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Molecular Determinants for Drug-Receptor Interactions

1. Solid-State Structure and Conformation of the Novel Nootropic Agent 2-Pyrrolidone-*N*-Acetamide: X-Ray and Theoretical SCF-MO Studies

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SUMMARY

The crystal and molecular structure of 2-pyrrolidone-*N*-acetamide was determined by X-ray analysis. Crystal (monoclinic) data were as follows: $a = 16.376(8)$, $b = 6.413(5)$, $c = 6.493(5)$ Å; b = 92.21(5)°, $Z = 4$, space group $P2_1/n$. The 2-pyrrolidone ring and the amide group are planar, their planes being almost perpendicular (dihedral angle between the normals is 88.2°) with the C═O fragment of the amide group directed toward the ring (in a perpendicular *trans* arrangement). All bond angles and distances were in good agreement with expected standard values. In the crystals, two molecules from a dimer through N(2)(X,Y,Z)----O(2) (1 − X, 1 − Y, 1 − Z) and its symmetrical equivalent, linked by hydrogen bonds of 2.95 Å, with an additional hydrogen bond of 2.93 Å between N(2)(X,Y,Z) and O(1)(X,Y, 1 + Z). The N(1) atom of the ring is not involved in any such interactions. Geometry and conformation of the 2-pyrrolidone ring were reviewed. The results of quantum mechanical calculations, carried out using an *ab initio* method with an STO-3G basis set indicate for the free molecule a preferred, twisted *cis* conformation that appears essentially determined by the intramolecular hydrogen bond between the O(1) atom and the amide group. The shape of the minimum energy zone (wide and shallow) and the small energy difference between the twisted *cis* conformation and the one found in the crystal suggest that in solution the conformation of the solid is partially retained and that an equilibrium is likely to occur between several energetically preferred conformations.

INTRODUCTION

One of the most important factors determining pharmacological activity is the electronic and spatial structure which governs the fit of the drug to a suitable portion of the biophase, the receptor. In particular, previously found conformation-activity relationships indicate that several drug molecules engage their receptor in the preferred conformation, at least in the initial contact (1, 2).

The conformation of a molecule, which is strictly related to its electronic structure, can be determined experimentally by physical methods in the crystal state (X-ray diffraction), in the solution state (NMR spectroscopy, dipole moment), and in the gas phase (electron diffraction). Theoretical quantum-mechanical methods are also applied to investigate the conformation and the electronic structure of the "isolated molecule," although it is recognized that the effect of a solvent medium is of importance if the results of the conformational investigation are to have relevance in the biophase. However, it should be stressed here that the complete understanding of the conformational and electronic properties of drug molecules, which is essential to an elucidation of their precise mode of action, can be achieved by the simultaneous use of several independent techniques that are complementary to each other; in this way the shortcomings of each single experimental or theoretical technique are overcome. Such verification and mutual reinforcement between theoretical and experimental findings are applied here to investigate the conformational properties of 2-PNA,[4] which is now currently used in clinical

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[4] The abbreviation used is: 2-PNA, 2-pyrrolidone-*N*-acetamide.

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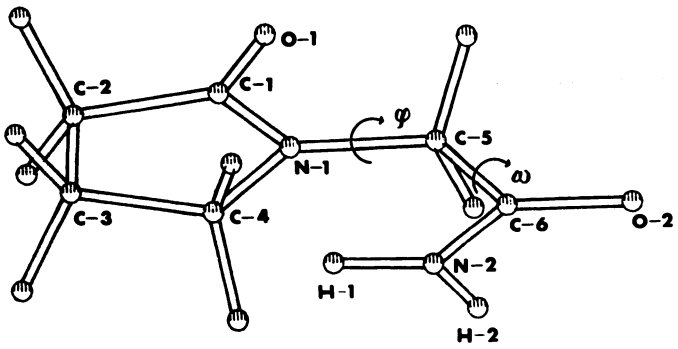


FIG. 1. *Perspective view of the 2-PNA molecule in the conformation* $\omega = \varphi = 0$

The planes C(1),N(1),C(4) and C(5),C(6),N(2) are coplanar. The assumed rotation sense is shown by the *arrows*. The molecular plane lies on the *x,y* plane of the reference axis that makes an angle of 30° with the plane of the paper. The numbering scheme of the atoms is also shown.

practice owing to its potent and specific neuropharmacological activity.

The first human pharmacological studies on 2-PNA showed its efficacy against motion sickness and vertigo of cerebrovasculaar origin (ref. 3 and references therein). Further investigations, initiated after 1967, demonstrated that 2-PNA is a drug that selectively enhances the efficiency of interhemispheric communication and, accordingly, preferentially facilitates cortically integrated mental functions (4). New pharmacoclinical data from both animal and human studies permitted a differential and experimental definition of "nootropic drug," the term "nootropic" being proposed to indicate a new class of psychoactive drugs that characteristically interfere with higher telencephalic integrative activity by a direct and selective action (5). The main features of 2-PNA from the clinical point of view correspond to its therapeutic efficacy in postconcussion syndrome, in post-traumatic coma, in enhancing learning acquisition and resistance by the brain to physical and chemical injuries, and in geropsychiatry and related chronic brain syndrome (6–8).

The biochemical basis of action of 2-PNA has been investigated more recently, and some effects on cortical metabolism have been considered responsible for the activity of 2-PNA on the central nervous system (9–11). The lack of conformational and structural information, which could be essential in an interpretation of the mechanism of action in molecular terms, prompted us to undertake the present study of 2-PNA as an isolated molecule and in the crystal state. In this work, X-ray structure analysis was combined with theoretical SCF-MO calculations in order to predict whether the conformation found in the solid state is unique and can be entirely retained in solution and thus in the biophase.

The rationale behind this endeavor also suggested that subsequent comparison of the conformation of 2-PNA with other central nervous system-active drugs might reveal information about structural requirements for receptor binding and about possible structural considerations for the design of new nootropic agents.

TABLE 1

Positional and thermal parameters of non-hydrogen atoms

Atom	Positional parameters ($\times 10^4$)[a]		
	X/a	Y/b	Z/c
C(1)	3345 (5)	620 (14)	69 (13)
C(2)	3700 (6)	−1146 (15)	−1124 (13)
C(3)	3986 (7)	−2663 (16)	473 (15)
C(4)	3913 (6)	−1615 (15)	2587 (16)
C(5)	3283 (5)	1775 (15)	3689 (14)
C(6)	4038 (5)	3021 (15)	4304 (13)
N(1)	3437 (4)	267 (11)	2087 (10)
N(2)	4034 (5)	3869 (12)	6186 (10)
O(1)	3002 (4)	2200 (11)	−623 (10)
O(2)	4600 (4)	3182 (11)	3122 (10)

Atom	Thermal parameters ($\times 10^2$)[b]					
	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	3.49	3.83	3.82	−0.81	−0.45	0.73
C(2)	7.62	5.04	3.59	−1.09	1.08	−1.29
C(3)	8.16	4.93	4.59	0.87	0.62	0.08
C(4)	6.88	3.72	5.77	0.36	−0.84	0.59
C(5)	3.45	5.08	5.78	−0.28	0.75	−0.39
C(6)	4.15	4.23	4.76	0.41	1.46	1.60
N(1)	5.00	3.47	3.59	−0.57	0.41	0.41
N(2)	6.31	5.66	3.58	−0.79	0.93	−0.58
O(1)	5.83	5.59	5.92	1.02	−0.12	1.78
O(2)	6.86	5.30	6.39	−1.94	1.99	−0.94

[a] Estimated standard deviations are shown in parentheses.

[b] The anisotropic temperature factor expression used was of the form $\exp[-2\pi^2(U_{11}a^{*2}h^2 + U_{22}b^{*2}k^2 + \ldots\ldots\ldots + 2U_{12}a^*b^*hk + \ldots\ldots)]$.

EXPERIMENTAL PROCEDURE

The sample of 2-PNA (gift from ucb-Smith, Torino, Italy) was crystallized from isopropanol (m.p. 154°). A small crystal of irregular shape and badly defined planes, elongated along [100], was also collected and sealed in a glass capillary tube to be used for X-ray diffraction data collection.

Crystal data. Crystal data were as follows: $C_6H_{10}N_2O_2$, FW = 142.2; monoclinic, space group $P2_1/n$ (an alterna-

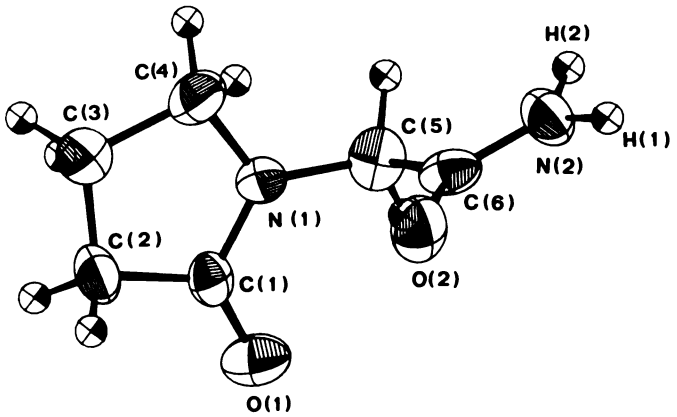


FIG. 2. *Numbering system, molecular conformation (viewed along the a axis), and thermal ellipsoids for 2-PNA*

Hydrogen atoms are artificially small for clarity.

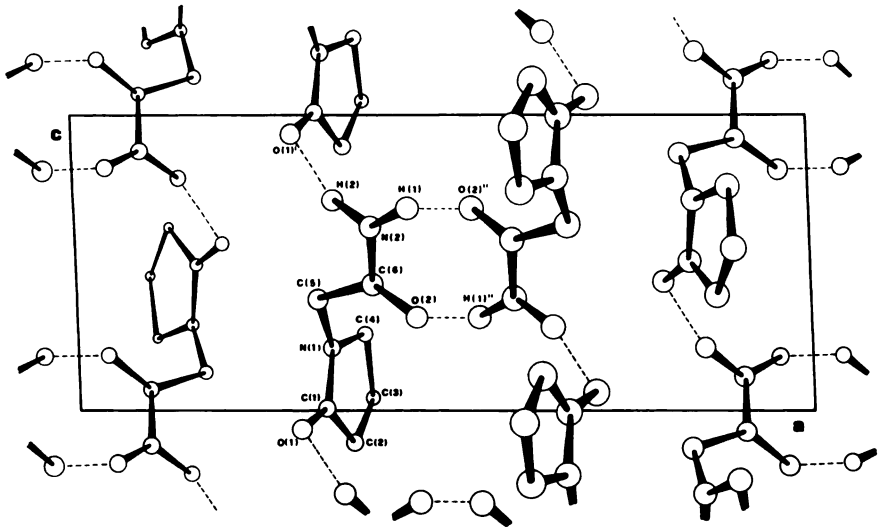


FIG. 3. *Crystal structure projected along the b axis, showing the hydrogen atom-bonding system in 2-PNA*

tive setting of the conventional space group $P2_1/c$); a = 16.376(8), b = 6.413(5), c = 6.493(5) Å; B = 92.21(5)°; U = 681.4 Å^3, D_m = 1.37 (by flotation in hexane/CCl_4), Z = 4, D_x = 1.385 gcm^{-3}; F(OOO) = 304. Mo-Kα radiation, λ = 0.7107 Å; μ(Mo-Kα) = 0.7 cm^{-1}.

Three-dimensional X-ray diffraction data from the small crystal fragment were collected on a computer-controlled four-circle Philips PW1100 diffractometer by use of Mo-Kα radiation with graphite monochromator (50 kV, 35 mamp). A coupled $\vartheta - 2\vartheta$ step scan with a counting time of 0.03° sec^{-1} and a peakwidth of 1.5 + 0.3 tgϑ were used. In the range 2ϑ = 3–50°, 1430 observations covering one-fourth of reciprocal space were collected. This number reduced to 1205 symmetry-independent reflections, of which only 600 were defined as observed having $F_0 \geq 3\sigma(F_0)$. This phenomenon can be explained by the small size of the crystal used for the measurements. The data were corrected for Lorentz and polarization effects but not for absorption or extinction.

Structure determination and refinement. The structure was solved by direct-phase determination (12) and refined by least-squares with anisotropic temperature factors for all of the non-hydrogen atoms, by use of observed reflections only and unit weights. Atomic scattering factors for non-hydrogen atoms were taken from Cromer and Weber (13) and for hydrogen from the international tables (14). The symbolic addition procedure led to an E map that contained all of the non-hydrogen atoms, and the initial R factor was 0.22. After six peaks at reasonable locations for hydrogen atoms had appeared on a difference map (the hydrogen atoms bonded to C(3), and C(5) did not appear), all of the hydrogen atoms were assigned tetrahedral positions 1.07 Å from the parent carbon atoms and a planar location 1.07 Å from the N(2) atom. Hydrogen parameters were put as fixed during the refinement, with a common temperature factor of 5 Å^2. The designation of the O(2) and N(2) atoms in the amide group is supported by the bond distances, the temperature factors, and the hydrogen atom peaks in the difference map. The final R factor was 0.092. The maximal peak height in the final difference-Fourier synthesis was 0.49 eÅ^{-3}.

It must be mentioned here that we were unable to decide between $P2_1$ and $P2_1/n$. In fact, we found that the 205 reflection was present with medium intensity and the 203 reflection with weak but observable intensity. On the other hand, there was no evidence for any twinning, all of the unit cells derived from the Weissenberg photographs being consistent with those given by the diffractometer. In any case, even if the crystal under study was not properly a single crystal, it behaved on the Philips PW1100 as though it were, with space group $P2_1/n$. Moreover, a careful examination of the crystal, when the refinement procedure was accomplished, showed the presence of a very small misoriented portion of the sample (satellite crystal). This occurrence can affect adversely the intensity of some reflections. However, we know of no one practical method of performing any appropriate correction. After transformation of the atomic coordinates, the model was refined in the space group $P2_1$, but in this hypothesis some bond lengths and angles became unrealistic and some temperature factors not positively definite.

QUANTUM MECHANICAL CALCULATIONS

Ab initio molecular orbital theory (restricted Hartree-Fock with STO-3G basis set) (15) was used to investigate the conformational energy of 2-PNA. All calculations were carried out using the standard Gaussian 70 program (16). The adopted geometric parameters were assumed on the basis of the known structures of the component 2-pyrrolidone and acetamide moieties. In particular, the geometry of the ring was that correspnding to the minimal-energy full-planar structure calculated by means of consistent force field analysis of the vibrational spectrum (17); bond lengths and angles of the acetamide group were those reported by an X-ray structure analysis of the solid (18). The standard values of 1.09 Å and 1.01 Å were assumed for all of the C—H and N—H bond lengths,

TABLE 2

Molecular geometry in 2-PNA

Bond lengths (Å)[a]			
C(1)—C(2)	1.50	N(1)—C(1)	1.33
C(1)—O(1)	1.23	N(1)—C(5)	1.45
C(2)—C(3)	1.48	C(5)—C(6)	1.51
C(3)—C(4)	1.54	C(6)—O(2)	1.23
C(4)—N(1)	1.47	C(6)—N(2)	1.34

Bond angles[b]			
N(1)—C(1)—C(2)	110.4°	C(4)—N(1)—C(5)	119.7°
N(1)—C(1)—O(1)	122.0	C(1)—N(1)—C(5)	125.2
O(1)—C(1)—C(2)	127.6	N(1)—C(5)—C(6)	112.2
C(1)—C(2)—C(3)	104.6	C(5)—C(6)—O(2)	120.3
C(2)—C(3)—C(4)	107.7	O(2)—C(6)—N(2)	124.7
C(3)—C(4)—N(1)	102.8	C(5)—C(6)—N(2)	115.0
C(4)—N(1)—C(1)	113.4		

Nonbonded contacts (Å)					
C(1)---C(3)	2.36	C(2)---O(1)	2.46	C(5)---O(2)	2.38
C(1)---C(4)	2.34	C(3)---N(1)	2.35	C(6)---N(1)	2.46
C(1)---C(5)	2.47	C(4)---C(5)	2.52	N(1)---O(1)	2.25
C(2)---C(4)	2.44	C(5)---N(2)	2.41	N(1)---O(2)	2.73
C(2)---N(1)	2.33	C(5)---O(1)	2.83	N(2)---O(2)	2.27

Least-squares planes[c]

Plane	*P*	*Q*	*R*	*S*
1 N(1),C(1),C(2),C(3),C(4) [N(1) −0.04,C(1)0.00, C(2)0.04,C(3) −0.06,C(4)0.06,C(5)0.12, O(1)0.00]	14.49	2.98	−0.38	5.03
2 C(5),C(6),O(2),N(2) [C(5),C(6),O(2),N(2)0.00,C (1) −0.22,C(2)0.66,N(1)0.51, H(1)0.01,H(2)0.02]	6.70	−5.29	2.43	2.15

Torsion angles[d]			
N(1)—C(1)—C(2)—C(3)	−2.5°	C(4)—N(1)—C(1)—C(2)	−5.0°
C(1)—C(2)—C(3)—C(4)	8.5	C(4)—N(1)—C(5)—C(6)	−73.1
C(2)—C(3)—C(4)—N(1)	−11.0	C(1)—N(1)—C(5)—C(6)	89.1
C(3)—C(4)—N(1)—C(1)	10.0	N(1)—C(5)—C(6)—N(2)	157.3

Hydrogen bonds			
N(2)---O(1)[i][e]	2.93 Å; N(2)—H(2)	1.07 Å; H(2)---O(1)[i]	1.94 Å;
		N(2)—H(2)---O(1)[i]	151°
N(2)---O(2)[ii]	2.95 Å; N(2)—H(1)	1.07 Å; H(1)---O(2)[ii]	1.94 Å;
		N(2)—H(1)---O(2)[ii]	157°

[a] Estimated standard deviation, taking into account the accuracy of cell dimensions, 0.02 Å.

[b] Estimated standard deviation, taking into account the accuracy of cell dimensions, 1.4°.

[c] Least-squares planes [with the deviations (Å) of relevant atoms in brackets] are given by the formula $Px + Qy + Rz = S$, where x, y, and z are fractional unit-cell coordinates.

[d] Clockwise rotation of the first-quoted bond is taken as positive; anti-clockwise rotation is taken as negative (Ref. 22).

[e] The codes for symmetry-related atoms are as follows: the symbol i has the symmetry code x, y, $1 + z$; the symbol ii has the symbol code $1 - x$, $1 - y$, $1 - z$.

respectively. The N(1)—C(5) distance (1.47 Å) was assumed to be equal to the value found for the 2-pyrrolidone-*N*-methyl fragment in the crystal structure of oxotremorine (19).

Calculations were performed for each conformation corresponding to the possible combinations of the angles ω, φ, from 0 to 360°, at 20° intervals. The angles ω and φ were assumed to change in clockwise direction, along the correspondng N(1)-C(5) and C(5)-C(6) axes, starting from the $\omega = \varphi = 0°$ conformation outlined in Fig. 1.

Plotting of the perspective-view drawings of 2-PNA was made by using the PLUTO computer program (20).

RESULTS AND DISCUSSION

X-ray analysis. The final atomic positional parameters with their standard deviations, and thermal factors for the non-hydrogen atoms are listed in Table 1. An ORTEP (21) plot of the molecular conformation in the solid state is shown in Fig. 2, and the packing is illustrated in Fig. 3. The molecular geometry, including a listing of interatomic distances and angles, least-square planes, torsion angles, and hydrogen bond geometry, is presented in Table 2. The dimensions and conformation of the 2-pyrrolidone ring in 2-PNA are reported in Table 3 and Table 4 together with a review of the data available for this ring in different systems.

The reliability factor for the structure is larger than that commonly achieved, owing to the fact that the crystal was not a properly single one and the number of reflections was limited when compared with the number of refined parameters. However, there is little doubt that the packing is correct. The values of bond lengths and angles also indicate that the conformation derived from the analysis is fully reliable, since these parameters appear to be quite regular when compared with previously known structures (Table 3), the differences being within 2σ. In particular, the C(1)—N(1) distance in the five-membered ring (1.33 Å) is shorter than that of a single C-N bond, whereas the C(1)—O(1) bond length (1.23 Å) is somewhat longer than the usual carbonyl bond length, thus indicating a partial conjugation between the π-bonding of C(1)—O(1) and the nitrogen atom lone pair.

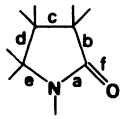
The conformation of the ring is an interesting feature, since among all of the previously reported structures (see Table 4) the 2-pyrrolidone moiety is essentially planar only in 2-PNA and oxotremorine sesquioxalate (19).

Another salient result is the dihedral angle (88.2°) between the mean planes of the ring and the amide group: these are perpendicular within the limit of experimental error. In the solid state the 2-PNA molecule shows an important feature owing to the dimer formed by two molecules through N(2)(X,Y,Z)----O(2) (1 −X, 1 − Y, 1 − Z) and its symmetry equivalent O(2)(X, Y, Z)----N(2) (1 − X, 1 − Y, 1 − Z) linked by hydrogen atom bonds of 2.95 Å. This is the determining factor, presumably, of the mutual orientation of the hetero ring and the amide group in 2-PNA in the crystal. An additional hydrogen atom bond of 2.93 Å is formed between N(2)(X,Y,Z) and O(1)(X,Y,1 + Z). The geometrical configurations of these bonds (Table 2) are quite appropriate.

Theoretical calculations. The energy contour map of 2-PNA as an isolated molecule is shown in Fig. 4. Two equivalent energy minima are seen which correspond to the conformation $\omega = 60$, $\varphi = 90$ shown in Fig. 5. This

TABLE 3

Dimensions of the 2-pyrrolidone ring



Compound	Distances (Å)						Angles							Compound ref.
	a	b	c	d	e	f	ab	bc	cd	de	ea	af	fb	
L-5-Iodiomethylpyrrolid-2-one	1.35	1.47	1.52	1.56	1.45	1.24	110°	105°	106°	102°	114°	124°	125°	*a* (23)
L-5-Carboxamide pyrrolid-2-one	1.35	1.46	1.53	1.54	1.49	1.23	109	106	103	104	113	125	126	*a* (23)
Trimethyl-4-(2-oxopyrrolidin-1-yl)but-2-ynyl ammonium iodide	1.36	1.50	1.52	1.52	1.47	1.23	108	105	104	103	113	125	127	*b* (24)
4-Hydroxy-4,5-dimethyl-3,5-diphenylpyrrolidin-2-one	1.34	1.52	1.55	1.57	1.46	1.23	108	103	103	101	115	126	126	*c* (25)
Oxotremorine sesquioxalate	1.33	1.50	1.54	1.50	1.46	1.22	109	104	107	104	115	124	126	*d* (19)
3*R*-(1′-*S*-aminocarboxymethyl)-2-pyrrolidone-5*S*-carboxylic acid	1.35	1.53	1.53	1.55	1.45	1.23	107	104	102	103	113	126	126	*e* (26)
1-(2-Bromophenyl)pyrrolidin-2-one	1.33	1.52	1.54	1.52	1.48	1.19	109	104	106	103	115	125	126	*f* (27)
1,3-Dioxole-2-spiro-4′-(3′,3′-diethylpyrrolidin-2′-one)	1.33	1.53	1.55	1.53	1.46	1.23	110	100	105	102	114	125	125	*g* (28)
2-Pyrrolidone-α-cyclodextrin complex	1.39	1.46	1.50	1.54	1.47	1.26	113	105	107	106	109	122	125	*h* (29)
2-Pyrrolidone-*N*-acetamide	1.33	1.50	1.48	1.54	1.47	1.23	110	105	108	103	113	122	128	Present work
Mean	1.35	1.50	1.52	1.54	1.47	1.23	109	104	105	103	113	124	126	

result indicates the conformationally flexible nature of 2-PNA, owing to the broad and shallow minimal zone of conformational energy for which, in a wide range about the minimum, several possible conformations can be populated.

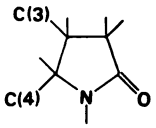
Two additional considerations are in order: (a) some conformations, corresponding to the *dotted areas* in Fig. 4, are energetically forbidden, and thus the possibility of essentially "free rotation" about the N(1)—C(5) and C(5)—C(6) bonds is to be ruled out for the molecule "isolated" as well as in solution; (b) the factor determining the preferred conformation appears to be the intramolecular hydrogen bond established between O(1) and H(2).

The changes in the calculated atomic charges, as the angles ω,φ vary, show how these parameters affect in a meaningful way the atoms directly involved in the hydrogen atom bonding. Although the remaining ring atoms do not change with ω,φ, their electronic charge, the —N—CO portion of the ring becomes more polar, i.e., N(1) less negative and O(1) more negative, for conformations near the minimum (see Table 5). An analogous trend is observable for the H(2) atom that increases its positive charge [in parallel with the negative charge of N(2)] and therefore its capacity to interact with O(1) through the space. The minimum of electronic energy is achieved for the conformation $\omega = 60$, $\varphi = 120$ (−1040.95 against −1035.52 a.u. calculated for the conformation $\omega = 60$, $\varphi = 90$), in which the above changes in electron charge are more pronounced. However, this difference does not contribute to a decrease in the total energy of the conformation $\omega = 60$, $\varphi = 120$ until, or below, the absolute minimal value found for $\omega = 60$, $\varphi = 90$, since the term due to the nuclear repulsion energy is considerably higher in the former conformation (555.569 versus 550.137 a.u. for $\omega = 60$, $\varphi = 90$). Such a difference between the nuclear repulsion energy terms also seems reasonably attributable to the interaction between the hydrogen-bonded atoms, their distance being 2.437 Å when $\omega = 60$, $\varphi = 90$ and 1.682 Å when $\omega = 60$, $\varphi = 120$. In the minimal energy conformation, clearly the O(1)—H(2) distance takes its optimal value for attractive interaction, whereas repulsive forces become preponderant below this value.

In conclusion, we see that, although the twisted *cis* conformation (60, 90) is calculated to be the global mini-

TABLE 4

Conformation[a] of 2-pyrrolidone ring for the compounds reported in Table 3



Compound ref.	Form of the ring	Deviations (Å) from the amide group N—C(1)—C(2)‖O	
a (23)	Puckered half-chair	C(3) +0.18	C(4) − 0.06
a (23)	Puckered half-chair	C(3) +0.23	C(4) −0.17
b (24)	Puckered half-chair	C(3) +0.26	C(4) −0.18
c (25)	Puckered envelope	C(3) +0.51	
d (19)	Substantially planar		
e (26)	Puckered envelope	C(3) +0.48	
f (27)	Puckered envelope	C(3) +0.10	
g (28)	Puckered envelope	C(3) +0.47	
h (29)	Puckered envelope	C(3) +0.10	
Present work	Substantially planar		

[a] Ref. 30.

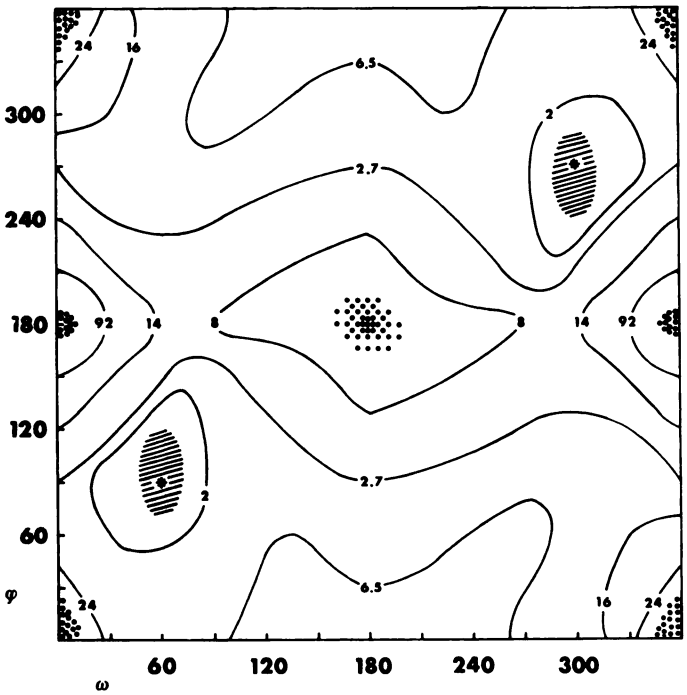


FIG. 4. *Contour map of theoretical conformational energy of 2-PNA as a function of the two internal rotation angles*

The figure reported on each isoenergy curve (in kilocalories per mole) is relative to the minimum taken as zero and marked by *asterisks*. The *dotted areas* correspond to extremely high energy values and therefore to forbidden conformations. The *dashed areas* denote the low-energy zones about the absolute minimum marked by *asterisks*.

mum, it is not observable in the solid state. However, it should be considered that the calculated energy difference between the two conformations is very small (about 2.5 Kcal mole^{-1} higher for the solid-state conformation) and thus that it falls within the limits of accuracy of the whole theoretical approach which, is well known, essentially depends on the basis set and on the assumed geometry. On this basis, some lack of reliability of the quantum mechanical method is limited to its capacity to

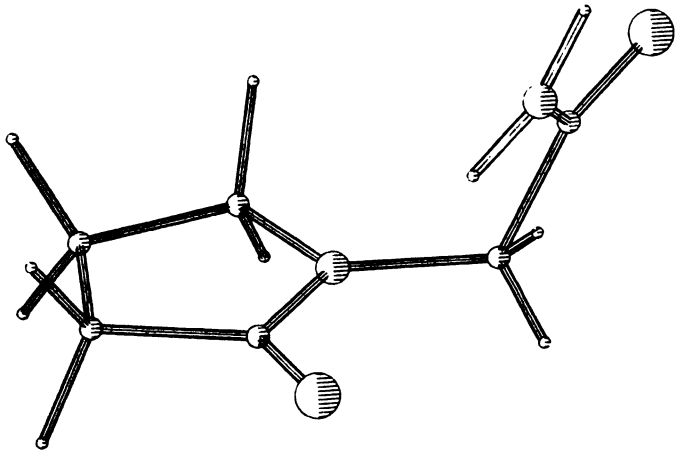


FIG. 5. *Perspective view of 2-PNA in the conformation ω = 60, φ = 90*

Hydrogen atoms are very small for clarity.

TABLE 5

Calculated atomic charges for 2-PNA in selected conformations

Atom	(ω, φ)			
	(60, 120)	(0, 90)	(60, 90)	(90, 90)
C(1)	0.321	0.301	0.305	0.306
C(2)	−0.128	−0.130	−0.129	−0.129
C(3)	−0.104	−0.105	−0.104	−0.104
C(4)	0.000	−0.004	−0.001	−0.001
C(5)	−0.034	−0.031	−0.033	−0.028
N(1)	−0.302	−0.313	−0.305	−0.303
N(2)	−0.469	−0.438	−0.443	−0.443
C(6)	0.286	0.294	0.289	0.287
H(1)	0.197	0.213	0.212	0.214
H(2)	0.250	0.206	0.216	0.214
O(1)	−0.321	−0.300	−0.316	−0.315
O(2)	−0.311	−0.307	−0.301	−0.302

distinguish the absolute global minimum within a wide range of conformations which scarcely differ from each other in their total energy content. With this in mind, the hypothesis seems plausible of a not-unique local minimum and thus the occurrence, in solution, of separate conformers of nearly equal energy. Such a hypothesis is in agreement with the views of Caillet *et al.* (21), who pointed out that the packing forces in the crystal can also stabilize a higher energy conformation and suggested that conditions for 2-PNA in the crystallization milieu have altered the relative stability to support the crystallization of one form over the other. Therefore, integration with complementary experimental data, such as dipole moment and NMR spectroscopic methods to determine the conformation of 2-PNA in solution, appears crucial for checking the reliability of theoretical predictions for the free molecule as well as for accurate comparison of the conformational results from separate methods.

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