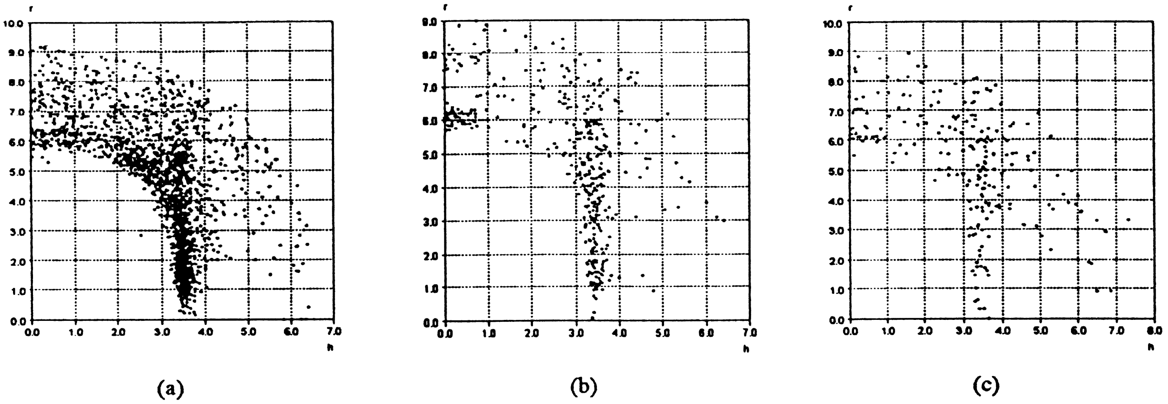
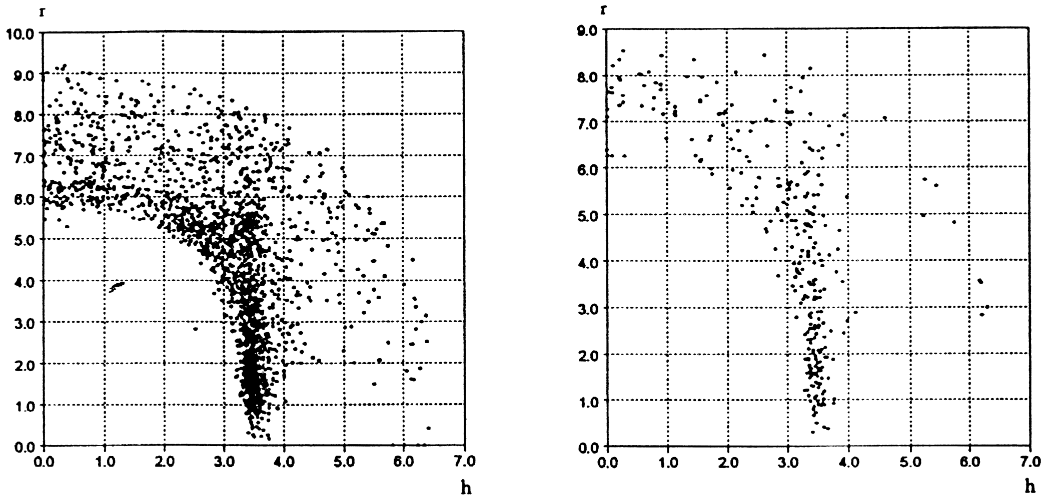


Fig. 11. Scatter plots of *r* versus h in crystal structures of stacked monosubstituted benzene (a), pyridines (b) and 1,3,5-triazine (c) derivatives.

attractive interactions. Thus perfect stacking ($r = 0$, $\varphi = 0°$) is very rare. The crystal state imposes severe limitations on angular stacking parameters. Errors in experimental determination of ring-atom positions may result in apparent inclination of stacked rings up to 2°, even in the case of rings symmetrically related (except by a centre of symmetry). Stacking may be utilized to design the molecular arrangement in the crystal state, especially when strong hydrogen bonds are not possible or absent.

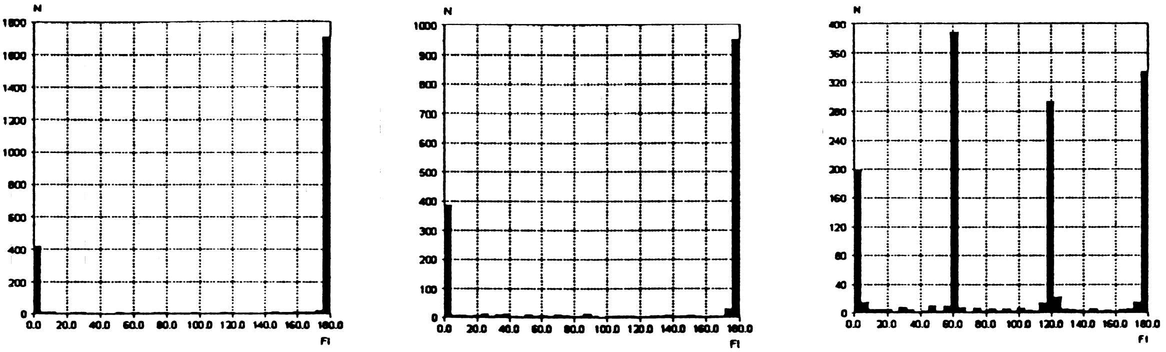
Acknowledgements

The work was supported by the State Committee for Scientific Research (KBN), under grant No. 3 T09A 035 12.



(a) (b)

Fig. 12. Scatter plots for unprotonated (a) and protonated (b) pyridine crystal structures.



(a) (b) (c)

Fig. 13. Populations of ϕ angles in crystal structures of pyridine (a), pyrimidine (b) and *s*-triazine (c) derivatives, with $\theta \leq 10°$.

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