tion rates for chromium(V). The same type of expression (eq 25), with appropriately modified constants, can be derived for the oxidation in the presence of acrylamide. Figure 3 shows that a good straight line plot can be obtained if the data given in Table V are plotted according to eq 25. It is gratifying to find an excellent agreement between the relative rates for the chromic acid oxidation of cyclobutanol with respect to oxalic acid determined from eq 25 in the presence of acrylamide ($k_5/k_6 = 0.61$) and those determined from eq 16 in the absence of acrylamide ($k_5/k_6 = 0.63$).

$$\frac{3 - x}{2x - 1} = \frac{k_5}{k_6}\frac{[\mathrm{ROH}]}{[(\mathrm{CO_2H})_2]} \qquad (25)$$

The striking difference between the behavior of acrylonitrile and acrylamide is most likely the result of the considerably higher electronegativity of the –CN group as compared with the $-CONH_2$ group. The different behavior of the two polymer radicals could be caused either by the change in reactivity of the radical toward oxidation or toward dimerization. However, as the activation energy for the dimerization reaction is expected to be quite low, it is more plausible to assume that the difference in the behavior of the two radicals is a result of a considerably reduced reactivity toward oxidation resulting from the introduction of the strongly electronegative cyano group. It thus seems that the decrease in oxidation rates with increasing electronegativity of substituents observed in alcohols,[18,19] aldehydes[20] or carboxylic acids[21] also holds in the oxidation of free radicals.

(18) J. Roček, *Collect. Czech. Chem. Commun.*, **25**, 1052 (1960).
(19) H. Kwart and P. S. Francis, *J. Amer. Chem. Soc.*, 77, 4907 (1955).
(20) J. Roček, *Tetrahedron Lett.*, **No. 5**, 1 (1959).
(21) F. Mareš and J. Roček, *Collect. Czech. Chem. Commun.*, **26**, 2389 (1961).

On the Conformation and Synthesis of Diketopiperazines. 3,4-Dehydroproline Anhydride

Isabella L. Karle,[1] H. C. J. Ottenheym,[2] and B. Witkop*[2,3]

Contribution from the Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, D. C. 20375, and the National Institute for Arthritic and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014. *Received June 22, 1973*

Abstract: The amino acid 3,4-dehydro-D,L-proline was prepared from pyrrole-2-carboxylic acid and converted to the hydrochloride of the methyl ester with thionyl chloride in methanol. Liberation of the amino group with triethylamine resulted in the spontaneous formation of the diketopiperazine. Crystal structure analysis by X-ray diffraction showed that both halves of the molecule have the same configuration; *i.e.*, the dimerization occurred between two L molecules or two D molecules rather than between an L and a D molecule. The diketopiperazine ring occurs in a folded conformation with a dihedral angle of 139°. Hydrogen atoms on the two C^{α} atoms are axial and cis to each other. The space group is $P4_12_12$ with $a = 5.607 \pm 0.003$ Å, $c = 28.753 \pm 0.009$ Å, and four molecules in the unit cell.

Cyclic dipeptides with (modified) prolyl constituents occur in a number of natural products, such as the toxic principle prolyl-2(1′,1′-dimethylallyl)tryptophyldiketopiperazine[4] extracted from moldy maize meal, the therapeutic agent zizyphin,[5] and also in the epidithiodiketopiperazine systems of sporidesmin,[6] gliotoxin,[7] and chaetoxin,[8] for example.[9] The interest in 3,4-dehydroproline anhydride (IV) is twofold: first, as a possible intermediate suitable for the synthesis of natural products containing an epidithiodiketopiperazine system (I), the anhydride of 3,4-dehydroproline (IV) was synthesized. It was expected that replacement of the allylic hydrogens in the α positions by halogen would lead to intermediates which could then be converted to V by sulfur nucleophiles.[10] In the course of this work it was necessary to determine the exact structure of IV, in particular the stereorelationship of the two α-hydrogen atoms, since a disulfide bridge could be introduced only with the two α hydrogens in a cis relationship. X-Ray diffraction analysis of a single crystal of 3,4-dehydroproline anhydride established that both prolyl groups have identical configurations; or in other words, that the two hydrogen atoms in the diketopiperazine ring are on the same rather than on opposite sides as would be the case in a molecule composed of a D- and an L-prolyl group.

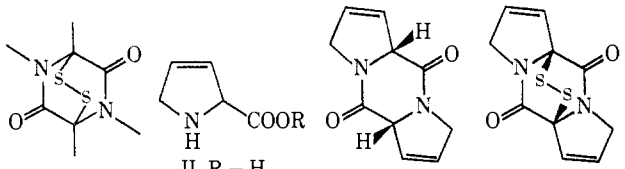
Our second interest is the conformation of the diketopiperazine ring in cyclic dipeptides as a function of

(1) Naval Research Laboratory.
(2) National Institutes of Health.
(3) Address correspondence to this author.
(4) P. S. Steyn, *Tetrahedron*, **29**, 107 (1973).
(5) E. Zbiral, E. L. Ménard, and J. M. Müller, *Helv. Chim. Acta*, **48**, 404 (1965).
(6) J. Fridrichsons and A. McL. Mathieson, *Acta Crystallogr.*, **18**, 1043 (1965).
(7) J. Fridrichsons and A. McL. Mathieson, *Acta Crystallogr.*, **23**, 439 (1967).
(8) H. P. Weber, *Acta Crystallogr., Sect. B*, **28**, 2945 (1972).
(9) H. C. J. Ottenheyn, T. F. Spande, and B. Witkop, *J. Amer. Chem. Soc.*, **95**, 1989 (1973). Since submission of this manuscript elegant syntheses of epidithiodiketopiperazines of dehydroglyotoxin and sporidesmin A have been reported by Y. Kishi, T. Fukuyama, and S. Nakatsu, *J. Amer. Chem. Soc.*, **95**, 6490 (1973).
(10) *Cf.* F. E. Oehler, F. Tataruch, and U. Schmidt, *Chem. Ber.*, **105**, 3658 (1972).

Table I. Fractional Coordinates, Thermal Parameters,[a] and Standard Deviations

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
N	0.4410 (3)	0.5471 (3)	0.2973 (0)	3.40	2.78	4.71	−0.43	−0.09	−0.20
C^{α}	0.3483 (4)	0.3407 (4)	0.2711 (1)	3.19	2.46	5.60	0.06	−0.00	−0.25
C^{β}	0.1346 (4)	0.2742 (4)	0.2999 (1)	3.99	3.82	5.96	−0.96	−0.04	0.87
C^{γ}	0.1191 (4)	0.4052 (4)	0.3374 (1)	4.39	4.82	5.38	−0.62	0.73	0.78
C^{δ}	0.3167 (5)	0.5843 (4)	0.3411 (1)	5.36	3.73	4.96	−0.78	0.54	0.01
C′	0.2956 (4)	0.4049 (4)	0.2212 (1)	2.83	2.75	5.21	0.11	0.29	−0.73
O	0.1244 (3)	0.3258 (3)	0.1995 (0)	3.30	4.70	6.25	−1.24	−0.46	−0.74
H^{α}	0.4671 (48)	0.2167 (46)	0.2704 (7)						
H^{β}	0.0381 (48)	0.1306 (50)	0.2904 (7)						
H^{γ}	0.0016 (55)	0.3983 (46)	0.3633 (8)						
H^{δ_1}	0.4120 (47)	0.5568 (48)	0.3702 (8)						
H^{δ_2}	0.2591 (55)	0.7651 (52)	0.3406 (7)						

[a] Thermal parameters are expressed in the form $T = \exp[-1/4(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)]$ where the B_{ij} values are in ångströms squared.



I

II, R = H
III, R = CH_3

IV

V

the nature of the substitution (substituents) on the C^{α} atoms. Thus far, the diketopiperazine ring in various crystalline compounds has been observed to be planar or to be folded to a lesser or greater degree, *i.e.*, by ~25° or by ~40°. Furthermore, the substituents on the C^{α} atoms have been observed to be either in the axial or quasiequatorial position, again, depending upon the nature of substitution.

Structure Analysis

The material with formula $C_{10}H_{10}N_2O_2$ crystallizes in the noncentrosymmetric space group $P4_12_12$ with a = 5.607 ± 0.003 Å and c = 28.753 ± 0.009 Å. The molecular weight is 190.2, V_{cell} = 903.9 Å^3, calcd density = 1.397 g/cm^3 for four molecules in the unit cell. Each asymmetric unit contains one-half of a molecule; hence the twofold rotation axis, which is one of the symmetry elements in the $P4_12_12$ space group, must also be contained in the molecule, thereby demonstrating that both halves of the molecule have the same configuration. X-Ray intensity data for 518 independent reflections with $2\theta_{max}$ = 126° were measured on a four-circle automatic diffractometer using the θ–2θ scan technique with 2.0° + $2\theta(\alpha_2)$ − $2\theta(\alpha_1)$ scan over 2θ. The scan rate was 2°/min and a background count was made for 10 sec at either end. All reflections with $2\theta \leq 126°$ were considered observed except those which corresponded to the space group extinctions. Lorentz and polarization corrections were made, the data were placed on an absolute scale by means of a K curve, and normalized structure factors, $|E|$, were derived. For obtaining the $|E|$ values in space group $P4_12_12$, the following ϵ values are used: ϵ = 4 for 00l; ϵ = 2 for h00, 0k0, and hh0; and ϵ = 1 for all other reflections.

Phase angles for the individual $|E_{hkl}|$'s were derived directly from the intensities by means of the symbolic addition procedure[11] for noncentrosymmetric space groups. For space group $P4_12_12$, the origin is specified by assigning an appropriate value to two reflections from the following groups: (gu0, ug0), (g0u, 0gu), (u0g, 0ug), or (u0u, 0uu). The parity groups within each set of parentheses are equivalent in this tetragonal space group. Accordingly, the phases for reflections 102 and 3,0,21 were assigned the values of 0 and $3\pi/4$, respectively. No enantiomorph specification was needed since the choice of the space group $P4_12_12$ over $P4_32_12$ already had accomplished the enantiomorph specification. Two additional reflections were assigned the following symbols: $\phi_{2,2,22} = a(0 \text{ or } \pi)$ and $\phi_{508} = m(+\pi/2 \text{ or } -\pi/2)$, in order to implement the sum of angles formula, a relationship directly implied by inequality 34 from the complete set of inequalities describing the relationships among structure factors.[12] It was readily apparent from multiple phase indications that $a = \pi$ and $m = +\pi/2$. Refinement of the phases obtained from the sum of angles formula and extension of the phase determination for all $|E_{hkl}| > 1.0$ by means of the tangent formula[13] yielded a set of 153 phases from which an E map was computed. The seven maxima in the E map corresponded to one-half of the molecule.

The five H atoms were located in a difference map computed after an anisotropic least-squares refinement of the seven heavy atoms. Least-squares refinement of the coordinates of C, N, O, and H atoms and the thermal parameters for the C, N, and O atoms resulted in an R factor of 4.0% for all the data.[14] It was assumed that the thermal factors of the H atoms were equal to those of the atom of attachment. Fractional coordinates are listed in Table I. The coordinates x', y', z' for the atoms of the other half of the molecule are derived by symmetry operation (1 − y), (1 − x), ($1/2$ − z). Conformational angles are shown in Table II.

Description of Structure

The conformation of the molecule is shown in the stereodiagram in Figure 1 and the bond lengths and angles are represented in Figure 2. Lengths and angles for bonds containing the hydrogen atoms are listed in Table III. The molecule has C_2 symmetry with the twofold rotation axis perpendicular to the average plane of the diketopiperazine ring. The diketopiperazine ring consists of two planar peptide groups where the

(11) See, *e.g.*, J. Karle and I. L. Karle, *Acta Crystallogr.*, **21**, 849 (1966).

(12) J. Karle and H. Hauptman, *Acta Crystallogr.*, **3**, 181 (1950).
(13) J. Karle and H. Hauptman, *Acta Crystallogr.*, **9**, 635 (1956).
(14) See paragraph at end of paper regarding supplementary material.

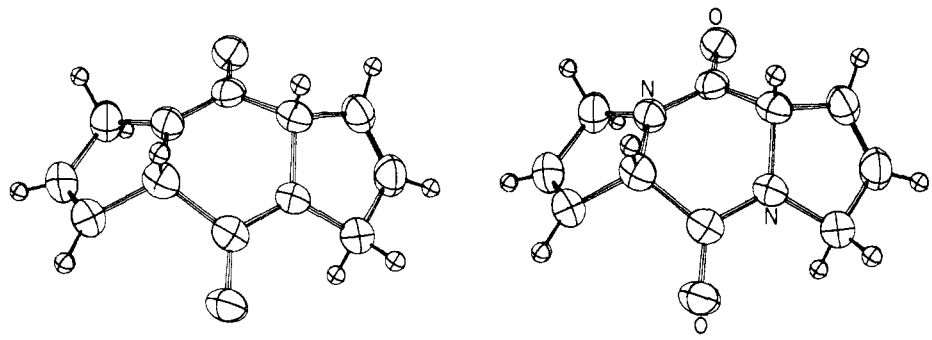


Figure 1. A stereodiagram of 3,4-dehydroproline anhydride prepared from the observed coordinates of the atoms by a computer program written by C. K. Johnson, Oak Ridge National Laboratory.

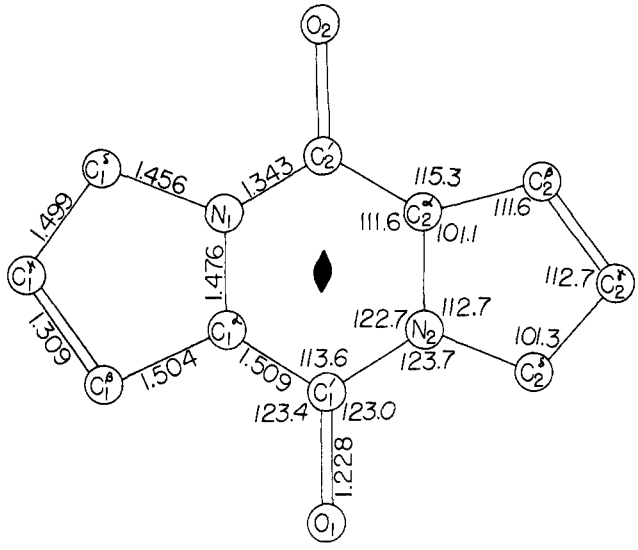


Figure 2. Bond lengths and angles. The standard deviations for the distances are 0.003 Å while the standard deviations for the angles are 0.2°, based on the least-squares refinement of the coordinates and thermal factors.

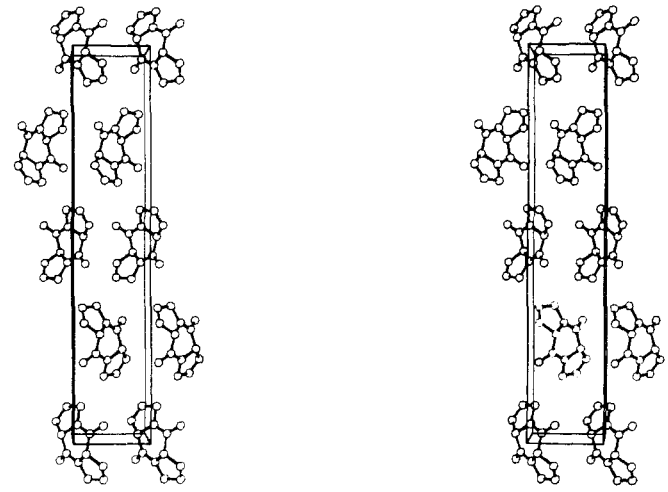


Figure 3. A stereodiagram of the packing. Eight molecules are shown although the cell contains the equivalent of four molecules. The axial directions are $a \rightarrow$ and $c \uparrow$.

Table II. Torsional Angles for 3,4-Dehydroproline Anhydride[a]

Angle	Peptide notation	Deg
$C_i^{\alpha}C_i'N_{i+1}C_{i+1}^{\alpha}$	ω	1.0
$N_iC_i^{\alpha}C_i'N_{i+1}$	ψ	37.0
$C_{i-1}'N_iC_i^{\alpha}C_i'$	ϕ	−39.5
$NC^{\alpha}C^{\beta}C^{\gamma}$	χ_1	−4.3
$C^{\alpha}C^{\beta}C^{\gamma}C^{\delta}$	χ_2	0.2
$C^{\beta}C^{\gamma}C^{\delta}N$	χ_3	4.1
$C^{\gamma}C^{\delta}NC^{\alpha}$	χ_4	−7.0

[a] 0° = cis conformation.

Table III. Bond Lengths and Angles[a] Involving Hydrogen Atoms

Length, Å		Angle, deg	
C^{α}–H^{α}	0.96	$C'C^{\alpha}H^{\alpha}$	106
		$C^{\beta}C^{\alpha}H^{\alpha}$	112
		$NC^{\alpha}H^{\alpha}$	110
C^{β}–H	1.01	$C^{\alpha}C^{\beta}H^{\beta}$	119
		$C^{\gamma}C^{\beta}H^{\beta}$	129
C^{γ}–H^{γ}	1.00	$C^{\beta}C^{\gamma}H^{\gamma}$	129
		$C^{\delta}C^{\gamma}H^{\gamma}$	118
C^{δ}–H^{δ_1}	1.00	$C^{\gamma}C^{\delta}H^{\delta_1}$	110
C^{δ}–H^{δ_2}	1.05	$C^{\gamma}C^{\delta}H^{\delta_2}$	114
		$NC^{\delta}H^{\delta_1}$	116
		$NC^{\delta}H^{\delta_2}$	106
		$H^{\delta_1}C^{\delta}H^{\delta_2}$	109

[a] Standard deviations are 0.02 Å for the bond lengths and 1.1° for the angles.

maximum deviation of any atom in a peptide group from the least-squares plane of the peptide group is 0.006 Å. The two peptide groups meet along the line joining C_1^{α} with C_2^{α} with a dihedral angle of 139.5°, thus the diketopiperazine ring has a markedly folded conformation. The rings in the dehydroprolyl residues have the envelope conformation with the N atom 0.105 Å out of the plane formed by the C^{α}, C^{β}, C^{γ}, and C^{δ} atoms. Hydrogen atoms on the C_1^{α} and C_2^{α} atoms are in the axial positions with an intramolecular H···H separation of 2.775 Å. Bond lengths and angles in the diketopiperazine moiety in 3,4-dehydroproline anhydride are almost identical with those found in *cyclo*-L-Pro-L-Leu.[15]

Figure 3 illustrates the packing of the molecules in the unit cell. The molecules are related by a fourfold screw axis parallel to the *c* direction. In the *a* direction, the scoop-shaped molecules nestle within each other. The closest intermolecular approaches are O···C^{γ} at 3.46 Å and O···C^{δ} at 3.22 Å between molecules adjacent in the *c* direction and O···C^{α} at 3.29 Å and O···C^{β} at 3.41 Å between molecules adjacent in the *a* direction. The closest C···C distance is 3.78 Å.

(15) I. L. Karle, *J. Amer. Chem. Soc.*, **94**, 81 (1972).

Table IV. Comparison of Structural Parameters for Various Cyclic Dipeptides and Derivatives

	Conf[a]	Fold,[c] deg	O=C′ , deg N	N , deg	Cα , deg N	Ref
cyclo-(Gly-Gly)(DKP)		180	118.9	126.0	115.1	18
N,N′-diMe-DKP		180	118.1	124.6	117.0	19
cyclo-(D-Ala-L-Ala)		180	118.6	127.9	113.4	20
cyclo-(L-Ser-L-Tyr)	FP	~180				21
cyclo-(Gly-L-Tyr)	FP	~160–170	119	126	113 (mean)	24
cyclo(-L-Ala-L-Ala)	E	151	116.8 116.9	125.9 126.2	112.0 110.5	20, *d*
N,N′-diMe(S_4)DKP		159	118.0	122.6	115.4	*e*
cyclo-(L-Pro-Gly)	E	142	113.6 114.2	122.3 122.6	110.8 111.8	16
cyclo-(L-Pro-L-Leu)	E	143	113.9 114.0	123.5 123.0	110.9 110.7	15
cyclo-(L-DHPro[b]-L-DHPro[b])	E	139	113.6	122.7	111.6	This study
Sporidesmin [*cyclo*-(L-Pro-L-Ala)](S_2)R	E	135	113.5 110.0	115.1 121.7	112.3 110.5	6
Gliotoxin [*cyclo*-(L-Pro-L-Ser)](S_2)R′	E	130	114	118	111 (mean)	7
Chaetocin [*cyclo*-(L-Pro-L-Ser)](S_2)R″	E	130	112	118	111 (mean)	8
Aranotin acetate [*cyclo*-(L-Pro-L-Pro)](S_2)R‴	E	Skewed boat	111	119	112 (mean)	17
Average trans peptide			116	122	111	22
Cis prolyls in antamanide			118	125	111	23

[a] Conformation of side chains on the Cα: E = quasiequatorial; FP = axial, flagpole. [b] DHPro = dehydroproline. [c] 180° = planar ring. [d] E. Benadetti, P. Corradini, and C. Pedone, *Biopolymers*, **7**, 751 (1969). [e] B. R. Davis, I. Bernal, and U. Schmidt, *Angew. Chem.*, **84**, 640 (1972).

Discussion

It is not surprising that in the reaction to form 3,4-dehydroproline anhydride, dimerization occurs between either L or D molecules rather than between L and D molecules. If a planar peptide group is assumed, then it is not possible to build a model of a D,L molecule.[15a] Furthermore, the constraints imposed by the rings in the prolyl residues necessitate a folded diketopiperazine ring with the H atoms on the Cα atoms in an axial position. Although a model with a planar diketopiperazine ring can be constructed for an unsymmetrical anhydride containing only one prolyl residue, the *cyclo*-(L-Pro-Gly) molecule[16] and the *cyclo*-(L-Pro-L-Leu) molecule[15] have a folded diketopiperazine ring with nearly the same dihedral angle as 3,4-dehydroproline anhydride and the two α-hydrogen atoms are also in a cis relationship. In fact, the natural products sporidesmin,[6] gliotoxin,[7] chaetocin,[8] and aranotin acetate[17] all contain a moiety consisting of a symmetric anhydride of L-proline, or an unsymmetric anhydride of L-proline with L-alanine or L-serine, and a dithio bridge between the Cα atoms of the diketopiperazine ring. A comparison of the fold and the bond angles in the diketopiperazine rings in these molecules (Table IV) shows a marked similarity to *cyclo*(L-Pro-L-Leu) and 3,4-dehydroproline anhydride. The dihedral angle of the fold in the diketopiperazine ring was calculated between the least-squares planes formed by the atoms C_1^α, C_1', N_2, C_2^α and C_2^α, C_2', N_1, C_1^α. [Each peptide group in the substances listed in Table IV is planar or nearly so. The maximum value of the torsional angle about the C–N bond (ω) is 8°.] Hence the geometry of the diketopiperazine ring is not changed appreciably by the addition of an epidithio bridge.

A study of the structural parameters listed in Table IV shows that a planar ring has been found for diketopiperazine,[18] *N,N′*-dimethyldiketopiperazine,[19] and *cyclo*-(D-Ala-L-Ala),[20] with each molecule possessing a center of symmetry. Among all the optically active molecules, only *cyclo*-(L-Ser-L-Tyr)[21] is reported to have an approximately planar ring. As the fold in the diketopiperazine ring increases, the internal angles at C′ and N decrease significantly, 4° or more. The values of these angles differ somewhat from the average of those found for trans peptide groups.[22] There is a correspondence between the angular values in the planar or nearly planar diketopiperazine rings, and the values for the C′ and N angles, 118 and 125°, respectively, found for the cis prolyl residues in the decapeptide antamanide.[23] Thus it appears that a variety of stable conformations have been found for the diketopiperazine ring, depending upon local factors.

The internal angle at the Cα atom remains relatively

(15a) NOTE ADDED IN PROOF. *cyclo*-(L-Pro-L-Pro) and *cyclo*-(L-Pro-D-Pro) have been synthesized by ring closure of the linear dipeptides. Conformational energy calculations indicate that the diketopiperazine ring in *cyclo*-(L-Pro-D-Pro) assumes a flattened chair form which implies nonplanar peptide groups rather than the boat form established for *cyclo*-(L-Pro-L-Pro) [P. E. Young, V. Madison, and E. R. Blout, *J. Amer. Chem. Soc.*, **95**, 6142 (1973)].

(16) G. R. Pettit, R. B. von Dreele, G. Bollinger, P. M. Traxler, and P. Brown, *Experientia*, **29**, 521 (1973).

(17) D. B. Cosulich, N. R. Nelson, and J. H. van den Hende, *J. Amer. Chem. Soc.*, **90**, 6519 (1968).

(18) R. Degeilh and R. E. Marsh, *Acta Crystallogr.*, **12**, 1007 (1959).

(19) P. Groth, *Acta Chem. Scand.*, **23**, 3155 (1969).

(20) E. Sletten, *J. Amer. Chem. Soc.*, **92**, 172 (1970).

(21) L. E. Webb and C. F. Lin, American Crystallographic Association Meeting, Ames, Iowa, 1971, Abstract G10, p 56.

(22) R. E. Marsh and J. Donohue, *Advan. Protein Chem.*, **22**, 249 (1967).

(23) I. L. Karle, J. Karle, T. Wieland, W. Burgermeister, H. Faulstich, and B. Witkop, *Proc. Nat. Acad. Sci. U. S.*, **70**, 1836 (1973); I. L. Karle, to be submitted for publication.

constant, 111–112°, if there is a side chain on C^{α}. Without substitution, the angle at C^{α} increases to 115–117°. Aliphatic side chains are in equatorial or pseudo-equatorial positions whereas in the two examples with L-tyrosine, the side chain is in an axial position with the aromatic moiety folded over the diketopiperazine ring in the flag-pole conformation.[21,24]

Experimental Section

Melting points are uncorrected.

3,4-Dehydro-D,L-proline (II). This compound was prepared as described previously.[25,26] In our hands the yield never exceeded 35%: mp 239–241° dec, tlc (*sec*-butyl alcohol–acetic acid–water, 4:2:1) one spot, ninhydrin-positive. Its spectroscopic characteristics were identical with those previously reported.[26,27]

3,4-Dehydro-D,L-proline Methyl Ester Hydrochloride (III). To 20 ml of methanol, chilled at −10°, 3.0 ml of thionyl chloride was added dropwise, followed by 3.85 g (30.4 mmol) of 3,4-dehydro-D,L-proline. The clear solution was slowly warmed to 30°, and stirred at this temperature for 16 hr. From the dark brown solution the solvent was removed. After two portions of 50 ml of methanol had been added and removed *in vacuo*, the oily residue was dried *in vacuo* over KOH and finally crystallized from methanol–ether to yield 4.55 g (92%) of needles: mp 133–134° (recrystallized from chloroform–hexane); tlc (*sec*-butyl alcohol–acetic acid–water, 4:1:1) one spot, ninhydrin-positive; ir (KBr) 2700 ($^{+}NH_2$), 1740 (C=O), and 685 cm^{-1} (*cis*-vinyl protons); nmr ($CDCl_3$, δ 6.08 (mult, 2, $C_{3,4}$-H), 5.30 (mult, 1, C_2-H), 4.27 (mult, 2, C_5-H_2)) 3.87 (s, 3, OCH_3).

3,4-Dehydroproline Anhydride (IV). A solution of 3.55 g (22 mmol) of the ester hydrochloride III in the minimal amount of anhydrous methanol was made strongly alkaline with triethylamine. The triethylamine hydrochloride was completely precipitated by the addition of 60 ml of ether, and subsequent cooling at −10°. The salt was collected by filtration and washed with ether; the filtrate was concentrated to dryness, yielding 1.90 g of colorless oil which crystallized after being kept for several days in a vacuum desiccator. Unreacted starting material was removed by crystallization (benzene, or chloroform–hexane) or by ion-exchange chromatography (Dowex 40W-X8, H^{+} form). The compound is soluble in hot benzene, water, and chloroform, and insoluble in petroleum ether: yield, 1.55 g (37%) of flat plates; mp 208–210°; tlc (*sec*-butyl alcohol–acetic acid–water, 4:2:1, or 5% methanol–chloroform) one spot, ninhydrin-negative; ir (KBr) 1660 (broad, C=O) and 705 cm^{-1} (*cis*-vinyl protons); nmr ($CDCl_3$) δ 6.12 (mult, 4, vinylic protons), 5.09 (broad mult, 2, α-H), 4.30 (broad mult, 4 H, C_5-H_2); mass spectrum principal peaks at *m/e* 190 (M^{+}), 162 (M − CO), 145, 135, 123, 96, 95 (M/2), 68 (base peak), 67 (pyrroline).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.31; H, 5.30; N, 14.64.

Supplementary Material Available. Observed and calculated structure factors will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-539.

(24) L. E. Webb and C. F. Lin, *J. Amer. Chem. Soc.*, **93**, 3818 (1971).
(25) A. Corbella, P. Gariboldi, and G. Jommi, *Chem. Ind. (London)*, 583 (1969).
(26) A. V. Robertson and B. Witkop, *J. Amer. Chem. Soc.*, **84**, 1697 (1962).
(27) L. F. Johnson, A. V. Robertson, W. R. J. Simpson, and B. Witkop, *Aust. J. Chem.*, **19**, 115 (1966).

The Factors Influencing Stereochemistry in the Reduction of Conformationally Mobile 2-Alkylcyclohexanones by Sodium Borohydride[1]

Donald C. Wigfield* and David J. Phelps

Contribution from the Department of Chemistry, Carleton University, Ottawa, Canada. *Received July 19, 1973*

Abstract: Stereochemical product ratios of reduction of eight 2-substituted cyclohexanones by $NaBH_4$ in 2-propanol, and rates of reduction of eight such ketones have been measured at a variety of temperatures, thus permitting the calculation of the specific activation parameters for axial and equatorial attack by borohydride. These data permit the tackling of the question of the preferred conformation for reduction of conformationally mobile systems and also show that epimerization of the 2 substituent does not play a major role in determining stereochemical product ratio. These main conclusions and the magnitudes of the steric interactions involved in the reduction of 2-alkylcyclohexanones are summarized.

The origin of the marked stereochemical control in the reduction of cyclohexanones with metal hydride reducing agents such as sodium borohydride is a fascinating but persisting puzzle in organic chemistry. Unhindered ketones are reduced to yield a large predominance of equatorial alcohol, but this preferred mode of attack is rapidly diminished, and eventually inverted, with increasing steric hindrance around the carbonyl group. Despite a great deal of experimentation and speculation, the origin and cause of this behavior remains obscure.[2]

Our approach to this problem has been to try and obtain independent information about the transition states involved in the reduction of a variety of ketones. As a result of this work, it has become increasingly clear to us that in this regard there are different types of "hindered ketones." The majority of compounds in

(1) Support by the National Research Council of Canada is gratefully acknowledged.

(2) See, for example, (a) E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970); (b) D. C. Wigfield and D. J. Phelps, *Can. J. Chem.*, **50**, 388 (1972), and references therein.