The Crystal Structure of 3-(Adenin-9-yl)-*N*-(2-succinimidyl)-propionamide and Hydrogen Bonding Scheme of Anticonvulsant Drugs with Adenine

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3-(Adenin-9-yl)-*N*-(2-succinimidyl)propionamide† has been synthesized as a model for studying the interaction between cyclic ureide and adenine, and its crystal structure examined. The crystals are monoclinic, the space group $P2_1/c$, with unit-cell dimensions of a=10.861(1), b=12.766(1), c=9.753(1) Å, β=91.10(1)°, and Z=4. The ureide moiety is hydrogen bonded to adenine with NH···N(1) (2.903(3) Å) and O···HN(6) (2.955(3) Å). A comparison of the hydrogen bonding patterns of the related compounds with adenine suggests that cyclic ureide anticonvulsant drugs possess the capability of interacting with N(1) and N(6) sites of adenine.

Many compounds containing cyclic ureide skeleton, such as barbiturate, hydantoin and succinimide derivatives, have been used extensively as anticonvulsant and antiepileptic drugs.[1] It is known that barbiturate/hydantoin derivatives form stronger hydrogen bonds with adenine than the other nucleic acid bases.[2] This is an interesting observation because it is suspected that some adenine-related complexes play a role in nerve transmission.[3]

To understand the structural aspects of their interaction, we have synthesized 3-(adenin-9-yl)-*N*-(2-succinimidyl)propionamide as a model and determined its crystal structure.

Experimental and Structure Determination

3-(Adenin-9-yl)propionic acid (**1**) was prepared by the method reported by Kondo, Miyata, and Takemoto[4] and DL-asparagine methyl ester hydrochloride (**2**) was derived from DL-asparagine. The condensation of **1** and **2** by dicyclohexylcarbodiimide method gave *N*-[3-(adenin-9-yl)propionyl]-DL-asparagine methyl ester, and the product was spontaneously converted into 3-(adenin-9-yl)-*N*-(2-succinimidyl)propionamide in a methanol solution saturated with ammonia.

Colourless plate crystals were obtained from an aqueous solution. Density was measured by flotation in a mixture of cyclohexane and carbon tetrachloride. A crystal, 0.35×0.35×0.1 mm³ in size, was mounted on a Rigaku automated four-circle diffractometer. Nickel-filtered Cu $K\alpha$ radiation (λ=1.54184 Å) was used. The accurate unit-cell dimensions were derived from the 2θ values of 34 high-angle reflexions. Crystallographic data are summarized in Table 1. Intensities were measured on the diffractometer by means of ω scanning ($2°<2\theta<125°$), the scan speed being 4°/min and scan width 1.2° plus α_1–α_2 divergence. Five reference reflexions monitored periodically showed no significant intensity deterioration. Corrections were made for Lorentz and polarization factors, but not for absorption effects. A total of 2153 independent reflexions were obtained, 378 of which had no net intensities; the observational threshold value, F_{lim}, was 1.96. The standard deviations were estimated by the equations $\sigma^2(F_o)=\sigma_P^2(F_o)+qF_o^2$, where $\sigma_P(F_o)$ was evaluated by counting statistics and $q(1.22\times10^{-5})$ was derived from the variations of the monitored reflexions.

TABLE 1. CRYSTAL DATA FOR 3-(ADENIN-9-YL)-*N*-(2-SUCCINIMIDYL)PROPIONAMIDE

Chemical formula: $C_{12}H_{13}N_7O_3$	
Space group: $P2_1/c$	
a/Å=10.861(1)	V/Å³=1683.5(1)
b/Å=12.766(1)	Z=4
c/Å=9.753(1)	D_m/g cm^{-3}=1.49
β/°=91.10(1)	D_x/g cm^{-3}=1.490

† 2-Succinimidyl=2,5-dioxo-3-pyrrolidinyl

The structure was solved by the direct method using MULTAN 78 programme[5] and the atomic parameters were refined by the full-matrix least-squares method. The quantity minimized was $\sum\omega(|F_o|-|F_c|)^2$, where $\omega=1/\sigma^2(F_o)$. In the refinement, the zero-reflexions with $|F_c|>F_{lim}$ were included by assuming $F_o=F_{lim}$ and $\omega=\omega(F_{lim})$. All the hydrogen atoms were found on a difference map and included in the refinement.

The final R value was 0.059 for 1875 reflexions with $|F_o|>3\sigma(F_o)$; the maximum shift of parameters in the last cycle was 0.1σ for C, N, O, and 0.3σ for H. Atomic scattering factors were taken from Ref. 6. The atomic parameters of the non-hydrogen atoms are listed in Table 2.[7]

Results and Discussion

Molecular Structure. Figure 1 shows a stereoscopic view of 3-(adenin-9-yl)-*N*-(2-succinimidyl)propionamide molecule. Bond lengths and angles are shown in Fig. 2.

The dimensions of the adenine moiety are in good agreement with those found in 9-methyladenine,[8] 3-(adenine-9-yl)propionamide[9] and 3-(adenin-9-yl)propionic acid.[10] The adenine moiety is planar with maximum displacement of 0.016 Å for N(9) from the least-squares plane. The bond lengths and angles of the succinimide moiety are similar to those found in 2-(3-bromo-4-ethoxyphenyl)succinimide.[11] The succinimide moiety has a half-chair form; the value of P defined by Pitzer and Dorath[12] is −13.3°, which is between those of E_2 and ${}_1T_2$. The deviations of C(15) and C(16) from the plane [C(17), N(18), C(19)] are 0.150 Å and −0.083 Å, respectively. This conformation is different from the envelope form of 2-(3-bromo-4-ethoxyphenyl)succinimide. The dihedral angle between two amide planes [C(19), O(19), N(18)] and [C(17), O(17), N(18)] is 5.7°.

As shown in Fig. 1, the molecule is extended; torsion

angles, N(9)-C(11)-C(12)-C(13) and C(11)-C(12)-C(13)-N(13) are 69.5° and −149.5°, respectively. The conformation is similar to that found in the complex 3-(adenin-9-yl)propionamide : 1-methylthymine dihydrate[13] and 3-(adenin-7-yl)propionamide monohydrate.[14] The dihedral angle between the adenine and the mean plane of succinimide moiety (C(15), C(16), C(17), O(17), N(18), C(19), O(19)) is 6.2(1)°.

Table 2. Fractional coordinates and equivalent isotropic temperature factors of the non-hydrogen atoms in 3-(adenin-9-yl)-*N*-(2-succinimidyl)propionamide

Atom	*x*	*y*	*z*	*B*/Å²
N (1)	0.8782 (2)	0.3078 (2)	0.3446 (3)	2.9⟨10⟩
C (2)	0.9222 (3)	0.3974 (2)	0.2916 (4)	3.4⟨13⟩
N (3)	1.0051 (2)	0.4102 (2)	0.1940 (3)	3.2⟨12⟩
C (4)	1.0454 (3)	0.3171 (2)	0.1478 (3)	2.6⟨5⟩
C (5)	1.0107 (3)	0.2194 (2)	0.1935 (3)	2.5⟨4⟩
C (6)	0.9226 (3)	0.2160 (2)	0.2955 (3)	2.6⟨8⟩
N (6)	0.8799 (3)	0.1266 (2)	0.3494 (3)	3.2⟨15⟩
N (7)	1.0728 (2)	0.1418 (2)	0.1249 (3)	3.2⟨9⟩
C (8)	1.1426 (3)	0.1926 (2)	0.0392 (3)	3.2⟨8⟩
N (9)	1.1295 (2)	0.3005 (2)	0.0480 (2)	2.7⟨7⟩
C (11)	1.2000 (3)	0.3806 (2)	−0.0248 (3)	3.0⟨7⟩
C (12)	1.3096 (3)	0.4157 (2)	0.0628 (4)	3.0⟨8⟩
C (13)	1.4045 (3)	0.3295 (2)	0.0753 (3)	2.9⟨6⟩
O (13)	1.4321 (2)	0.2750 (2)	−0.0233 (2)	3.5⟨9⟩
N (14)	1.4604 (2)	0.3174 (2)	0.1977 (3)	3.1⟨8⟩
C (15)	1.5612 (3)	0.2446 (3)	0.2131 (3)	3.2⟨7⟩
C (16)	1.5306 (3)	0.1267 (3)	0.1994 (4)	3.7⟨15⟩
C (17)	1.6315 (3)	0.0833 (3)	0.1116 (3)	3.7⟨5⟩
O (17)	1.6519 (2)	−0.0086 (2)	0.0884 (2)	4.9⟨19⟩
N (18)	1.6973 (2)	0.1665 (2)	0.0572 (3)	3.2⟨8⟩
C (19)	1.6574 (3)	0.2628 (3)	0.1038 (3)	3.1⟨6⟩
O (19)	1.6951 (2)	0.3466 (2)	0.0651 (2)	3.9⟨13⟩

The equivalent isotropic temperature factors are calculated from anisotropic thermal parameters using the equation $B=8\pi^2(U_1+U_2+U_3)/3$, where U_1, U_2, and U_3 are principal components of the mean square displacement matrix U. Values in ⟨ ⟩ are anisotropicity defined by $(\Sigma(B-8\pi^2U_i)/3)^{1/2}$ and those in ( ) are e.s.d.'s; they refer to the last decimal places.

Crystal Structure. The crystal structure viewed along the b axis is shown in Fig. 3. The geometries of hydrogen bonds are given in Table 3. The succinimide moiety is linked to the adenine moiety at $(1+x, 1/2-y, 1/2+z)$ by the hydrogen bonds, N(18)H···N(1) and O(19)···HN(6). The dihedral angle between the least-squares planes of these two moieties is 5.2(1)°. These and the N(6)H···N(3) hydrogen bonds between the molecules related by the two-fold screw make sheets parallel to (101) as shown in Fig. 4.

Another hydrogen bond N(14)H···O(13) between peptide groups links the sheets together. This N(14)H seems to make a bifurcated hydrogen bond, though the N(14)H···O(17) distance is rather long (3.297(4) Å).

The adenine moieties related by the c glide are stacked on each other at the distance of 3.558(5) Å for C(2)···C(8) and 3.412(4) Å for N(1)···C(8). Another closest contact is 3.456(4) Å between C(6) at (x, y, z) and C(8) at $(-1+x, y, z)$.

Interaction between Cyclic Ureide and Adenine. Figure 5 shows the hydrogen bonding patterns found

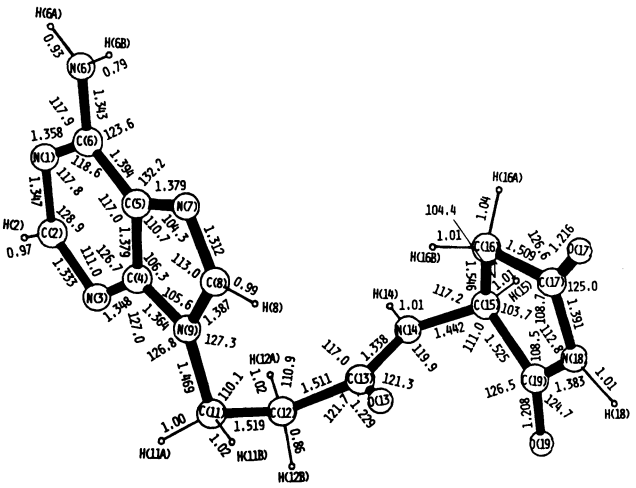


Fig. 2. Atomic numbering and bond lengths (l/Å) and angles (ϕ/°) in 3-(adenin-9-yl)-*N*-(2-succinimidyl)-propionamide. E.s.d.'s for bond lengths and angles are 0.004–0.005 Å and 0.3°, respectively.

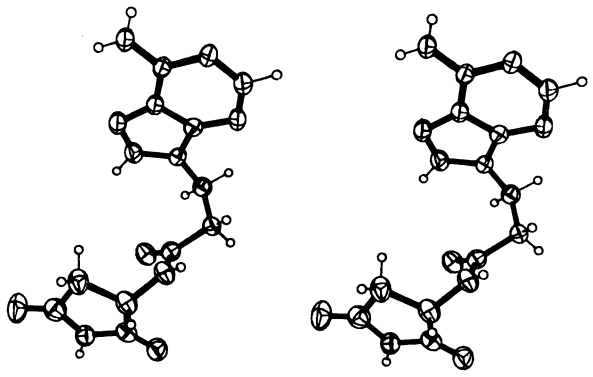


Fig. 1. Stereoscopic view of 3-(adenin-9-yl)-*N*-(2-succinimidyl)propionamide with 50% probability ellipsoids.

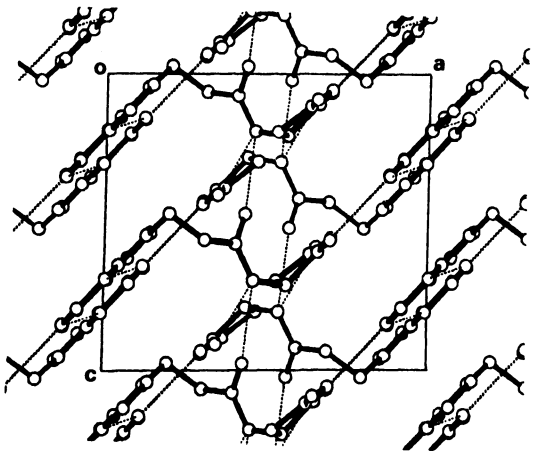


Fig. 3. Crystal structure of 3-(adenin-9-yl)-*N*-(2-succinimidyl)propionamide projected along the b axis.

in the adenine complexes with several cyclic ureide derivatives. Barbiturates interact with adenine through the two kinds of double hydrogen bonds; type 1 is a combination of NH···N(1) and O···HN(6) and type 2 is NH···N(7) and O···HN(6).[15,16] The present crystal exhibits the hydrogen bonds of type 1, while the scheme in parabanic acid with a similar cyclic ureide skeleton is type 2.[17] Recently it has been reported that 2-thiohydantoin interacts with adenine at the N(3) or N(7) site.[18]

In order to examine the preferential hydrogen bonding sites of adenine, the formation energies of possible complexes were calculated by CNDO/2 approximation[19] (Table 4). The formation energies with barbi-

Table 3. Hydrogen bonds in 3-(adenine-9-yl)-*N*-(2-succinimidyl)propionamide

E.s.d.'s are given in parentheses referring to the last decimal places.

X-H···Y	X···Y(*l*/Å)	XHY(*φ*/°)
N(6)-H(6A)···O(19)[i]	2.955(3)	172(2)
N(6)-H(6B)···N(3)[ii]	3.064(4)	170(3)
N(14)-H(14)···O(13)[iii]	2.986(3)	114(2)
N(14)-H(14)···O(17)[iv]	3.297(4)	156(3)
N(18)-H(18)···N(1)[v]	2.903(3)	165(3)

Symmetry codes:

i) $-1+x, \frac{1}{2}-y, \frac{1}{2}+z$ iv) $3-x, \frac{1}{2}+y, \frac{1}{2}-z$

ii) $2-x, -\frac{1}{2}+y, \frac{1}{2}-z$ v) $1+x, \frac{1}{2}-y, \frac{1}{2}+z$

iii) $x, \frac{1}{2}-y, \frac{1}{2}+z$

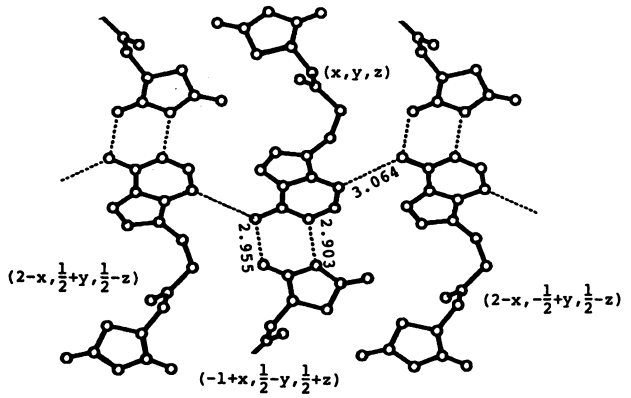


Fig. 4. Hydrogen bonds in the molecular sheet of 3-(adenin-9-yl)-*N*-(2-succinimidyl)propionamide.

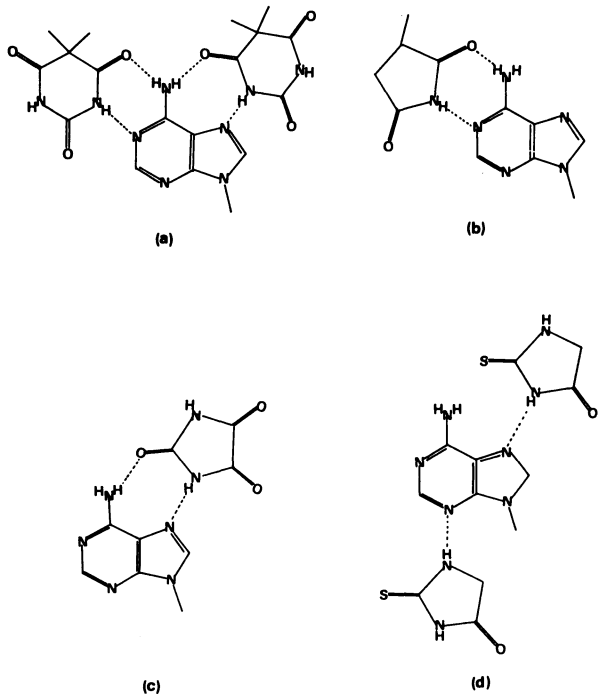


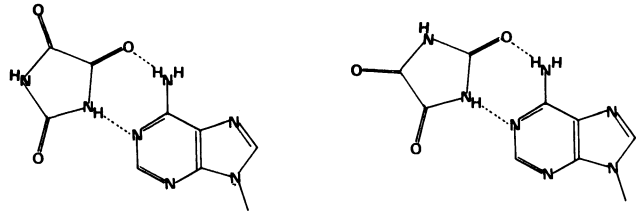
Fig. 5. The hydrogen bonding patterns of (a) adenine-barbiturate[15,16] (b) adenine-succinimide (the present study), (c) adenine-parabanic acid[17] and (d) adenine-2-thiohydantion[18].

Table 4. The difference in formation energy (ΔE/kcal mol^{-1}) between type 1 and type 2 of some cyclic ureides and 9-methyladenine by CNDO/2 calculation

Type 1 is a combination of NH···N(1) and O···NH(6) and type 2 is NH···N(7) and O···NH(6). 1 cal=4.186 J.

	Barbiturate	Parabanic acid	2-Methylsuccinimide
E(Type 2)-*E*(Type 1)	+0.2	−1.6(I) −2.0(I′)	−0.4

In the calculation, hydrogen bond geometries are taken from Ref. 15, Ref. 17, and the present study. Type 1 of parabanic acid (two modes, I and I′) and type 2 of 2-methylsuccinimide are hypothetical structures.



(I) (I′)

turate are almost the same for the two types of hydrogen bonding. In the case of the parabanic acid, however, the type 1 is distinctly less stable than the type 2. These results are consistent with the hydrogen bonding patterns found in the respective crystals, suggesting that the hydrogen bonding scheme in model crystals comes from the inherent nature of the components. In the present combination of adenine and succinimide, there is no significant difference in formation energy so that the other type (type 2) would be found if the crystallizing condition is adjusted suitably.

While barbiturate and succinimide derivatives have anti-convulsant effect, parabanic acid and 2-thiohydantoin containing similar molecular skeleton do not exhibit such effect.[1] Activity and inactivity seem to be associated with the different hydrogen bonding patterns; that is cyclic ureide anticonvulsant drugs possess the capability of interacting with N(1) and N(6) sites of adenine.

Recently, it has been reported that diphenyl hydantoin and pentobarbital inhibit the protein synthesis in rat brain.[20-22] This side effect can be explained by the argument that they might interact with adenine at N(1) and N(6), which are the sites forming the Watson-Crick base pair.

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