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Structural Features of Four Tryptophan Metabolite–Picric Acid Molecular Complexes

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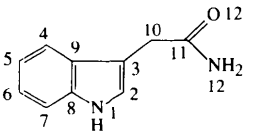
Abstract

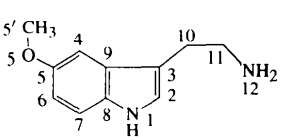
In order to elucidate the structural features of tryptophan metabolite–picric acid molecular interactions, crystal structures of four molecular complexes have been determined: (1) indole-3-acetamide–picric acid, $C_{10}H_{10}N_2O.C_6H_3N_3O_7$, M_r = 403.315, triclinic, $P\bar{1}$, a = 8.027 (3), b = 15.900 (8), c = 7.176 (2) Å, α = 91.10 (3), β = 106.76 (3), γ = 77.24 (4)°, V = 854.4 (6) Å^3, Z = 2, D_m = 1.547 (3), D_x = 1.567 g cm^{-3}, μ(Cu $K\alpha$) = 9.97 cm^{-1}, $F(000)$ = 416, T = 293 K, final R = 0.067 for 2497 observed reflections [$F_o \geq 3\sigma(F_o)$]. (2) Indole-3-acetonitrile–picric acid, $C_{10}H_8N_2.C_6H_3N_3O_7$, M_r = 385.299, triclinic, $P\bar{1}$, a = 7.930 (1), b = 16.166 (3), c = 6.777 (1) Å, α = 95.98 (2), β = 105.09 (1), γ = 96.64 (2)°, V = 824.9 (3) Å^3, Z = 2, D_m = 1.539 (3), D_x = 1.550 g cm^{-3}, μ(Cu $K\alpha$) = 9.65 cm^{-1}, $F(000)$ = 396, T = 293 K, final R = 0.072 for 2205 observed reflections [$F_o \geq 3\sigma(F_o)$]. (3) Indole-3-acetic acid–picric acid, $C_{10}H_9NO_2.C_6H_3N_3O_7$, M_r = 404.300, triclinic, $P\bar{1}$, a = 7.628 (5), b = 16.715 (6), c = 6.850 (2) Å, α = 93.78 (6), β = 99.96 (7), γ = 100.19 (3)°, V = 842.5 (7) Å^3, Z = 2, D_m = 1.576 (3), D_x = 1.593 g cm^{-3}, μ(Cu $K\alpha$) = 10.75 cm^{-1}, $F(000)$ = 416, T = 293 K, final R = 0.079 for 1901 observed reflections [$F_o \geq 3\sigma(F_o)$]. (4) 5-Methoxytryptamine picrate, $C_{11}H_{15}N_2O^+.C_6H_2N_3O_7^-$, M_r = 419.358, monoclinic, $C2/c$, a = 25.086 (2), b = 6.722 (1), c = 22.507 (2) Å, β = 91.90 (2)°, V = 3793.4 (6) Å^3, Z = 8, D_m = 1.460 (3), D_x = 1.469 g cm^{-3}, μ(Cu $K\alpha$) = 9.14 cm^{-1}, $F(000)$ = 1744, T = 293 K, final R = 0.079 for 2335 observed reflections [$F_o \geq 3\sigma(F_o)$]. All crystal structures formed the stacking layers consisting of both molecules, where the indole and picric acid planes were stacked parallel, with an interplanar spacing of *ca* 3.4 Å. Several types of indole ring–picric acid stacking modes were observed, depending on the hydrogen bond and/or electrostatic short contact patterns between the polar groups of both molecules. Including the crystal structures of picrates of L- and DL-tryptophans, serotonin and tryptamine so far analyzed, the structural features of tryptophan metabolite–picric acid molecular interactions have been summarized, especially for the aromatic stacking modes.

Introduction

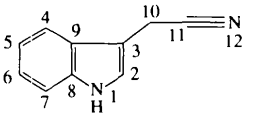
Tryptophan metabolites, widely distributed in living cells, function in various biologically important roles, and are well recognized for the tryptophan residue in protein and the indolealkylamine, such as serotonin or tryptamine, in neurotransmitters. Since the indole ring has a high ability to form stacking (including partial charge-transfer) interactions with the aromatic acceptor (Slifkin, 1971; McCormick, 1977; Hélène & Maurizot, 1981; Hélène & Lancelot, 1982), because of its excellent π-electron donating ability (Pullman & Pullman, 1958), the elucidation of the complex structure with the aromatic biomolecule could be very important in understanding the biological functions of tryptophan metabolites.



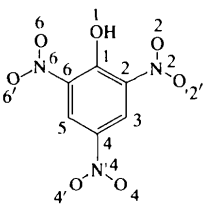
Indole-3-acetamide (IAM)



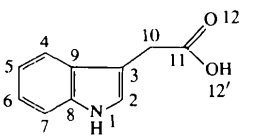
5-Methoxytryptamine (5MT)



Indole-3-acetonitrile (IAN)



Picric acid (PA)



Indole-3-acetic acid (IAA)

Fig. 1. Chemical structures and atomic numberings used in this work.

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Table 1. *Experimental details*

	(1)	(2)	(3)	(4)
Crystal data				
Chemical formula	$C_{16}H_{13}N_5O_8$	$C_{16}H_{11}N_5O_7$	$C_{16}H_{12}N_4O_9$	$C_{17}H_{17}N_5O_8$
Chemical formula weight	403.315	385.299	404.300	419.358
Cell setting	Triclinic	Triclinic	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$C2/c$
a (Å)	8.027 (3)	7.930 (1)	7.628 (5)	25.086 (2)
b (Å)	15.900 (8)	16.166 (3)	16.715 (6)	6.722 (1)
c (Å)	7.176 (2)	6.777 (1)	6.850 (2)	22.507 (2)
α (°)	91.10 (3)	95.98 (2)	93.78 (6)	90.0
β (°)	106.76 (3)	105.09 (1)	99.96 (7)	91.90 (2)
γ (°)	77.24 (4)	96.64 (2)	100.19 (3)	90.0
V (Å^3)	854.4 (6)	824.9 (3)	842.5 (7)	3793.4 (6)
Z	2	2	2	8
D_x (Mg m^{-3})	1.567	1.550	1.593	1.469
Radiation type	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$
Wavelength (Å)	1.54184	1.54184	1.54184	1.54184
No. of reflections for cell parameters	22	22	21	22
θ range (°)	23–30	20–29	22–30	20–29
μ (mm^{-1})	0.997	0.965	1.075	0.914
Temperature (K)	293	293	293	293
Crystal form	Plate	Plate	Plate	Plate
Crystal size (mm)	0.60 × 0.40 × 0.10	0.40 × 0.30 × 0.10	0.50 × 0.30 × 0.10	0.40 × 0.40 × 0.10
Crystal color	Red	Red	Red	Red
Data collection				
Diffractometer	Rigaku AFC-5*R*	Rigaku AFC-5*R*	Rigaku AFC-5*R*	Rigaku AFC-5*R*
Data collection method	ω–2θ scans	ω–2θ scans	ω–2θ scans	ω–2θ scans
Absorption correction	None	None	None	None
No. of measured reflections	2929	2867	2855	3231
No. of independent reflections	2929	2867	2855	3231
No. of observed reflections	2497	2205	1901	2335
Criterion for observed reflections	$F_o \geq 3\sigma(F_o)$	$F_o \geq 3\sigma(F_o)$	$F_o \geq 3\sigma(F_o)$	$F_o \geq 3\sigma(F_o)$
θ_{max} (°)	64.9	65.0	64.9	64.9
Range of h, k, l	$-10 \rightarrow h \rightarrow 10$ $-19 \rightarrow k \rightarrow 19$ $0 \rightarrow l \rightarrow 9$	$-9 \rightarrow h \rightarrow 9$ $-19 \rightarrow k \rightarrow 19$ $0 \rightarrow l \rightarrow 8$	$-9 \rightarrow h \rightarrow 9$ $-20 \rightarrow k \rightarrow 20$ $0 \rightarrow l \rightarrow 8$	$-30 \rightarrow h \rightarrow 30$ $0 \rightarrow k \rightarrow 8$ $0 \rightarrow l \rightarrow 27$
No. of standard reflections	4	4	4	4
Frequency of standard reflections	Every 100 reflections	Every 100 reflections	Every 100 reflections	Every 100 reflections
Intensity decay (%)	1	5	4	2
Refinement				
Refinement on	Full-matrix least-squares on F	Full-matrix least-squares on F	Full-matrix least-squares on F	Full-matrix least-squares on F
R	0.067	0.072	0.079	0.079
wR	0.091	0.097	0.085	0.123
S	1.2581	1.0005	1.5231	0.7134
No. of reflections used in refinement	2497	2205	1901	2335
No. of parameters used	314	293	271	271
H-atom treatment	Isotropic refinement	Isotropic refinement	Isotropic refinement	Isotropic refinement
Weighting scheme	$w = [\sigma^2(F_o) + g(F_o)^2]^{-1}$	$w = [\sigma^2(F_o) + g(F_o)^2]^{-1}$	$w = [\sigma^2(F_o) + g(F_o)^2]^{-1}$	$w = [\sigma^2(F_o) + g(F_o)^2]^{-1}$
g converged to	0.007997	0.014884	0.001873	0.121010
$(\Delta/\sigma)_{max}$	0.35	0.65	0.03	0.36
$\Delta\rho_{max}$ (e Å^{-3})	0.25	0.30	0.38	0.38
$\Delta\rho_{min}$ (e Å^{-3})	−0.20	−0.29	−0.35	−0.29
Extinction method	Lp	Lp	Lp	Lp
Source of atomic scattering factors	*International Tables for X-ray Crystallography* (1974, Vol. IV)	*International Tables for X-ray Crystallography* (1974, Vol. IV)	*International Tables for X-ray Crystallography* (1974, Vol. IV)	*International Tables for X-ray Crystallography* (1974, Vol. IV)
Computer programs				
Data collection	Rigaku AFC-5*R* Program	Rigaku AFC-5*R* Program	Rigaku AFC-5*R* Program	Rigaku AFC-5*R* Program
Cell refinement	Rigaku AFC-5*R* Program	Rigaku AFC-5*R* Program	Rigaku AFC-5*R* Program	Rigaku AFC-5*R* Program
Data reduction	Rigaku AFC-5*R* Program	Rigaku AFC-5*R* Program	Rigaku AFC-5*R* Program	Rigaku AFC-5*R* Program
Structure solution	*MULTAN*87 (Main *et al.*, 1987)	*MULTAN*87 (Main *et al.*, 1987)	*MULTAN*87 (Main *et al.*, 1987)	*MULTAN*87 (Main *et al.*, 1987)
Structure refinement	*SHELX*76 (Sheldrick, 1976)	*SHELX*76 (Sheldrick, 1976)	*SHELX*76 (Sheldrick, 1976)	*SHELX*76 (Sheldrick, 1976)
Preparation of material for publication	The Universal Crystallographic Computing System – Osaka	The Universal Crystallographic Computing System – Osaka	The Universal Crystallographic Computing System – Osaka	The Universal Crystallographic Computing System – Osaka

Concerning the tryptophan metabolite–biomolecule complexes, crystallographic studies are rather few (Ishida, 1988, 1992) because of the relatively difficult preparation of single crystals suitable for X-ray study. On the other hand, it is well known that picric acid (PA) forms stable complexes with various aromatic compounds through ionic or π-bonding, thus being frequently used for the identification or qualitative analysis of compounds. As part of the series elucidating the structural features of tryptophan metabolite–picric acid molecular interactions, therefore, we have already analyzed the crystal structure of the L-tryptophan–PA (1:1) complex (Ishida *et al.*, 1993). In this paper, we deal with the (1:1) molecular complexes of indole-3-acetamide (IAM) (1), indole-3-acetonitrile (IAN) (2), indole-3-acetic acid (IAA) (3) and 5-methoxytryptamine (5MT) (4) with PA, and discuss the structural features of interaction, including the results of picrate complexes with DL-tryptophan, tryptamine (Gartland, Freeman & Bugg, 1974) and serotonin (Thewalt & Bugg, 1972). The chemical structures of IAM, IAN, IAA, 5MT and PA, together with their atomic numberings used in this work, are shown in Fig. 1

Experimental

The complex crystals were prepared from an aqueous (3) or ethanol (1, 2 and 4) solution containing an equimolar amount of tryptophan metabolite and PA, by slow evaporation at room temperature (293 K). These crystals were all tinged with red, which is in contrast to its components, colorless tryptophan metabolite or yellow PA, suggesting the charge-transfer interaction of both molecules. The crystal density was measured by the flotation method using a benzene–carbon tetrachloride mixture at 293 K.

X-ray data were collected with a Rigaku AFC-5*R* diffractometer using graphite-monochromated Cu $K\alpha$ radiation (λ = 1.5418 Å) at 293 K. Details for cell parameter determination and the reflectional intensity data collection are given in Table 1. Intensity data within $2 \le 2\theta \le 130°$ were measured by employing an ω–2θ scan mode. Four standard reflections monitored every 100 reflections showed no significant time-dependence (< ±2%).

Each crystal structure was solved by direct methods using *MULTAN*87 (Debaerdemaeker, Germain, Main, Tate & Woolfson, 1987). The positional parameters of non-H atoms were refined by full-matrix least-squares with anisotropic temperature parameters using *SHELX*76 (Sheldrick, 1976). The positions of the H atoms were located on the difference Fourier map and were included in subsequent refinements with isotropic temperature parameters; H atoms which were not unequivocally located at the map were excluded from the refinement, *i.e.* H(1) of PA in (2), H(1) and H(5) of PA, and H(12′) of IAA in (3). Only in the solution of (3)

Table 2. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å²) *for* (1)–(4)

$U_{eq} = (1/3)\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
Complex (1)				
Picric acid				
C(1)	0.3238 (4)	0.2201 (2)	0.3542 (4)	0.046 (2)
O(1)	0.3289 (3)	0.1439 (2)	0.2796 (4)	0.063 (1)
C(2)	0.1742 (4)	0.2887 (2)	0.3317 (4)	0.048 (2)
N(2)	−0.0042 (4)	0.2788 (2)	0.2261 (4)	0.057 (2)
O(2)	−0.0259 (4)	0.2060 (2)	0.1933 (5)	0.089 (2)
O(2′)	−0.1232 (4)	0.3426 (2)	0.1740 (6)	0.087 (2)
C(3)	0.1869 (4)	0.3680 (2)	0.4098 (4)	0.047 (2)
C(4)	0.3509 (4)	0.3799 (2)	0.5146 (4)	0.050 (2)
N(4)	0.3649 (4)	0.4637 (2)	0.5965 (4)	0.064 (2)
O(4)	0.2328 (5)	0.5219 (2)	0.5546 (5)	0.088 (2)
O(4′)	0.5104 (4)	0.4708 (2)	0.7024 (4)	0.083 (2)
C(5)	0.5036 (4)	0.3154 (2)	0.5434 (4)	0.050 (2)
C(6)	0.4868 (4)	0.2376 (2)	0.4643 (4)	0.046 (2)
N(6)	0.6522 (4)	0.1713 (2)	0.4934 (5)	0.065 (2)
O(6)	0.7870 (4)	0.1945 (3)	0.4925 (7)	0.113 (3)
O(6′)	0.6513 (5)	0.0963 (2)	0.5118 (6)	0.099 (3)
Indole-3-acetamide				
N(1)	0.5714 (4)	0.2096 (2)	0.9849 (5)	0.064 (2)
C(2)	0.5236 (5)	0.1368 (2)	0.9039 (5)	0.059 (2)
C(3)	0.3432 (4)	0.1520 (2)	0.8257 (4)	0.047 (2)
C(4)	0.1035 (4)	0.2936 (2)	0.8087 (5)	0.054 (2)
C(5)	0.0865 (6)	0.3789 (3)	0.8598 (6)	0.072 (2)
C(6)	0.2366 (7)	0.4102 (2)	0.9614 (6)	0.082 (3)
C(7)	0.4041 (6)	0.3596 (3)	1.0117 (5)	0.073 (2)
C(8)	0.4214 (4)	0.2743 (3)	0.9574 (4)	0.054 (2)
C(9)	0.2747 (4)	0.2397 (2)	0.8576 (4)	0.044 (2)
C(10)	0.2409 (6)	0.0883 (2)	0.7217 (5)	0.068 (2)
C(11)	0.1431 (4)	0.0505 (2)	0.8383 (4)	0.050 (2)
N(12)	0.0797 (4)	−0.0168 (2)	0.7641 (4)	0.060 (2)
O(12)	0.1219 (4)	0.0791 (2)	0.9908 (4)	0.092 (2)
Complex (2)				
Picric acid				
C(1)	0.8160 (5)	0.8595 (2)	0.7966 (5)	0.049 (2)
O(1)	0.9034 (5)	0.9366 (2)	0.8366 (5)	0.075 (2)
C(2)	0.9045 (5)	0.7902 (2)	0.8156 (5)	0.050 (2)
N(2)	1.0986 (5)	0.8021 (3)	0.8812 (6)	0.077 (3)
O(2)	1.1780 (5)	0.8682 (4)	0.9781 (9)	0.136 (4)
O(2′)	1.1680 (5)	0.7444 (3)	0.8275 (9)	0.126 (3)
C(3)	0.8200 (5)	0.7087 (2)	0.7797 (5)	0.055 (2)
C(4)	0.6372 (5)	0.6952 (2)	0.7181 (5)	0.048 (2)
N(4)	0.5451 (6)	0.6088 (2)	0.6887 (5)	0.068 (2)
O(4)	0.6364 (6)	0.5524 (2)	0.7126 (6)	0.098 (3)
O(4′)	0.3864 (6)	0.5986 (2)	0.6459 (6)	0.096 (3)
C(5)	0.5416 (5)	0.7598 (2)	0.6899 (5)	0.048 (2)
C(6)	0.6299 (5)	0.8409 (2)	0.7274 (5)	0.049 (2)
N(6)	0.5242 (6)	0.9087 (2)	0.6961 (6)	0.076 (2)
O(6)	0.3685 (5)	0.8901 (3)	0.6072 (8)	0.119 (3)
O(6′)	0.5976 (6)	0.9805 (2)	0.7517 (8)	0.117 (3)
Indole-3-acetonitrile				
N(1)	0.5183 (4)	0.6931 (2)	0.1748 (5)	0.059 (2)
C(2)	0.5980 (6)	0.6239 (3)	0.1994 (6)	0.063 (2)
C(3)	0.7771 (6)	0.6463 (2)	0.2654 (6)	0.057 (2)
C(4)	0.9640 (5)	0.7957 (2)	0.3454 (5)	0.050 (2)
C(5)	0.9451 (6)	0.8796 (2)	0.3455 (6)	0.060 (2)
C(6)	0.7806 (7)	0.9053 (2)	0.2890 (6)	0.064 (2)
C(7)	0.6277 (6)	0.8482 (3)	0.2285 (6)	0.062 (2)
C(8)	0.6453 (5)	0.7634 (2)	0.2260 (5)	0.049 (2)
C(9)	0.8096 (5)	0.7358 (2)	0.2841 (5)	0.045 (2)
C(10)	0.9105 (7)	0.5872 (3)	0.3145 (8)	0.076 (3)
C(11)	1.0398 (7)	0.5959 (3)	0.1976 (9)	0.077 (3)
N(12)	1.1393 (7)	0.6053 (4)	0.107 (1)	0.125 (4)
Complex (3)				
Picric acid				
C(1)	0.3231 (7)	0.8560 (3)	0.8394 (7)	0.056 (3)
O(1)	0.4344 (7)	0.9282 (3)	0.8760 (7)	0.066 (3)
C(2)	0.3722 (6)	0.7807 (3)	0.8672 (7)	0.052 (3)
N(2)	0.5628 (6)	0.7773 (4)	0.9495 (8)	0.074 (3)

Table 2 (*cont.*)

	x	y	z	U_{eq}
O(2)	0.6756 (6)	0.8380 (3)	0.9565 (9)	0.114 (4)
O(2′)	0.5945 (6)	0.7134 (3)	1.0080 (8)	0.110 (4)
C(3)	0.2532 (7)	0.7074 (3)	0.8300 (7)	0.052 (3)
C(4)	0.0739 (6)	0.7088 (3)	0.7563 (7)	0.049 (3)
N(4)	−0.0568 (7)	0.6298 (3)	0.7148 (7)	0.067 (3)
O(4)	0.0042 (7)	0.5682 (3)	0.7054 (8)	0.101 (4)
O(4′)	−0.2160 (6)	0.6326 (3)	0.6918 (9)	0.115 (4)
C(5)	0.0121 (7)	0.7795 (3)	0.7228 (7)	0.054 (3)
C(6)	0.1338 (8)	0.8517 (3)	0.7652 (7)	0.059 (3)
N(6)	0.066 (1)	0.9275 (4)	0.7361 (9)	0.093 (4)
O(6)	−0.0873 (8)	0.9216 (3)	0.645 (1)	0.135 (5)
O(6′)	0.165 (1)	0.9915 (3)	0.798 (1)	0.152 (6)
O(1′)	−0.147 (2)	0.780 (1)	0.646 (2)	0.09 (1)
Indole-3-acetic acid				
N(1)	−0.0196 (5)	0.7057 (3)	0.2223 (6)	0.057 (3)
C(2)	0.0464 (7)	0.6357 (3)	0.2496 (8)	0.056 (3)
C(3)	0.2296 (6)	0.6550 (3)	0.3190 (7)	0.049 (3)
C(4)	0.4460 (7)	0.7978 (3)	0.3878 (7)	0.054 (3)
C(5)	0.4444 (8)	0.8789 (4)	0.3774 (9)	0.069 (4)
C(6)	0.283 (1)	0.9075 (3)	0.3152 (9)	0.075 (4)
C(7)	0.1208 (8)	0.8543 (3)	0.2601 (8)	0.063 (4)
C(8)	0.1206 (6)	0.7720 (3)	0.2671 (7)	0.049 (3)
C(9)	0.2792 (6)	0.7405 (3)	0.3314 (7)	0.045 (3)
C(10)	0.3549 (7)	0.5962 (3)	0.3782 (8)	0.057 (3)
C(11)	0.4190 (7)	0.5566 (3)	0.2083 (8)	0.056 (3)
O(12)	0.3254 (5)	0.5403 (2)	0.0411 (6)	0.073 (3)
O(12′)	0.5758 (3)	0.5361 (3)	0.2550 (6)	0.082 (3)
Complex (4)				
Picric acid				
C(1)	0.7870 (2)	−0.0420 (7)	0.3849 (2)	0.038 (2)
O(1)	0.7744 (1)	−0.0978 (6)	0.4346 (2)	0.052 (2)
C(2)	0.7681 (2)	0.1388 (8)	0.3565 (2)	0.045 (3)
N(2)	0.7300 (2)	0.2592 (7)	0.3880 (2)	0.054 (3)
O(2)	0.6990 (2)	0.1804 (8)	0.4199 (3)	0.090 (3)
O(2′)	0.7300 (2)	0.4358 (7)	0.3777 (2)	0.085 (3)
C(3)	0.7832 (2)	0.2061 (7)	0.3024 (2)	0.043 (2)
C(4)	0.8185 (2)	0.0950 (8)	0.2701 (2)	0.043 (2)
N(4)	0.8354 (2)	0.1655 (9)	0.2147 (2)	0.062 (3)
O(4)	0.8152 (2)	0.3140 (8)	0.1924 (2)	0.077 (3)
O(4′)	0.8705 (2)	0.0764 (9)	0.1896 (2)	0.099 (4)
C(5)	0.8380 (2)	−0.0833 (8)	0.2921 (2)	0.043 (2)
C(6)	0.8229 (2)	−0.1504 (7)	0.3470 (2)	0.039 (2)
N(6)	0.8448 (2)	−0.3414 (7)	0.3663 (2)	0.047 (2)
O(6)	0.8664 (2)	−0.4469 (6)	0.3281 (2)	0.072 (3)
O(6′)	0.8427 (2)	−0.3907 (7)	0.4174 (2)	0.071 (3)
5-Methoxytryptamine				
N(1)	0.9076 (2)	0.2089 (8)	0.4179 (3)	0.076 (4)
C(2)	0.8947 (2)	0.1563 (9)	0.4769 (4)	0.069 (4)
C(3)	0.9190 (2)	−0.0206 (7)	0.4918 (2)	0.044 (2)
C(4)	0.9788 (2)	−0.250 (1)	0.4300 (3)	0.063 (3)
C(5)	1.0028 (3)	−0.264 (1)	0.3760 (3)	0.069 (4)
O(5)	1.0337 (3)	−0.4336 (9)	0.3677 (2)	0.100 (4)
C(5′)	1.0583 (6)	−0.461 (2)	0.3141 (5)	0.15 (1)
C(6)	0.9951 (3)	−0.120 (1)	0.3344 (3)	0.076 (4)
C(7)	0.9649 (3)	0.043 (1)	0.3400 (3)	0.072 (4)
C(8)	0.9391 (2)	0.0661 (9)	0.3967 (2)	0.054 (3)
C(9)	0.9468 (2)	−0.0778 (8)	0.4406 (2)	0.048 (3)
C(10)	0.9177 (2)	−0.126 (1)	0.5497 (2)	0.059 (3)
C(11)	0.8791 (2)	−0.2983 (8)	0.5514 (2)	0.051 (3)
N(12)	0.8237 (2)	−0.2310 (6)	0.5408 (2)	0.047 (2)

was the problem of disorder encountered. The progress of Fourier refinement revealed the disorder of the PA hydroxyl group with two distinct positions [O(1) and O(1′) atoms] at C(1) and C(5) atoms, as shown in Fig. 1. This disorder was modeled by splitting respective molecules with occupancies of $\frac{2}{3}$ and $\frac{1}{3}$, as the result of the refinement; after the completion of this crystal analysis, the crystal structure of the same complex was solved by Soriano-Garcia & Toscano (1995), where no disorder was reported in spite of essentially the same crystal. The R values of the present complex crystals were rather higher than usual, and this may be due in part to the thin-layered crystal habit of the complexes. The atomic scattering factors and terms of anomalous dispersion corrections were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). The crystallographic calculations were performed using The Universal Crystallographic Computing System-Osaka (1979). The final atomic coordinates and U_{eq} values for the non-H atoms are given in Table 2.*

Atomic net charges, dipole moments and their directions of 3-methylindole (for tryptophan, IAM, IAN and IAA), 5-methoxy-3-methylindole (for 5MT) or 5-hydroxy-3-methylindole (for serotonin) and PA (neutral and anionic forms) were calculated by the quantum chemical MNDO method (Dewar & Thiel, 1977). The stabilities of the respective electronic energies were used to verify the convergence in the iteration calculations.

All numerical calculations were performed on a MicroVAXII computer at the Computation Center, Osaka University of Pharmaceutical Sciences.

Results and discussion

Molecular structures

Stereoscopic views of four tryptophan metabolites are shown in Fig. 2, where PA in complex (1) is also shown as a representative molecular conformation; no notable conformational differences were observed among the four PA molecules of (1)–(4). Selected torsion angles are listed in Table 3. Compared with the bond lengths of general organic compounds (Allen *et al.*, 1987), no significant discrepancies were observed, and those of (1)–(4) are all in agreement within the e.s.d.'s. No significant deformation from planarity was observed for the indole ring of the tryptophan metabolites and the benzene ring of PA molecules in all the complexes. Concerning the molecular conformation of PA, the nitro groups were commonly twisted out of the benzene plane, ranging from −36 to 23° around the C—N bond (Table 3), and such a tilting appears to be a conformational feature of the PA molecule.

As judged from the electron-density map, (1) consists of a (1:1) complex of neutral PA and IAM; the bond lengths of C(1)—O(1) = 1.312 (4) Å in PA and C(11)—N(12) = 1.322 (4) and C(11)═O(12) = 1.220 (4) Å in IAM also suggest the neutral structures of both molecules. IAM takes the side-chain conformation of χ = 104.5 (4)° and φ = −168.1 (3)°, which belongs to a

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates, complete geometry and short contacts less than 3.4 Å have been deposited with the IUCr (Reference: AS0686). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

rather rare conformation in the related tryptophan (Ishida *et al.*, 1993) or tryptamine (Inoue, Sakaki, Wakahara & Tomita, 1978).

Crystal (2) consists of the 1:1 complex of IAN and neutral PA; although the phenolic OH proton was not clearly detected on the electron-density map, the C(1)—O(1) bond length [1.318 (5) Å] suggests that PA is not deprotonated, and the C(11)—N(12) bond [1.127 (8) Å] of IAN is in the normal range of C≡N triple bonds (Allen *et al.*, 1987). The χ torsion angle [124.5 (5)°] of IAN is slightly higher than the most frequently observed value (χ = 100–110°) of tryptamine (Inoue, Sakaki, Fujiwara & Tomita, 1978; Ishida, Hamada, Inoue & Wakahara, 1990*a*).

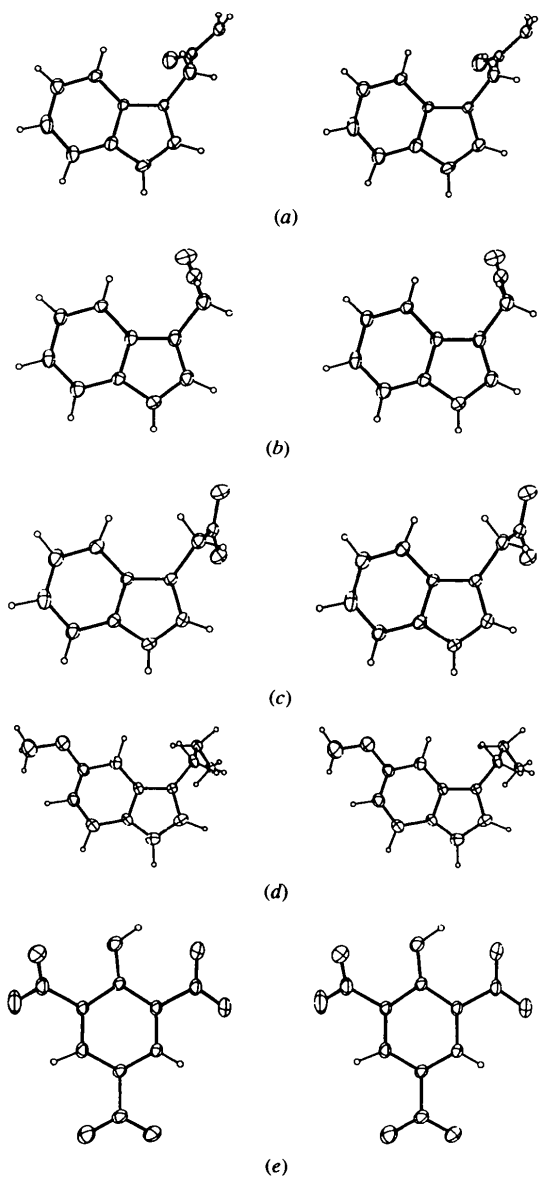

Fig. 2. Stereoscopic molecular conformations of (*a*) IAM, (*b*) IAN, (*c*) IAA, (*d*) 5MT and (*e*) PA. Among the four different PA molecular conformations in complexes (1)–(4), (*e*) was selected from (1) as a representative molecular conformation.

Table 3. *Conformational torsion angles* (°) *of indole-3-acetamine (IAM), indole-3-acetonitrile (IAN), indole-3-acetic acid (IAA), 5-methoxytryptamine (5MT) and PA molecules*

Torsion angle	IAM	IAN	IAA	5MT
C(2)—C(3)—C(10)—C(11):χ	104.5 (4)	124.5 (5)	83.3 (6)	100.6 (6)
C(9)—C(3)—C(10)—C(11)	−77.6 (3)	−57.7 (4)	−98.9 (5)	−81.1 (5)
C(3)—C(10)—C(11)—N(12):φ	−168.1 (3)			−62.2 (4)
C(3)—C(10)—C(11)—O(12)	12.2 (4)		−32.6 (7)	
C(3)—C(10)—C(11)—O(12′)			151.8 (4)	
C(4)—C(5)—O(5)—C(5′)				178.8 (9)
C(6)—C(5)—O(5)—C(5′)				−0.2 (8)

	PA1*	PA2*	PA3*	PA4*
C(1)—C(2)—N(2)—O(2)	15.0 (3)	23.1 (5)	−12.6 (5)	−31.7 (5)
C(1)—C(2)—N(2)—O(2′)	−164.6 (1)	−154.7 (5)	165.7 (6)	152.1 (5)
C(3)—C(4)—N(4)—O(4)	−6.1 (3)	−2.9 (4)	15.8 (5)	−7.1 (5)
C(3)—C(4)—N(4)—O(4′)	174.4 (4)	176.1 (5)	164.4 (6)	172.7 (6)
C(5)—C(6)—N(6)—O(6)	−35.5 (4)	−12.0 (4)	−12.8 (6)	−13.8 (4)
C(5)—C(6)—N(6)—O(6′)	146.5 (4)	171.2 (5)	169.2 (8)	164.8 (5)

* PA1–PA4 represent PA's in complexes (1)–(4), respectively.

Crystal (3) consists of a neutral (1:1) complex of IAA and PA, as suggested from the bond lengths and angles of the carboxyl (IAA) and phenolic (PA) groups, although the H atoms attached to these groups were not clearly identified on the electron-density map. The molecular conformation of IAA belongs to type I (χ = 83–126°, φ = −30–0°), one of the most frequently observed conformations for IAA analogs (Ishida, Hamada, Inoue & Wakahara, 1990*b*). The phenolic O atom of PA was split into two positions [O(1) and O(1′) atoms] with

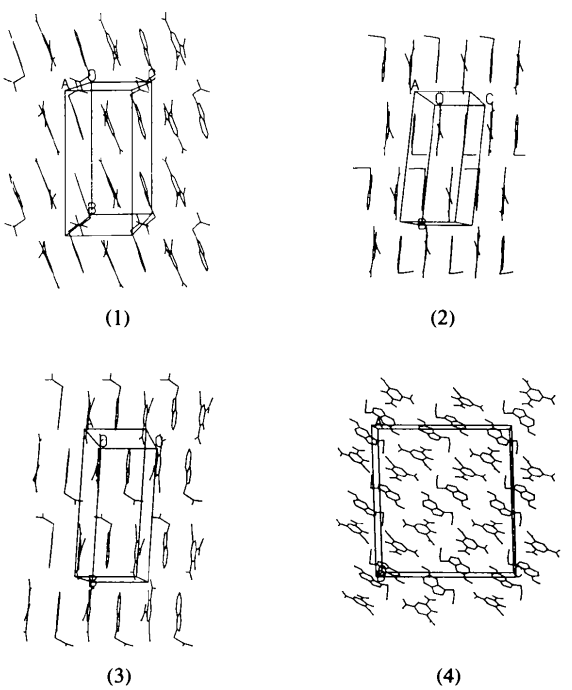

Fig. 3. Molecular packings in the complex crystal structures of (1)–(4).

Table 4. *Possible hydrogen bonds*

D at *x*, *y*, *z*	*A*	Symmetry operation of *A*	Distance (Å) *D*···*A*	H···*A*	Angle (°) ∠*D*—H···*A*
Complex (1)					
N(1)I*	O(2)P	$x+1, y, z+1$	3.135 (5)	2.20 (4)	173 (3)
N(12)I	O(12)I	$-x, -y, 2-z$	3.018 (4)	2.03 (4)	170 (3)
O(1)P	O(12)I	$x, y, z-1$	2.608 (4)	1.68 (4)	153 (3)
Complex (2)					
N(1)I	N(12)I	$x-1, y, z$	3.069 (5)	2.34 (4)	139 (4)
O(1)P	O(1)P	$2-x, 2-y, 2-z$	2.832 (5)†		
Complex (3)					
N(1)I	O(2′)P	$x-1, y, z-1$	3.082 (7)	2.09 (6)	171 (5)
O(12′)I	O(12)I	$1-x, 1-y, -z$	2.615 (6)		
O(1)P‡	O(1)P	$1-x, 2-y, 2-z$	2.771 (7)†		
O(1′)P‡	O(2)P	$x-1, y, z$	2.91 (2)		
Complex (4)					
N(1)I	O(6)P	$x, y+1, z$	3.221 (7)	2.18 (5)	160 (4)§
N(1)I	O(6′)P	$x, y+1, z$	3.146 (7)	2.24 (5)	139 (4)§
N(12)I	O(1)P	x, y, z	2.802 (5)	1.82 (5)	157 (4)
N(12)I	O(1)P	$\frac{3}{2}-x, -\frac{1}{2}-y, 1-z$	2.788 (5)	1.97 (5)	168 (4)
N(12)I	O(2′)P	$\frac{3}{2}-x, \frac{1}{2}-y, 1-z$	3.046 (7)	2.43 (5)	131 (4)

* The suffix letters I and P indicate tryptophan metabolite and picric acid molecules, respectively.
† There is no direct evidence of hydrogen bonds concerning this short contact.
‡ Occupancy is $\frac{2}{3}$ for O(1)P and $\frac{1}{3}$ for O(1′)P.
§ Bifurcated.

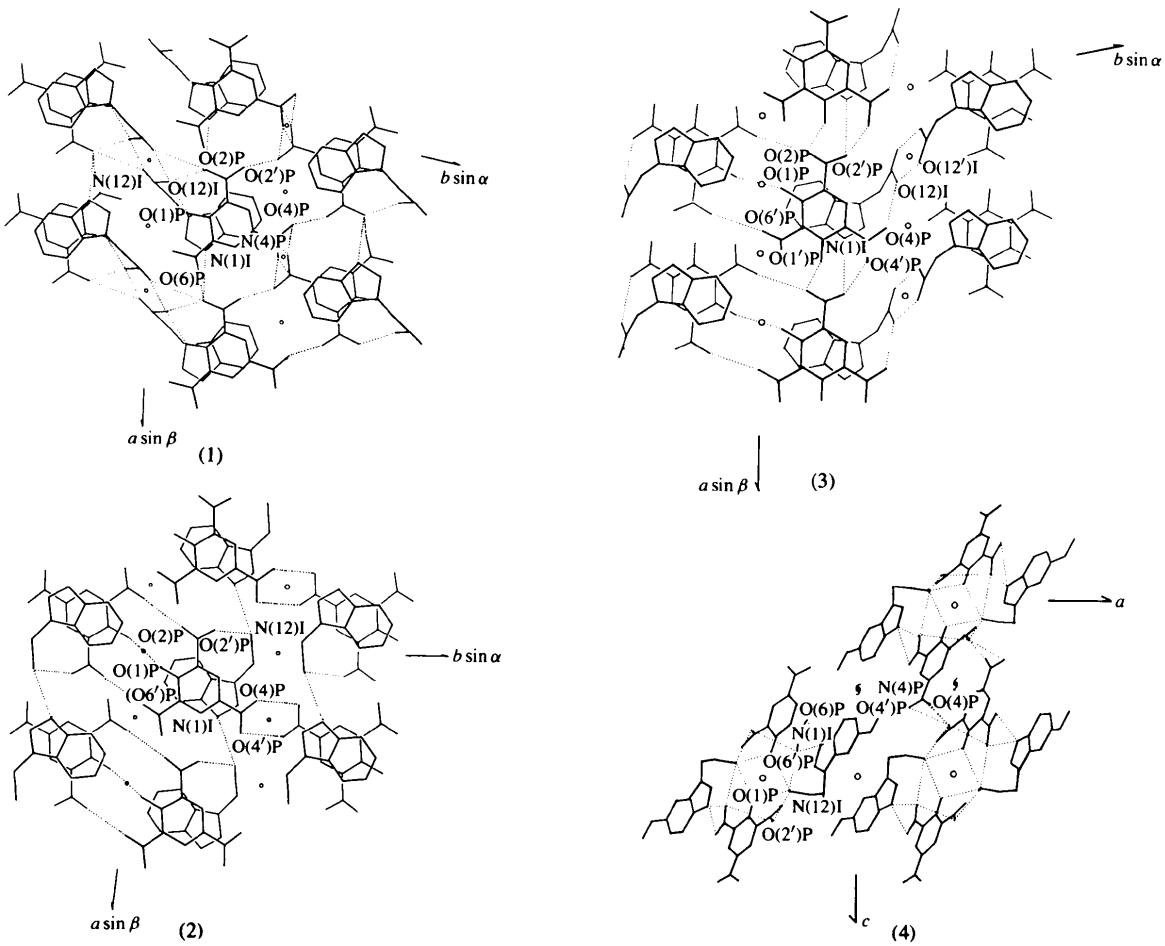

Fig. 4. Hydrogen-bonding and/or electrostatic short-contact network formed in the complex crystals of (1)–(4). The dotted lines represent possible hydrogen bonds or electrostatic short contacts of ≤ 3.22 Å, respectively.

the occupancies of $\frac{2}{3}$ and $\frac{1}{3}$, respectively, which are covalently connected to C(1) and C(5), as shown in Fig. 1. Because of the symmetrical disposition of the three nitro groups in the PA molecule, such a disorder would be possible.

In the crystal of (4), three H atoms were tetrahedrally located around N(12) of 5MT on an electron-density map, and the bond lengths C(11)—N(12) = 1.474 (7) (5MT) and C(1)—O(1) = 1.232 (6) Å (PA) indicate an ionic salt formation between cationic 5MT and anionic PA with the amino N(12) protonated and the phenolic O(1) deprotonated, respectively. The molecular conformation of 5MT belongs to a conformer I (χ = 90–110°, φ = –80 to –60°), which corresponds to the most stable and popular conformation for tryptamine, serotonin and 5MT molecules (Inoue, Sakaki, Fujiwara & Tomita, 1978; Ishida, Hamada, Inoue & Wakahara, 1990*a*). The methoxyl group of 5MT is located *trans* with respect to the indole C(4) atom, and this is a rare case for 5-methoxyindole compounds, most taking the *cis* orientation with the torsion angle C(4)—C(5)—O(5)—C(5′) being –10–0° (Ishida, Hamada, Inoue & Wakahara, 1990*a*).

Crystal structures and hydrogen bonds

Perspective views of crystal structures are shown in Fig. 3. The networks of hydrogen bonding and electrostatic interactions formed in the respective crystal structures are schematically depicted in Fig. 4, and the hydrogen bonds are summarized in Table 4; a list of short contacts less than 3.4 Å has been deposited.

A structural feature observed commonly in the crystal packings of (1)–(3) is that each molecule is alternately piled up along the crystallographic *c* axis to form an infinite column of ....IA–PA–IA–PA....., where IA represents IAM, IAN or IAA (Fig. 3). On the other hand, the crystal structure of (4) forms the infinite layer consisting of columns of ...5MT–5MT–PA–PA... extended along the [$\bar{1}$01] axis. This difference between the molecular packings of (1)–(3) and (4) is due to the different hydrogen-bonding pattern formed between the component molecules. As is obvious from Fig. 4, the component molecules in (1)–(3) are linked with each other by hydrogen bonds and/or electrostatic short contacts in each infinite column, while (4) forms a unit structure of two complex pairs around a center of symmetry as a result of intermolecular hydrogen bonds of the 5MT amino group with PA phenol and nitro O atoms. A packing mode similar to that of (4) has been found in the complex crystals formed by a salt bridge between the acid and amine components, such as 5MT–IAA (Sakaki *et al.*, 1976) and tryptamine–phenylacetic acid (Inoue, Sakaki, Fujiwara & Tomita, 1978) complexes.

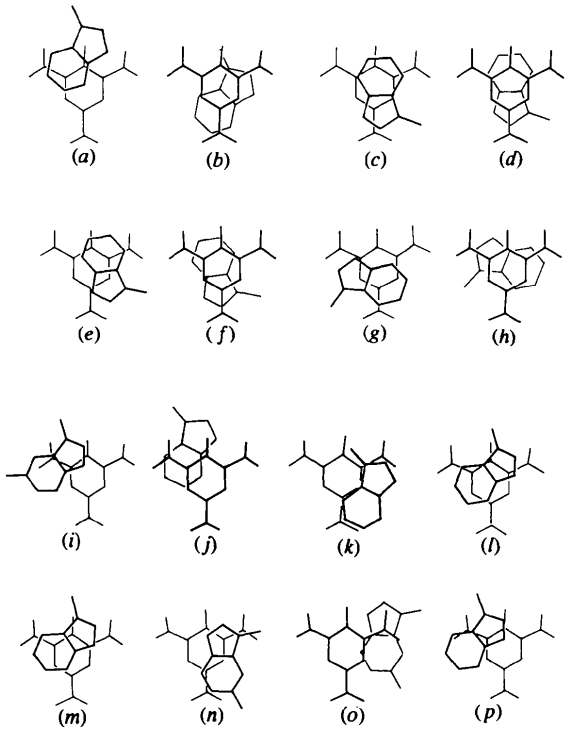

Fig. 5. Schematic stacking interaction modes between the indole ring and PA benzene ring observed in the tryptophan metabolite–PA complex crystals.

Stacking interaction of indole ring with PA molecule

The stacking modes between the indole and PA benzene rings observed in (1)–(4) are shown in Fig. 5, where those in L-tryptophan picrate (5; Ishida *et al.*, 1993), DL-tryptophan picrate (6; Gartland, Freeman & Bugg, 1974), serotonin picrate (7; Thewalt & Bugg, 1972) and tryptamine picrate (8; Gartland, Freeman & Bugg, 1974) are also shown for comparison. The stacking parameters are summarized in Table 5, where the dipole moments and their directions of the indole ring and PA molecule (neutral or anionic form) were calculated using the MNDO method. Taking into consideration the molecular symmetry of PA and the relative orientation between two aromatic rings, the stacking mode of the indole ring with respect to PA was roughly classified into eight groups of *A*–*D* and *A*′–*D*′, where the respective modes of *A*′–*D*′ belong to the same categories as *A*—*D*, although the sides of the PA plane interacting with the indole ring are opposite each other.

A common feature observed in all interaction pairs is that two aromatic rings are arranged almost parallel (dihedral angle = 1–9°) with an interplanar spacing (3.3–3.5 Å) close to 3.4 Å, the minimum van der Waals separation distance between aromatic rings (Table 5). This stacking interaction, which includes a partial π–π charge transfer, is an essential and characteristic phenomenon for the tryptophan metabolite–PA molecular complex characterized by the red coloration.

There is, however, a considerable variation concerning the stacking mode of indole–PA aromatic rings,

Table 5. *Structural parameters for stacking interaction between the indole ring of tryptophan metabolite and PA in a 1:1 complex crystal*

Complex	Stacking mode in Fig. 5	Averaged interplanar spacing (Å)	Dihedral angle (°)	Angle between dipole moments (°)*	Torsion angle of indole and PA (°)†	Notation
(1)	(a)	3.30	4.2 (1)	173	33	*A*
	(b)	3.33	4.2 (1)	173	−33	*A′*
(2)	(c)	3.36	1.1 (2)	148	−106	*B*
	(d)	3.40	1.1 (2)	148	106	*B′*
(3)	(e)‡	3.33	1.5 (2)	144	−103	*B*
	(f)‡	3.38	1.5 (2)	144	103	*B′*
	(g)§	3.33	1.5 (2)	100	140	*C*
	(h)§	3.33	1.5 (2)	100	−140	*C′*
(4)	(i)	3.40	4.7 (2)	104	17	*A*
(5)	(j)	3.34	2.5	160	−46	*A′*
	(k)	3.40	2.5	160	46	*A*
	(l)	3.51	8.2	76	18	*A*
(6)	(m)	3.42	9.1	72	16	*A*
(7)	(n)	3.29	4.7	163	−80	*D*
	(o)	3.33	4.7	163	80	*D′*
(8)	(p)	3.40	2.8	77	22	*A*

* The dipole moments of the indole ring of tryptophan metabolite and PA were calculated using 3-methylindole and neutral PA for (1), (2), (3), (5) and (6), 5-methoxy-3-methylindole and anionic PA for (4), 5-hydroxy-3-methylindole and anionic PA for (7), and 3-methylindole and anionic PA for (8), respectively. The dipole moments of 3-methylindole, 5-hydroxy-3-methylindole, 5-methoxy-3-methylindole, neutral PA and anionic PA are 2.01, 3.04, 3.48, 1.81 and 12.79 Debye, respectively.

† Torsion angle of C(10)I—C(3)I—C(1)P—O(1)P.

‡ Occupancy = $\frac{2}{3}$ in the crystal structure of (3).

§ Occupancy = $\frac{1}{3}$ in the crystal structure of (3).

and the relative orientation would be determined by the combination of various factors. In the modes of Figs. 5(*a*)–(*f*), (*j*), (*k*), (*n*) and (*o*), the dipole–dipole couplings play an important role in determining the relative orientation of the aromatic rings, while such a dipole interaction does not function in the stacking in Figs. 5(*g*)–(*i*), (*m*) and (*p*) because the two are almost at right angles. The MNDO calculations suggested that the HOMO (indole)–LUMO (PA) interaction and/or the electrostatic interaction contribute to some extent to determining the stacking geometry, because most of the atomic orbital coefficients in the short contact pairs show the same signs (suggesting the orbital coupling) and/or their atomic net charges are opposite each other (suggesting the electrostatic attraction) for several stacking pairs. It is also obvious that the orientation of both aromatic rings is significantly affected by the single and/or bifurcated NH···O hydrogen bonds between the indole NH and the nitro and/or phenol oxygens of PA. The high frequency of occurrences of the *A* (*A′*)- or *B* (*B′*)-type stacking mode, however, shows that it has an advantage for the molecular interaction between tryptophan metabolite and PA.

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