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**Packing interactions of crystallographically independent molecules in organic crystals.** By P. KARTHE, C.

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**Abstract**

An analysis of packing interactions has been carried out on 18 structures which possess two crystallographically independent molecules in the asymmetric unit each with a similar molecular conformation. The intermolecular interaction energy of each of the two molecules with each of its neighbours was calculated. The results indicate that the two molecules have a very similar interaction energy with their respective crystalline environments, with no particularly strong interaction between the two different molecules *A* and *B*.

**Introduction**

The packing of organic molecules in crystals has received much attention after the pioneering work of Kitaigorodskii three decades ago (Kitaigorodskii, 1961). A lot of this attention has been focused on attempts to explain the space-group distribution of reported crystal structures (Wilson, 1988). Other studies have sought to exploit packing principles in the design of solid-state reactions and new materials (Desiraju, 1989). We have been interested in crystal packing from the point of view of rationalizing the occurrence of two or more crystallographically independent molecules in the asymmetric unit as a function of the interactions of each molecule with the crystal environment. Padmaja, Ramakumar & Viswamitra (1990) have shown that about 8.3% of the structures in the Cambridge Structural Database (CSD; Allen *et al.*, 1979) have a *Z* value greater than the crystallographic multiplicity. About 3–12% of these may be due to an incorrect choice of the space group or the crystal system (Mighell, Himes & Rodgers, 1983; Baur & Tillmanns, 1986; Marsh & Herbstein, 1983). An unestimated but probably small (~10%; Desiraju, Calabrese & Harlow, 1991) fraction of the rest may be related by elements of pseudosymmetry. From the point of view of the interactions of the molecules with their neighbours and the packing energies, these latter examples can probably be considered very similar to crystal structures where a single molecule makes up the asymmetric unit.

Of the remaining examples, if the multiple molecules in the asymmetric unit are conformationally dissimilar, one may consider them as different molecular species for packing purposes. The situation would then be similar to crystals of molecular complexes. However, we wished to

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Table 1. *R.m.s. deviation of superposition of the two molecules in the asymmetric unit*

CSD refcode	Formula	R.m.s. deviation (Å)	<i>R</i>	Space group	Reference
AHGULP10	C <sub>6</sub> H <sub>6</sub> O <sub>4</sub>	0.052	0.0310	<i>P</i> 2 <sub>1</sub> ,2 <sub>1</sub>	Berking & Seeman (1971)
ANFFUR	C <sub>6</sub> H <sub>10</sub> O <sub>5</sub>	0.0241	0.0280	<i>P</i> 2 <sub>1</sub> ,2 <sub>1</sub>	Dreissig & Luger (1973)
ARAFPY10	C <sub>10</sub> H <sub>11</sub> NO <sub>5</sub>	0.5678	0.0500	<i>P</i> 2 <sub>1</sub> ,2 <sub>1</sub>	Hutcheon & James (1977)
BERZUT	C <sub>6</sub> H <sub>6</sub> O <sub>4</sub>	0.0765	0.0450	<i>P</i> 2 <sub>1</sub> ,2 <sub>1</sub>	Koll <i>et al.</i> (1982)
BIFTIF	C <sub>6</sub> H <sub>10</sub> O <sub>5</sub>	0.1614	0.0360	<i>P</i> 2 <sub>1</sub> ,2 <sub>1</sub>	Maluszynska <i>et al.</i> (1982)
BUJHAP	C <sub>9</sub> H <sub>13</sub> O <sub>3</sub>	0.2278	0.0538	<i>P</i> 2 <sub>1</sub>	Marni-Bettolo <i>et al.</i> (1983)
BUYROC10	C <sub>6</sub> H <sub>14</sub> O <sub>4</sub>	0.4179	0.0290	<i>P</i> 2 <sub>1</sub> ,2 <sub>1</sub>	Wingert <i>et al.</i> (1984)
COSGUM	C <sub>10</sub> H <sub>13</sub> NO <sub>4</sub>	0.7880	0.0490	<i>P</i> 2 <sub>1</sub>	Neuman <i>et al.</i> (1984)
CULCUH	C <sub>13</sub> H <sub>17</sub> O <sub>4</sub>	0.1037	0.0740	<i>P</i> 2 <sub>1</sub> ,2 <sub>1</sub>	Mulzer <i>et al.</i> (1985)
DUDMIY	C <sub>10</sub> H <sub>12</sub> O <sub>8</sub>	0.1089	0.0430	<i>P</i> 2 <sub>1</sub>	Fodor <i>et al.</i> (1986)
FABFUJ01	C <sub>7</sub> H <sub>9</sub> N <sub>3</sub> O	0.1230	0.0450	<i>P</i> 2 <sub>1</sub> ,2 <sub>1</sub>	Takenaka <i>et al.</i> (1986)
FMFCHR	C <sub>11</sub> H <sub>13</sub> O <sub>5</sub>	0.2838	0.0480	<i>P</i> 2 <sub>1</sub>	Bravic & Bideau (1980)
INOSIN11	C <sub>10</sub> H <sub>12</sub> N <sub>4</sub> O <sub>5</sub>	0.7564	0.058	<i>P</i> 2 <sub>1</sub> ,2 <sub>1</sub>	Subramanian (1979)
IPDGLF	C <sub>9</sub> H <sub>12</sub> N <sub>2</sub> O <sub>6</sub>	0.7357	0.0260	<i>P</i> 2 <sub>1</sub>	Takagi & Jeffrey (1979)
LEUCINO1	C <sub>6</sub> H <sub>13</sub> NO <sub>2</sub>	0.0084	0.058	<i>P</i> 2 <sub>1</sub>	Coll <i>et al.</i> (1986)
MXLPYR	C <sub>6</sub> H <sub>13</sub> O <sub>5</sub>	0.0741	0.031	<i>P</i> 2 <sub>1</sub>	Takagi & Jeffrey (1978)
STERIG	C <sub>11</sub> H <sub>10</sub> O <sub>6</sub>	0.0708	0.030	<i>P</i> 1	Fukama <i>et al.</i> (1975)
TYMCXA	C <sub>10</sub> H <sub>12</sub> N <sub>2</sub> O <sub>6</sub>	0.0667	0.039	<i>P</i> 2 <sub>1</sub>	Suck <i>et al.</i> (1974)

Table 2. *Total interaction energy (kJ mol<sup>-1</sup>) of each of the two molecules in the asymmetric unit with all its neighbours*

Refcode	Molecule <i>A</i>		Molecule <i>B</i>		Difference (%)
	No. of neighbours	Total energy	No. of neighbours	Total energy	
AHGULP10	14	-208	14	-202	2.9
ANFFUR	14	-380	14	-353	7.4
ARAFPY10	16	-479	14	-436	9.4
BERZUT	14	-235	14	-209	11.7
BIFTIF	13	-274	13	-267	2.6
BUJHAP	13	-59	13	-85	36.1
BUYROC10	15	-291	17	-332	13.1
COSGUM	15	-200	13	-291	37.0
CULCUH	16	-421	14	-400	5.0
DUDMIY	14	-319	14	-307	3.8
FABFUJ01	14	-367	14	-373	1.6
FMFCHR	14	-231	16	-222	4.0
INOSIN11	16	-475	18	-426	10.9
IPDGLF	16	-339	16	-345	1.8
LEUCINO1	14	-629	14	-650	3.3
MXLPYR	13	-359	13	-328	9.0
STERIG	15	-174	15	-173	0.6
TYMCXA	13	-345	13	-298	14.6

Table 3. Strongest interaction energy ( $\text{kJ mol}^{-1}$ ) of each of the two molecules in the asymmetric unit with a neighbour

Refcode	Molecule			Molecule		
	A with	Related by	Energy	B with	Related by	Energy
AHGULP10	A	$-1/2 + x, 3/2 - y, -z$	-31	A	$1/2 + x, 1/2 - y, -z$	-23
ANFFUR	A	$x, y, 1 + z$	-50	B	$1/2 - x, 1 - y, -1/2 + z$	-51
ARAFPY10	B	$1/2 + x, 1/2 - y, -z$	-119	A	$-1/2 + x, 1/2 - y, -z$	-119
BERZUT	A	$1 - x, -1/2 + y, 3/2 - z$	-41	A	$x, y, z$	-25
BIFTIF	B	$-x, 1/2 + y, 1/2 - z$	-35	A	$-x, -1/2 + y, 1/2 - z$	-35
BUJHAP	B	$-x, 1/2 + y, 1 - z$	-37	A	$-x, -1/2 + y, 1 - z$	-37
BUYROC10	A	$1/2 - x, -y, 1/2 + z$	-49	A	$x, y, z$	-43
COSGUM	B	$1 - x, -1/2 + y, 2 - z$	-65	A	$1 - x, 1/2 + y, 2 - z$	-65
CULCUH	B	$1/2 + x, 1/2 - y, 1 - z$	-243	A	$-1/2 + x, 1/2 - y, 1 - z$	-243
DUDMIY	A	$1 + x, y, z$	-53	B	$-1 + x, y, z$	-40
FABFUJ01	B	$x, y, z$	-64	A	$x, y, z$	-64
FMFCHR	B	$x, y, z$	-60	A	$x, y, z$	-60
INOSIN11	B	$x, y, -1 + z$	-152	A	$x, y, 1 + z$	-152
IPDGLF	A	$1 + x, y, z$	-76	B	$-1 + x, y, z$	-80
LEUCIN01	B	$1 - x, 1/2 + y, 1 - z$	-155	A	$1 - x, -1/2 + y, 1 - z$	-155
MXLPYR	A	$1 - x, -1/2 + y, -z$	-45	B	$1 - x, -1/2 + y, 1 - z$	-58
STERIG	A	$-x, y, -1 + z$	-54	B	$x, y, 1 + z$	-52
TYMCXA	B	$1 + x, y, z$	-114	A	$-1 + x, y, z$	-114

study those cases where the same molecular species crystallizes with more than one molecule in the asymmetric unit. Previous studies in our laboratory (Sona & Gautham, 1992; Gautham, 1992) have estimated the amount of conformational similarity between two crystallographically independent molecules. This was done by calculating the r.m.s. deviation in the atomic coordinates after superposing the two molecules. It was shown that the two molecules possess very much the same conformation in a large majority of the cases. In this paper we report a study of the packing interactions in crystals which possess two molecules in the asymmetric unit, where these are conformationally almost identical and where there is no obvious pseudosymmetry.

### Methods

The structures used in the present work were chosen from the 399 CSD entries used in the earlier study on conformational similarity (Sona & Gautham, 1992). Packing-energy calculations were performed on the 18 structures (Table 1) which fulfilled one or more of the following criteria: (a) molecules containing the elements C, N, O, H only; (b) no solvent molecules; (c) having an r.m.s. deviation of less than 1 Å on superposition of the two independent molecules; (d) no pseudosymmetrical relationship between the two molecules.

Intermolecular potential energies were calculated between each of the two molecules and each one of their neighbours, defined for the present purposes as any molecule in the crystal which had at least one of its atoms at less than 4.0 Å from at least one of the atoms of the reference molecule. The potential energy was taken to be the sum of the van der Waals interaction energy, the electrostatic energy and the energy of formation of hydrogen bonds, if present. The semi-empirical expressions and the constants for each of these three terms were taken from Momany, Carruthers, McGuire & Scheraga (1974). The partial charges of the atoms were calculated as suggested by Del Re (1958) and Renugopalakrishnan, Lakshminarayanan & Sasisekharan (1971). The force field (*i.e.* the atom-atom potential) so obtained has been shown to reproduce packing configurations and lattice energies in crystals of hydrocarbons, carboxylic acids, amines, amides and amino acids (Momany, Carruthers, McGuire &

Scheraga, 1974). It was chosen in the present case for application to a variety of compounds because of (a) the numerous applications which have shown that the simple atom-atom model is sufficient to reproduce physical constants in a large number of organic solids (Desiraju, 1989; He & Welberry, 1988; Craig & Mallett, 1982); (b) the absence of atoms other than C, N O and H in the present studies; and (c) the semi-qualitative nature of the results sought.

### Results and discussion

The results of the energy calculations are presented in Tables 2 and 3. Owing to the semi-empirical nature of the force field, precise quantitative inferences based on the energy values are probably dependent on the set of parameters chosen and, therefore, may be without much meaning. Thus, the discussion presented below is qualitative. Table 2 gives the total energy of interaction of each of the two molecules in the asymmetric unit with its crystal neighbours, taken as the sum of the individual intermolecular energies. In all but two (BUJHAP and COSGUM) of the 18 cases the interaction energy of one of the two molecules in the asymmetric unit (henceforth to be referred to as molecule *A*) with its neighbours is the same, to within 15%, as the interaction energy of the other molecule (molecule *B*) with its neighbours. This is despite the fact that in six cases, the number of close neighbours of molecule *A* is not the same as that of molecule *B*.

The major part of the interaction energy is as a result of the non-bonded van der Waals contacts, with the electrostatic energies playing a subsidiary role. The structure of the amino acid leucine (LEUCIN01) is an exception; the zwitterionic character of the molecule leads to an electrostatic energy with the neighbours of  $-380 \text{ kJ mol}^{-1}$  for molecule *A* and  $-422 \text{ kJ mol}^{-1}$  for molecule *B*. In all other cases, the electrostatic interaction energy makes up less than a third of the total. However, it is not insignificant as suggested by Kitaigorodskii (1973). In four cases (BUJHAP, FMFCHR, STERIG and TYMCXA) the contribution of the electrostatic energy to the total is repulsive and probably it is the van der Waals interaction term that ensures crystal integrity. Hydrogen bonds do not contribute very much to the overall packing energy in the present structures. Furthermore, there are no examples of a

hydrogen-bonded 'dimer' in the asymmetric unit, though these have been reported in the literature (Gautham, Seshadri, Viswamitra, Salisbury & Brown, 1983).

As may be seen from Table 3, molecule *A* makes the strongest contact with molecule *B* (or symmetry-related *B*) in about as many cases (ten out of 18) as with a symmetry-related molecule *A*. Similarly molecule *B* does not show any particularly strong interactions with molecule *A*. Of the ten structures in which molecule *A* associates more strongly with molecule *B*, in only five of them (*i.e.* ARAFPHY10, BUJHAP, CULCUH, FMFCHR and INOSIN11) is the energy of interaction of molecule *A* with molecule *B* significantly stronger than with any other neighbouring molecule. In the other five cases the difference between the best intermolecular interactions and the next-best interaction is less than 30%.

Previous comments (Kitaigorodskii, 1961; Desiraju, Calabrese & Harlow, 1991) on the rationale behind the presence of crystallographically independent molecules in the asymmetric unit have suggested the possibility of the molecules existing as dimers or oligomers in the solution state and then crystallizing out as such, leading to multiple formula units in the asymmetric unit. The present results suggest that, while this may be the correct explanation in some of the cases, there are many others which cannot be explained in this way.

An alternative rationalization could perhaps invoke the concept of 'quasi-equivalence' that has been proposed in the case of virus structures (Caspar & Klug, 1962). As applied to the present case, this would imply that there are two 'quasi-equivalent' modes of interaction of the molecule with its neighbours and both of these find a place in the crystal structure.

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