

shape of carbonyl compounds (Figure 5), it is uncertain whether or not the nature of the interactions of an aromatic CH group with them can be explained by the above CH...O hydrogen bond, since scarcely any reports have been published on the relationship between their shape and the strength of the CH...O hydrogen bonds with their oxygen atoms. A dipole-induced-dipole interaction would contribute to the carbonyl-phenyl interactions.

Conclusion

We have developed a novel and convenient method for evaluating the enthalpies of weak interactions between a phenyl group in a stationary liquid and a variety of molecules as samples with satisfactory accuracy by utilizing gas chromatography.

It has been found that the interactions of a phenyl group are (i) specific for the three-dimensional shape of molecules with which the phenyl group interacts and (ii) more attractive with cyclic molecules, which are similar in three-dimensional shape to the phenyl group, than with the corresponding acyclic molecules. The shape similarity effect holds for alkanes, alkenes, ethers, and carbonyl compounds.

The above effect on the weak interactions would underlie the "similarity recognition hypothesis"³⁹ that the three-dimensional shape similarity between groups in reacting molecules is responsible for more specific and precise molecular recognition than would otherwise be achieved. Moreover, the *shape-specific weak interactions* between groups in reacting molecules have recently been shown to control chemical selectivity.³⁵

This type of weak interactions would principally originate from the dispersion interaction or from the dispersion and dipole-induced-dipole interactions. Though such interactions depend on relative angular orientation between interacting groups (molecules), the present method is, of course, incapable of elucidating the orientation dependence of interaction enthalpies. The nature of the shape-specific weak interactions presented here will be better understood with the aid of quantum mechanical calculations.

Experimental Section

Materials. Commercially available silicone oils [OV-25 (**1**) and OV-101 (**2**), Gasukuro Kogyo] were used as received. They were coated

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on acid treated Celite 545 (Celite 545SK, Gasukuro Kogyo) in a weight ratio of 1 to 5. The stationary phases thus obtained were packed in stainless-steel tubes (3-mm internal diameter \times 2-m length). The samples **4-11** (mostly >99% purity) were commercially available (Tokyo Kasei Kogyo) and distilled before use.

Gas Chromatography. Gas chromatographic measurements were made on a Hitachi 063 or 263-50 equipped with a FID detector and a data processor (SIC Chromatocorder 11). The carrier gas was nitrogen with a flow rate of 20 mL min⁻¹. Retention time was measured from the methane (99.9% purity, Nishio Kogyo) peak to correct for the free space in the system.

Enthalpy Calculations. Retention time measurements were practically made for the mixture of a given sample and an appropriate internal standard (IS) at various temperatures using a pair of stationary phases each with liquid **1** or **2**. An IS was so chosen that (i) the α' mentioned below does not exceed about 10 since larger α' values cause an increase in errors and (ii) its peak completely separates from that of a given sample. The measurements were made at least 6 times each at the six temperatures, whose range was about 50 °C, for **1** and **2** (Figure 1). The relative retention (α')⁴⁰ was determined for the sample-IS pair. The slope of the $\ln \alpha'-T^{-1}$ plot for liquid **1** or **2**, which was evaluated by least-squares treatment based on eq 2, gave the $\Delta\Delta H'$ for the sample-IS pair.⁴¹ The $\Delta\Delta H'$ was then converted to the $\Delta\Delta H^\circ$ for the sample-*n*-octane pair (Tables I-IV) by summing the $\Delta\Delta H'$ for the sample-IS pair and the $\Delta\Delta H^\circ$ for the IS-*n*-octane pair.

Acknowledgment. We thank Dr. Motohiro Nishio for encouragement throughout this work.

Registry No. **2**, 9016-00-6; **3**, 111-65-9; **4a**, 71-43-2; **4b**, 592-57-4; **4c**, 110-83-8; **4d**, 110-82-7; **4e**, 142-68-7; **4f**, 123-91-1; **4g**, 505-22-6; **4h**, 96-47-9; **4i**, 10141-72-7; **5a**, 108-88-3; **5b**, 100-41-4; **5c**, 103-65-1; **5d**, 98-82-8; **5e**, 108-90-7; **5f**, 100-66-3; **5g**, 98-95-3; **5h**, 462-06-6; **5i**, 98-08-8; **5j**, 98-07-7; **6a**, 106-42-3; **6b**, 106-43-4; **6c**, 104-93-8; **6d**, 623-12-1; **6e**, 150-78-7; **6f**, 392-56-3; **7a**, 96-37-7; **7b**, 108-87-2; **7c**, 696-29-7; **7d**, 2207-01-4; **7e**, 6876-23-9; **7f**, 292-64-8; **8a**, 107-83-5; **8b**, 79-29-8; **9a**, 75-83-2; **9b**, 540-84-1; **9c**, 594-82-1; **10a**, 2235-12-3; **10b**, 592-48-3; **10c**, 592-41-6; **10d**, 110-54-3; **10e**, 628-28-4; **10f**, 110-71-4; **11a**, 107-87-9; **11b**, 120-92-3; **11c**, 108-94-1; **11d**, 823-76-7; **11e**, 98-86-2; **11f**, 141-78-6; **11g**, 96-48-0; **11h**, 542-28-9; **11i**, 127-19-5.

(40) The relative retention α' mentioned above corresponds to the α' when *n*-octane is used as an IS.

(41) The $\Delta\Delta H'$ corresponds to the $\Delta\Delta H^\circ$ when an IS is *n*-octane.

Crystal Structures of Two Simple N-Substituted Dihydronicotinamides: Possible Implications for Stereoelectronic Arguments in Enzymology

Arthur Glasfeld, Peter Zbinden, Max Dobler, Steven A. Benner,* and Jack D. Dunitz*

Contribution from the Laboratory for Organic Chemistry, Swiss Federal Institute of Technology, CH-8092 Zurich, Switzerland. Received October 19, 1987

Abstract: Crystal structures of *N*-(methoxymethyl)-1,4-dihydropyridine-3-carboxamide (**1**) and *N*-propyl-1,4-dihydropyridine-3-carboxamide (**2**) have been determined and analyzed with a goal of detecting possible stereoelectronic interactions between the nitrogen lone pair and the antibonding orbital of the α - β bond in these molecules. In both molecules, the dihydropyridine ring skeleton is nearly planar. However, the N-substituent carbon atom in both molecules lies significantly (0.26 and 0.21 Å, respectively) out of the ring plane, and the α - β bond is nearly perpendicular to this plane. This suggests that the interaction between the nitrogen lone pair and the antibonding orbital of the α - β bond is larger in **1** than in **2**. Ultraviolet spectral data suggest an estimate of 1-3 kcal/mol as the energy difference associated with the n - σ^* interaction, an energy sufficiently large to be the target of natural selection in the evolution of dehydrogenases dependent on nicotinamide cofactors.

Much of the discussion about the chemical and biochemical reactivity of NADH has been based on the assumption that the

1,4-dihydropyridine ring occurs in a boat conformation.^{1,2} The appealing feature of this model is that it places one hydrogen atom

Table I. Some Geometrical Properties of *N*-Substituted 1,4-Dihydropyridine Compounds

ref	best plane through atoms C(2), C(3), C(5), C(6) (dev in Å)						best plane through atoms C(2), C(6), C in R(1) (dev in Å): N(1)	torsion angle (deg) between C(2)–N(1) bond and α – β bond in R(1)
	C(2)	C(3)	C(5)	C(6)	N(1)	C(4)		
a	0.009	–0.009	0.009	–0.009	0.120	0.314	0.065	82.8
b	0.005	–0.005	0.005	–0.005	0.004	0.067	0.011	86.7
c	0.032	–0.030	0.032	–0.034	–0.029	0.009	0.094	101.3
d	0.012	–0.012	0.012	–0.012	–0.140	0.036	0.056	87.2
e	0.004	–0.004	0.004	–0.004	0.129	0.268	0.270	
f	0.000	0.000	0.000	0.000	0.002	–0.045	0.079	84.5
1	–0.006	0.006	–0.006	0.006	0.004	–0.021	0.086	100.3
2	–0.009	0.009	–0.009	0.009	–0.015	0.012	0.060	102.1

^aBundule, M. F.; Kemme, A. A.; Bleidelis, Y. Y.; Bisenieks, E. A.; Uldrikis, Y. R.; Dubur, G. Y. *Zh. Strukt. Khim.* **1981**, 22, 124. R(1) = R(4) = phenyl, R(2) = R(6) = methyl, R(3) = R(5) = ethoxycarbonyl, R(4') = H. ^bKarle, I. L. *Acta Crystallogr.* **1961**, 14, 497. R(1) = benzyl, R(2) = R(4) = R(4') = R(5) = R(6) = H, R(3) = carbamoyl. ^cKoyama, H. *Z. Kristallogr. Kristallgeom., Kristallphys., Kristallchem. Cryst. Phys., Diffraction, Theor. Gen. Crystallogr.* **1963**, 118, 51. R(1) = *n*-propyl, R(2) = R(4) = R(4') = R(5) = R(6) = H, R(3) = carbamoyl. ^dvan Lier, P. M.; Donkersloot, M. C. A.; Koster, A. S.; van Hooff, H. G. J.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1982**, 101, 119. R(1) = *n*-propyl, R(2) = R(4) = methyl, R(3) = *N*-(α -methylbenzyl)carbamoyl, R(4') = R(5) = R(6) = H. ^eIwasaki, F.; Watanabe, T.; Maeda, K. *Bull. Chem. Soc. Jpn.* **1987**, 60, 1255. R(1) = methyl, R(2) = R(4) = R(6) = phenyl, R(4') = benzyl, R(3) = R(5) = H. ^fHuml, K.; Jecny, J.; Kutschabsky, L.; Reck, G. *Acta Crystallogr. Sect. B: Cryst. Phys., Diffraction, Theor. Gen. Crystallogr.* **1973**, 35, 164. R(1) = ethyl, R(2) = R(4) = R(4') = R(6) = methyl, R(3) = R(5) = cyano.

in the pseudoaxial position, presumably favoring transfer; the appalling feature is that, after 30 years, it still lacks sound experimental foundation. The somewhat meager crystal structure evidence for *N*-substituted dihydropyridines to date shows that the dihydropyridine ring is essentially planar except in highly substituted derivatives where the deviations from planarity might be due to steric repulsions among the substituents. Some geometric data, calculated from published atomic coordinates, are given in Table I. The only evidence for a puckered conformation in a dihydropyridine ring comes from an interpretation of the ¹H NMR spectrum of NADH itself in terms of a Karplus-type relationship;³ even in this case, a pucker could be viewed as arising from a stacking interaction between the dihydropyridine and adenine moieties in this system, rather than being an intrinsic structural property of the dihydropyridine ring system.

While compelling evidence for the assumed boat conformation of the dihydropyridine ring is lacking, there is also no reliable structural information for molecules in which the dihydropyridine system is bound to ribose or to an analogous substituent with an ether O atom in the appropriate position. It seems important to fill this gap, because, according to well-known stereoelectronic arguments,⁴ pyramidalization at the ring nitrogen is an expected result of the interaction of the lone pair of electrons on nitrogen with the $\sigma^*(\text{C}–\text{O})$ orbital.

We have now determined the crystal structure of the *N*-methoxymethyl derivative **1** and report our results here. To facilitate comparisons, we have also redetermined and refined the crystal structure of the *N*-propyl derivative **2**, which was solved in projection by Koyama many years ago.⁵ Also, we combine spectroscopic data on these molecules with literature data to make an estimate of the energetic significance of *n*– σ^* overlap in dihydropyridinamides.

Experimental Section

Synthesis of Compounds. 1,4-Dihydro-1-(methoxymethyl)pyridine-3-carboxamide (**1**) was prepared by the method of Stewart and Norris.⁶ The crude material was recrystallized twice from degassed ethyl acetate. ¹H NMR (CDCl₃, 300 MHz): δ 2.95 (s, 2 H), 3.19 (s, 3 H), 4.42 (s, 2 H), 4.67 (m, 1 H), 6.00 (d, 1 H, *J* = 6 Hz), 6.64 (s, 2 H), 6.99 (s, 1 H). UV (MeOH): λ_{max} = 335 nm. Mp: 104.5–6 °C (lit.⁶ mp 106–7 °C).

1,4-Dihydro-1-propylpyridine-3-carboxamide (**2**), 3-Carbamoyl-1-propylpyridinium bromide was prepared following the procedure of An-

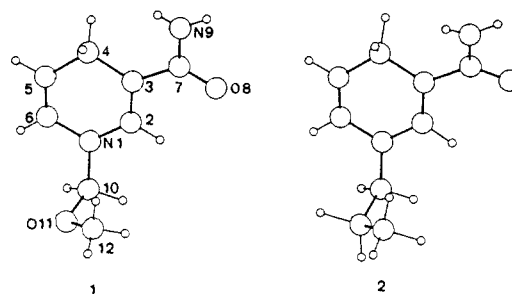


Figure 1. View of molecules **1** and **2** showing atomic numbering.³¹

derson and Berkelhammer.⁷ Reduction to the corresponding dihydropyridine derivative was performed by mixing the salt (34.4 mmol) with sodium dithionite (92 mmol) and sodium carbonate (181 mmol) in 100 mL of degassed water. The yellow oil that separated was recovered by extraction with 100 mL of methylene chloride; the organic phase was dried over MgSO₄ and evaporated under vacuum. The crude material was recrystallized twice from degassed ethyl acetate. ¹H NMR (CDCl₃, 300 MHz): δ 0.90 (t, 3 H, *J* = 7 Hz), 1.54 (h, 2 H, *J* = 7 Hz), 3.05 (t, 2 H, *J* = 7 Hz), 3.15 (s, 2 H), 4.71 (m, 1 H), 5.45 (s, 2 H), 5.71 (d, 1 H, *J* = 8 Hz), 7.02 (s, 1 H). UV (MeOH): λ_{max} = 355 nm. Mp: 89.5–90 °C (lit.¹ mp 88–91 °C).

Crystal Structure Analyses, General Remarks. For both crystal structure analyses, data were measured at room temperature on an ENRAF-Nonius CAD4 diffractometer equipped with graphite monochromator (Mo K α radiation, λ = 0.71069 Å). The structures were solved with direct methods using the program SHELX 86.⁸ All refinements were done by full-matrix least-squares analysis with anisotropic displacement parameters for C, N, and O atoms, isotropic for H atoms, using the program SHELX 76. The atomic numbering scheme for the two structures is shown in Figure 1.

Crystal Structures. 1,4-Dihydro-1-(methoxymethyl)pyridine-3-carboxamide (**1**): C₈H₁₂O₂N₂; *M_r* 168.20; *a* = 5.308 (1), *b* = 16.175 (8), *c* = 10.374 (3) Å; β = 101.87 (2)°; monoclinic; space group *P2₁/c*; *Z* = 4; ρ_{calc} = 1.28; (sin θ)/ λ_{max} = 0.594 Å^{–1}; 1527 independent reflections, 1091 with *I* > 3 σ (*I*); *R* = 0.050. The hydrogen positions of the methyl group (H(121), H(122), H(123)) were calculated under the assumption that the conformation about the C(12)–O(11) bond is staggered. The maximal residual electron density $\Delta\rho$ is 0.45 e·Å^{–3}, and the minimal is –0.21 e·Å^{–3}. Atomic coordinates and equivalent isotropic displacement parameters are given in Table IIA. Bond distances, angles, and selected torsion angles are listed in Table III.

1,4-Dihydro-1-propylpyridine-3-carboxamide (**2**). The crystal structure of **2** had already been solved in projection by Koyama.⁵ For our new measurements, the crystal was enclosed in a glass capillary to prevent oxidation: C₉H₁₄ON₂; *M_r* 166.22; *a* = 5.093 (2), *b* = 16.787 (4), *c* = 11.017 (3) Å; β = 101.92 (3)°; monoclinic; space group *P2₁/c*; *Z* = 4;

(1) Levy, H. R.; Vennesland, B. *J. Biol. Chem.* **1957**, 228, 85–96.

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Table II. Atomic Coordinates and Equivalent Displacement Parameters (U_{eq} , Å²) (Isotropic U for H Atoms) with Estimated Standard Deviations in Parentheses

	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}^a (U_{iso})
(A) For 1				
N(1)	-0.2364 (5)	0.1999 (2)	0.7139 (3)	0.053
C(2)	-0.1499 (6)	0.2684 (2)	0.7881 (3)	0.044
C(3)	-0.2835 (5)	0.3383 (2)	0.7865 (3)	0.040
C(4)	-0.5521 (6)	0.3474 (2)	0.7049 (4)	0.052
C(5)	-0.6287 (7)	0.2697 (2)	0.6275 (4)	0.058
C(6)	-0.4823 (7)	0.2042 (2)	0.6335 (4)	0.059
C(7)	-0.1611 (6)	0.4056 (2)	0.8725 (3)	0.042
O(8)	0.0638 (4)	0.4018 (1)	0.9347 (2)	0.055
N(9)	-0.3044 (6)	0.4723 (2)	0.8820 (3)	0.056
C(10)	-0.1040 (8)	0.1214 (2)	0.7363 (4)	0.065
O(11)	-0.2291 (6)	0.0651 (1)	0.8073 (3)	0.080
C(12)	-0.2216 (12)	0.0893 (3)	0.9388 (5)	0.101
H(2)	0.028 (6)	0.264 (2)	0.842 (3)	0.05
H(41)	-0.675 (6)	0.359 (2)	0.763 (3)	0.05
H(42)	-0.561 (6)	0.393 (2)	0.643 (3)	0.06
H(5)	-0.793 (7)	0.270 (2)	0.569 (3)	0.07
H(6)	-0.528 (7)	0.156 (2)	0.584 (3)	0.07
H(91)	-0.236 (7)	0.513 (2)	0.934 (4)	0.07
H(92)	-0.444 (7)	0.474 (2)	0.848 (3)	0.05
H(101)	0.086 (7)	0.129 (2)	0.789 (4)	0.08
H(102)	-0.104 (7)	0.096 (2)	0.638 (4)	0.08
H(121)	-0.320 (1)	0.044 (1)	0.987 (1)	0.17
H(122)	-0.315 (1)	0.149 (1)	0.940 (1)	0.15
H(123)	-0.024 (1)	0.094 (1)	0.991 (1)	0.17
(B) For 2				
N(1)	-0.1476 (7)	0.2092 (2)	0.7200 (4)	0.056
C(2)	-0.0765 (9)	0.2740 (3)	0.7942 (4)	0.047
C(3)	-0.2260 (7)	0.3400 (2)	0.7904 (4)	0.040
C(4)	-0.4954 (9)	0.3481 (3)	0.7017 (4)	0.054
C(5)	-0.5556 (10)	0.2745 (3)	0.6263 (5)	0.063
C(6)	-0.3919 (11)	0.2126 (3)	0.6342 (5)	0.065
C(7)	-0.1211 (8)	0.4047 (2)	0.8758 (4)	0.040
O(8)	0.1210 (5)	0.4121 (2)	0.9247 (3)	0.050
N(9)	-0.3011 (8)	0.4583 (2)	0.9000 (4)	0.048
C(10)	0.0006 (12)	0.1345 (3)	0.7388 (6)	0.073
C(11)	-0.1350 (17)	0.0721 (4)	0.8063 (7)	0.098
C(12)	-0.1790 (20)	0.0931 (5)	0.9288 (8)	0.110
H(2)	0.103 (8)	0.268 (2)	0.856 (4)	0.05
H(41)	-0.638 (8)	0.361 (3)	0.743 (4)	0.07
H(42)	-0.493 (8)	0.402 (3)	0.644 (4)	0.07
H(5)	-0.723 (10)	0.275 (3)	0.563 (4)	0.09
H(6)	-0.427 (9)	0.166 (3)	0.580 (4)	0.07
H(91)	-0.244 (8)	0.499 (2)	0.951 (4)	0.05
H(92)	-0.456 (9)	0.450 (3)	0.881 (4)	0.05
H(101)	0.172 (11)	0.145 (3)	0.795 (5)	0.10
H(102)	0.023 (10)	0.113 (3)	0.651 (5)	0.10
H(111)	-0.341 (21)	0.058 (6)	0.737 (10)	0.34
H(112)	-0.020 (13)	0.023(4)	0.820 (6)	0.14
H(121)	-0.273 (11)	0.150 (4)	0.934 (5)	0.12
H(122)	-0.248 (13)	0.053 (4)	0.980 (6)	0.15
H(123)	0.032 (17)	0.106 (5)	0.984 (7)	0.20

$$^a U_{eq} = \frac{1}{3} \sum a_i^* a_j^* a_i a_j U_{ij}$$

$\rho_{\text{calcd}} = 1.20$; $(\sin \theta) / \lambda_{\text{max}} = 0.594 \text{ \AA}^{-1}$; 1603 independent reflexions, 803 with $I > 3\sigma(I)$; $R = 0.047$. The maximal residual electron density $\Delta\rho$ is 0.27 e-\AA^{-3} , and the minimal is -0.19 e-\AA^{-3} . Atomic coordinates and equivalent isotropic displacement parameters are given in Table IIB. Bond distances, angles, and selected torsion angles are listed in Table III.

Results and Discussion

Crystal Structures. The first important result of our analysis is that the dihydropyridine ring in **1** is essentially planar, the largest deviation of any ring atom from the mean plane of the ring being 0.013 \AA for C(3), carrying the carboxamide substituent. This result clearly lends no support to the view that a boat conformation is induced by the presence of an *N*-alkoxy substituent.

Nevertheless, in **1** the methylene carbon C(10) is displaced out of the ring plane by $0.26 (1) \text{ \AA}$. The corresponding displacement of the ring nitrogen from the plane of its three substituent atoms is $0.086 (3) \text{ \AA}$. Since the C(10)–O(11) bond is steeply inclined

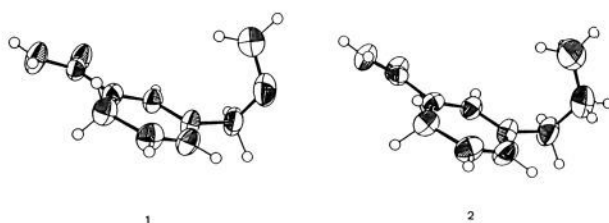


Figure 2. ORTEP diagrams of **1** and **2** with vibration ellipsoids drawn at the 50% probability level.³²

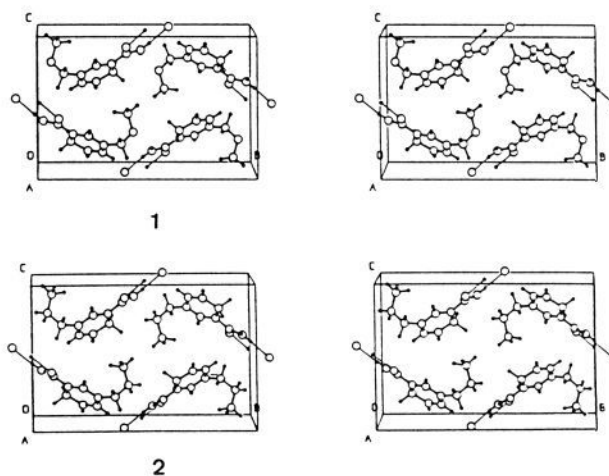


Figure 3. Stereoviews³² of the crystal packing of **1** and **2**. Note in both structures the association to dimers via hydrogen bonds across inversion centers.

to the ring plane (torsion angle C(2)–N(1)–C(10)–O(11), 102.1°) and hence periplanar to the nitrogen *p* orbital, one might be tempted to ascribe the slight pyramidality at the N(1) center to a stereoelectronic interaction between the nitrogen lone pair and the σ^* orbital of the C(10)–O(11) bond.

However, the methylene carbon C(10) from the dihydropyridine ring plane in the *N*-propyl derivative **2** is also displaced from the ring plane. The displacement is slightly less ($0.21 (1) \text{ \AA}$), corresponding to an out-of-plane displacement of $0.060 (5) \text{ \AA}$ at the ring nitrogen. The torsion angle C(2)–N(1)–C(10)–C(11) in **2** (100.3°) is comparable to that in **1**. This structural difference between **1** and **2** could be interpreted as evidence for a somewhat greater interaction between the ring-nitrogen *p* orbital and the σ^* orbital of the α – β bond in **1** than in **2**.

On the whole, the *N*-methoxymethyl and *N*-propyl derivatives (shown in Figures 1 and 2) are remarkably similar in structure. Aside from the somewhat greater pyramidality at nitrogen in **1**, there is a slight difference in the orientation of the amide group with respect to the ring plane; in **1** the twist angle about the C(3)–C(7) bond is 5.6° , and in **2** it is 20.6° , both with the same sense of rotation.

The similarity between the two structures extends to the crystal packing (Figure 3); the crystals are practically isostructural. In both crystals, the molecules are linked into centrosymmetric dimers by hydrogen bonding between the amide groups, the N...O distance being 2.90 \AA in **1** and 2.93 \AA in **2**. In **1** the second H atom of the amide group might be described as being engaged in a weak hydrogen bond to the methoxy O atom of a screw-axis related molecule; the N...O distance is 3.20 \AA , and the N–H...O angle is 143° . In **2**, the corresponding interaction is between the second amide H atom and the β -methylene carbon; as a result of the larger twist angle of the amide group, the N...C distance is increased to 3.8 \AA .

Moreover, the two sets of mean-square displacement amplitudes (MSDA's) show a high correlation, indicating that the nature of the internal motions in the two molecules is very similar. Although the atomic Gaussian displacement parameters (ADP's) from these room-temperature structures with limited resolution are not of

Table III. Bond Distances, Angles, and Torsion Angles for **1** and **2**

	1	2
(a) Bond Distances		
N(1)–C(2)	1.373	1.364
N(1)–C(6)	1.398	1.400
N(1)–C(10)	1.447	1.456
C(2)–C(3)	1.333	1.340
C(3)–C(4)	1.508	1.518
C(3)–C(7)	1.471	1.464
C(4)–C(5)	1.502	1.485
C(5)–C(6)	1.308	1.324
C(7)–O(8)	1.236	1.246
C(7)–N(9)	1.335	1.350
C(10)–O(11)	1.419	
C(10)–C(11)		1.530
O(11)–C(12)	1.412	
C(11)–C(12)		1.456
(b) Bond Angles		
C(2)–N(1)–C(6)	117.2	117.5
C(2)–N(1)–C(10)	121.5	122.4
C(6)–N(1)–C(10)	120.2	119.6
N(1)–C(2)–C(3)	124.2	124.2
C(2)–C(3)–C(4)	121.9	121.8
C(2)–C(3)–C(7)	116.9	117.6
C(4)–C(3)–C(7)	121.1	120.6
C(3)–C(4)–C(5)	109.8	109.9
C(4)–C(5)–C(6)	124.0	124.2
N(1)–C(6)–C(5)	122.8	122.4
C(3)–C(7)–O(8)	122.6	123.3
C(3)–C(7)–N(9)	117.1	116.7
O(8)–C(7)–N(9)	120.3	120.0
N(1)–C(10)–O(11)	112.5	
N(1)–C(10)–C(11)		112.7
C(10)–O(11)–C(12)	113.6	
C(10)–C(11)–C(12)		117.1
(c) Torsion Angles		
C(6)–N(1)–C(2)–C(3)	–1.0	0.4
C(10)–N(1)–C(2)–C(3)	–169.1	–171.0
C(2)–N(1)–C(6)–C(5)	–0.3	–2.2
C(10)–N(1)–C(6)–C(5)	167.9	169.4
C(2)–N(1)–C(10)–O(11)	102.1	
C(2)–N(1)–C(10)–C(11)		100.2
C(6)–N(1)–C(10)–O(11)	–65.6	
C(6)–N(1)–C(10)–C(11)		–70.9
N(1)–C(2)–C(3)–C(4)	2.4	0.6
N(1)–C(2)–C(3)–C(7)	180.0	–179.7
C(2)–C(3)–C(4)–C(5)	–2.3	0.0
C(7)–C(3)–C(4)–C(5)	–179.7	–179.7
C(2)–C(3)–C(7)–O(8)	6.6	21.0
C(2)–C(3)–C(7)–N(9)	4.6	20.2
C(3)–C(4)–C(5)–C(6)	1.1	–1.9
C(4)–C(5)–C(6)–N(1)	0.1	3.1
N(1)–C(10)–O(11)–C(12)	–67.4	
N(1)–C(10)–C(11)–C(12)		–58.6

^a Estimated standard deviations: 0.003–0.005 Å for **1**, 0.004–0.009 Å for **2**. ^b Estimated standard deviations: 0.3° for **1**, 0.4–0.6° for **2**.

the highest quality, the pattern of MSDA's along the interatomic vectors shows clearly that the molecules do not behave as rigid bodies in the crystal.⁹ Analysis of the ADP's with the program THMA11¹⁰ gave root-mean-square libration amplitudes about the N– α , α – β , and C(3)–C(7) bonds of 5.6 (5), 9.2 (8), and 10.6 (8)° for **1** and of 7.2 (5), 8.8 (12), and 9.0 (12)° for **2**, showing that the similarity between the two molecules extends even to the magnitudes of the main internal motions in the crystals.

Despite the overall similarity between the two structures, a detailed comparison of the bond lengths in the two structures reveals an interesting pattern. In the π system extending from N(1) to the amide carbonyl group, the bond distance N(1)–C(2)

Table IV. N-Substituted Pyridinium Compounds

compound	torsion angle, ^f deg
1,1'-(oxybis(methylene))bis(4-((hydroxyimino)methyl)pyridinium) dichloride	–40 ^a
2-[(hydroxyimino)methyl]-4'-carbonyl-1,1'-(oxybis(methylene)dipyridinium) dichloride monohydrate	79 ^b
2-allyl-2-azonia-7-azabiphenylene bromide	–58 ^c
1- <i>n</i> -butyl-4-(1,3-dioxindan-2-yl)pyridine	–9 ^d
1-ethyl-2-methyl-3-nitropyridinium iodide	0 ^e
nicotinamide adenine dinucleotide phosphate dihydrate lithium salt	15 ^f

^a Havere, W. v.; Lenstra, A. T. H.; Geise, H. J.; van den Berg, G. R.; Benschop, H. P. *Acta Crystallogr. Sect. B: Struct. Crystallogr. Cryst. Chem.* **1982**, *38*, 1635. ^b Havere, W. v.; Lenstra, A. T. H.; Geise, H. J.; van den Berg, G. R.; Benschop, H. P. *Bull. Soc. Chim. Belg.* **1982**, *91*, 219. First angle is that of the 2-[(hydroxyimino)methyl]pyridinium part of the molecule. ^c Kanoktanaporn, S.; Macbride, J. A. H.; King, T. J. *J. Chem. Res.* **1980**, *204*, 2911. ^d Magomedova, N. S.; Zavodnik, V. E.; Belskii, V. K. *Kristallografiya* **1981**, *26*, 706. ^e Tafeenko, V. A.; Aslandov, L. A. *Zh. Strukt. Khim.* **1980**, *21*, 79. ^f Saenger, W.; Reddy, B. S.; Muhlegger, K.; Weimann, G. *Nature (London)* **1977**, *267*, 225. ^g Smaller torsion angle between the α – β bond of the pyridinium N-substituent and a C–N bond in the pyridinium ring.

is 0.008 Å longer, C(2)–C(3) is 0.007 Å shorter, C(3)–C(7) is 0.007 Å longer, and C(7)–O(8) is 0.010 Å shorter in **1** than in **2**. Although these differences are extremely small and never exceed two joint estimated standard deviations, the pattern is again consistent with a somewhat greater interaction between the ring-nitrogen p orbital and the σ^* orbital of the α – β bond in **1** than in **2**. On the other hand, there are also larger, unexplained differences on the unsubstituted side of the dihydropyridine ring. Bond distances in the two structures otherwise require no special comment.¹¹

A search of the Cambridge Structural Database revealed an interesting regularity, as shown in Table I. The periplanar relationship of the ring-nitrogen p orbital to the α – β bond appears to be a characteristic feature of N-substituted dihydropyridines, irrespective of whether the α – β bond is polar or not. This is explained¹² in stereoelectronic terms by arguing that the HOMO (highest occupied molecular orbital) of the five-center, six-electron p system, which is heavily localized on the ring-nitrogen atom, can obtain an appreciable stabilization by delocalizing into the σ^* orbital of the α – β bond; such an interaction is maximized by the periplanar orientation of the two orbitals, which provides maximum overlap between them. As witnessed by the larger degree of pyramidalization in **1** than that in **2**, the interaction appears greater for a C–O bond than for a C–C bond, but it still has a conformationally directive influence in the latter.

A similar analysis of the conformations of N-substituted pyridinium derivatives shows no such preference for the perpendicular orientation of the α – β bond. Indeed, there are several structures, mainly of unbranched alkyl or β -alkoxy derivatives but including that of NAD⁺ itself,¹³ where the α – β bond lies quite close to the mean plane of the aromatic ring (Table IV), giving a nearly orthogonal relationship between the π and σ^* orbitals.

The structural results thus support the notion of a stereoelectronic interaction between the nitrogen lone pair and the σ^* orbital of the C(10)–O(11) bond. Such an interaction should also influence stereospecificity of hydride transfer from C(4).^{14–18}

(11) The one exception, the apparent shortness of the terminal C–C bond in the alkyl chain of **2** is probably an artifact caused by curvilinear motion of the methyl C atom arising from a large-amplitude torsional motion about the C(10)–C(11) bond. Also, the apparent shortness of the C(5)–C(6) bond in **1** is probably a result of molecular libration about an axis passing near the center of the dimer and perpendicular to the ring plane. Both bonds have more normal lengths when motional corrections are applied.

(12) To the extent to which "explanations" at this level can be said to explain anything.

(13) Saenger, W.; Reddy, B. S.; Muehlegger, K.; Weimann, G. *Nature (London)* **1977**, *267*, 225–229.

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(10) The latest (version of May 1987) in a series written by Professor K. N. Trueblood, UCLA. See: Trueblood, K. N. *Acta Crystallogr., Sect. A: Cryst. Phys., Diffraction, Theor. Gen. Crystallogr.* **1978**, *34*, 950–954.

Table V. UV Spectral Data of Some Selected N-Substituted Dihyronicotinamide Derivatives

N-substituent	α -acc?	λ_{\max}	solvent	ref
cyclopentyl	no	362/357	water/MeOH	a
<i>cis</i> -2'-carboxycyclopentyl	no	362/357	water/MeOH	a
ADP-pentyl	no	360	water (pH 6.0)	b
propyl	no	360/355	water/MeOH	a/j
2'-carboxybenzyl	no	358/356	water/MeOH	a
4'-carboxybenzyl	no	358/354	water/MeOH	a
2-hydroxyethyl	no	357	water (pH 10)	c
carboxymethyl	no	356	water (pH 10)	c
acetylonyl	no	353	water	c
isopropylcarboxymethyl	no	349	water	c
methylcarboxymethyl	no	347	water	c
ADP- α -D-ribosyl	yes ⁱ	346	water	d
ADP- β -D-arabosyl	yes ⁱ	346	water	d
α -D-xylofuranosyl	yes ⁱ	342		e
ADP- β -D-dideoxyribosyl	yes	342	water (pH 9.5)	f
cyanomethyl	yes	340	water	c
ADP- β -D-ribosyl	yes	338	water	d
ADP- α -D-arabosyl	yes ⁱ	342		e
ADP- β -D-dideoxyribosyl	yes	342	water (pH 9.5)	f
cyanomethyl	yes	340	water	c
ADP- β -D-ribosyl	yes	338	water	d
ADP- α -D-arabosyl	yes	338	water	d
methoxymethyl	yes	338/335	water/MeOH	c/j
β -D-xylofuranosyl	yes	337		e
benzylloxymethyl	yes	335	50% MeOH	g
β -D-ribofuranosyl	yes	333	water	h
tetraacetylglucopyranosyl	yes	332	50% MeOH	g

^aHajdu, J.; Sigman, D. S. *Biochemistry* **1977**, *16*, 2841-2846.
^bGoebbler, K. H.; Woenckhaus, C. *Justus Liebigs Ann. Chem.* **1966**, *700*, 180-186. ^cNorris, D. J.; Stewart, R. *Can. J. Chem.* **1977**, *55*, 1687-1695. ^dKam, B. L.; Malver, O.; Marschner, T. M.; Oppenheimer, N. J. *Biochemistry* **1987**, *26*, 3453-3461. ^eOppenheimer, N. J. *J. Carbohydr. Nucleosides, Nucleotides* **1978**, *5*, 251-260.
^fWoenckhaus, C.; Jeck, R. *Justus Liebigs Ann. Chem.* **1970**, *736*, 126-133. ^gWallenfels, K.; Gellrich, M. *Justus Liebigs Ann. Chem.* **1959**, *621*, 149-165. ^hPleiderer, G.; Sann, E.; Ortanderl, F. *Biochem. Biophys. Acta* **1963**, *73*, 39-49. ⁱCompounds contain hydroxyl groups *cis* and β to the dihyronicotinamide ring attached to a furanosyl ring. ^jThis work.

Indeed, there is now evidence that quite small differences in ground-state structure can be associated with large differences in the activation energy for bond-breaking and bond-making reactions.^{19,20} Along these lines, the high stereospecificity of Michael additions to 2,6-disubstituted 1,3-dioxin-4-ones has recently been correlated with the directionality of very small pyramidal distortions of formally sp² carbon atoms, distortions smaller than those reported here.²¹

UV Spectroscopy and Chemical Reactivity. Spectroscopic data permit an estimate of the energetic significance of donation from the nitrogen lone pair to the σ^* orbital of the adjacent bond. Donation is expected to cause shifts in the electronic spectrum of the dihyronicotinamide ring; the $n \rightarrow \pi^*$ transition, which gives rise to the absorption band between 330 and 365 nm, should shift to shorter wavelengths with increasing acceptor ability of the σ^*

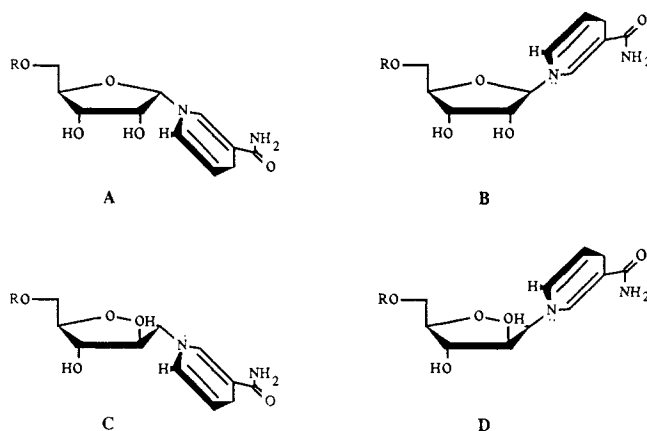


Figure 4. Structures of four nicotinamide adenine dinucleotides showing steric inhibition of conformations placing the lone pair on nitrogen anti-periplanar to the ribose C-O bond in α -NADH (A) and β -arabino-NADH (D), but not in either β -NADH (B) or α -arabino-NADH (C) (R = adenosine diphosphate).

orbital,²² provided that the molecule can adopt a conformation that permits the overlap of the two relevant orbitals. UV spectral data for 1,4-dihyronicotinamides (Table V) clearly show such a trend. Compounds with alkyl groups α to the nitrogen have λ_{\max} values ranging from 362 to 347 nm. Compounds with a σ acceptor substituent (e.g., a sugar ring oxygen, an ether oxygen, or a cyano group) all have absorbances less than 347 nm.²³ In particular, the λ_{\max} of **1** is 20 nm lower than that of **2**.

Of course, the influence of the substituent on λ_{\max} could in principle be due to causes other than $n \rightarrow \sigma^*$ overlap, including inductive and "through-space" effects. While no argument can be conclusive in this respect, the data in Table V argue against both of these as dominating influences.²⁴ Perhaps the most persuasive argument that the spectral shifts depend (at least in part) on $n \rightarrow \sigma^*$ overlap is gained from comparison of the λ_{\max} values for dihyronicotinamide derivatives with quite similar substituents: ADP- α -D-ribosyl (λ_{\max} = 346 nm), ADP- β -D-arabosyl (λ_{\max} = 346 nm), ADP- β -D-ribosyl (λ_{\max} = 338 nm), and ADP- α -D-arabosyl (λ_{\max} = 338 nm).^{25,26} The first pair of molecules bears a hydroxyl group *cis* to the anomeric C-N bond; the second pair does not. In the first pair, the *cis*-hydroxyl group sterically obstructs conformations that allow $n \rightarrow \sigma^*$ overlap (Figure 4); there is no such steric obstruction of overlap in the second pair. In the first pair, the λ_{\max} values are 346 nm; in the second pair, they are ca. 10 nm lower. This result cannot be explained by simple inductive effects, and through-space interactions are likewise too small to account for the difference,²⁷ which amounts to 2.0 kcal/mol in energetic terms. Thus, it is difficult to explain these spectral differences without involving $n \rightarrow \sigma^*$ overlap.

As the excited state of NADH and the electronic ground state of the transition state for the hydride transfer reaction are believed

(22) Maggiora, G.; Johansen, H.; Ingraham, L. L. *Arch. Biochem. Biophys.* **1969**, *131*, 352-8.

(23) For the compounds in this table measured in water and methanol, there is a small bathochromic shift (2-5 nm) on going to the more polar solvent. The effect has been discussed in terms of an increased dipole in the excited state in the more polar solvent, leading to its relative stabilization.

(24) For example, introducing a carboxyl substituent adjacent to the dihyronicotinamide ring appears to have no effect on λ_{\max} , as indicated by a comparison between the spectra of *N*-cyclopentylidihyronicotinamide and *N*-*cis*-2'-carboxycyclopentylidihyronicotinamide.

(25) Kam, B. L.; Malver, O.; Marschner, T. M.; Oppenheimer, N. J. *Biochemistry* **1987**, *26*, 3453-3461.

(26) The enzymatic reactivities of these analogues have been interpreted as evidence against a significant stereoelectronic interaction. This interpretation is based on a mistaken assumption that stereoelectronic features of α and β anomers of *N*-ribosylidihyronicotinamides are intrinsically different. In fact, α and β anomers are defined by the orientation of the substituent at the 4-position of the ribofuranose ring relative to the orientation of the nicotinamide moiety, an orientation that is irrelevant to stereoelectronic considerations, which depend only on the orientation of the lone pairs of electrons on nitrogen with respect to the carbon-oxygen bond.

(27) Hajdu, J.; Sigman, D. S. *Biochemistry* **1977**, *16*, 2841-2846.

(15) If we wish to evaluate the possibility that the stereoelectronic interaction in question could affect the evolution of an enzymatic active site, an estimate of its impact on reactivity is needed. It is now clear that variations in the behavior of enzymes amounting to less than 1 kcal/mol can be the targets of natural selection. This is an important point, discussed at length elsewhere.¹⁶ For now it must suffice to note work of Kreitman,¹⁷ showing that substitution of essentially any amino acid residue in the alcohol dehydrogenase from *Drosophila melanogaster* has selective impact, meaning that it influences the ability of the fly to survive and reproduce. Further, we have recently noted that the internal equilibrium constants of the heart and muscle isozymes of lactate dehydrogenase appear to be refined by natural selection to well within 1 kcal/mol of a kinetic optimum.¹⁸

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(20) Bürgi, H. B.; Dunitz, J. *J. Am. Chem. Soc.* **1987**, *109*, 2924-2926.

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to be analogous in structure,²² the stereoelectronic interaction can be expected to lower the rate of the latter reaction. Consistent with this expectation, molecules where $n-\sigma^*$ overlap is possible are less reactive as hydride donors than those without such overlap.^{6,28,29,30} Here again, only some of the difference in reactivity can be attributed to factors other than an interaction between the nitrogen lone pair and the adjacent σ^* orbital. Again, analogues of NADH containing a hydroxyl group *cis* and β to

the reduced ring, the anomers for which $n-\sigma^*$ overlap is sterically blocked, are the stronger reductants by 20 mV (1 kcal/mol), a difference that can only partly be assigned to through-space interactions.^{23,27}

Conclusions. Although the spectroscopic and structural data presented here for N-substituted dihydronicotinamides are consistent with a stereoelectronic interaction between the nitrogen lone pair and the σ^* orbital of the $\alpha-\beta$ bond, we find no evidence for a boat conformation of the dihydropyridine ring, which is practically planar in the two molecules **1** and **2**. The stabilization of the ground state due to $n-\sigma^*$ overlap could be as much as 2 kcal/mol. This appears to be sufficient to influence the evolution of enzymes dependent on nicotinamide cofactors.

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Crystal Structure of *cyclo*(Gly₁-L-Pro₂-D-Phe₃-L-Ala₄-L-Pro₅): A Cyclic Pentapeptide with a Gly-L-Pro δ Turn

A. N. Stroup,[†] A. L. Rockwell,[†] A. L. Rheingold, and L. M. Gierasch^{*,†}

Contribution from the Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716. Received November 5, 1987

Abstract: Synthesis and X-ray crystallography of the cyclic pentapeptide *cyclo*(Gly₁-L-Pro₂-D-Phe₃-L-Ala₄-L-Pro₅) has resulted in a novel hydrogen-bonded conformation. A *cis*-Gly₁-L-Pro₂ peptide bond was found with an intramolecular hydrogen bond between the amide proton of Gly₁ and the carbonyl oxygen of Pro₂, forming a δ turn. Conformational angles for the 2 \rightarrow 3 hydrogen-bonded residues are $\phi_1 = +109^\circ$, $\psi_1 = +94^\circ$, $\phi_2 = -73^\circ$, and $\psi_2 = +170^\circ$. A type I β turn with L-Ala₄ and L-Pro₅ in the corner positions, but lacking a hydrogen bond, precedes the δ turn. The peptide crystallized from methanol in the orthorhombic space group $P2_12_12_1$ with 12 water molecules per unit cell and cell dimensions $a = 11.238$ (3) Å, $b = 12.225$ (3) Å, and $c = 19.505$ (6) Å, $Z = 4$, and $R_F = 5.64\%$. All peptide and water protons were successfully located.

Cyclic pentapeptides have been used as model compounds for the study of reverse turns, particularly the β turn and the γ turn.¹⁻⁸ For cyclic pentapeptides with a DDDL chiral sequence or its inverse LDDL, a hydrogen-bonded type I or II β turn and often a γ turn are observed in the crystal structures¹ and in solution.^{2,3} Study of the title peptide *cyclo*(Gly₁-L-Pro₂-D-Phe₃-L-Ala₄-L-Pro₅) addresses the importance of chiral sequence and presence of prolines on the conformation of the cyclic pentapeptide backbone. The importance of these factors may be determined by comparing the conformation of the L-Ala analogue (title compound) with the D-Ala analogue, *cyclo*(Gly₁-L-Pro₂-D-Phe₃-D-Ala₄-L-Pro₅), which has a type II β turn conformation with L-Pro₂-D-Phe₃ in the $i + 1$ and $i + 2$ positions, respectively, and an inverse γ turn with L-Pro₅ in the $i + 1$ position, both in solution and crystalline states.⁹ An L residue preceding an L-proline is known to have strong conformational effects, especially on the preference for the *cis* and *trans* X-Pro bond isomers.¹⁰ Thus, one may predict the L-Ala₄-L-Pro₅ peptide bond would adopt the *cis* orientation due to the steric arrangement of side chains. However, this is not what is observed for the X-ray structure. Instead, the pentapeptide crystallizes with all peptide bonds *trans* except the Gly₁-L-Pro₂ bond, which is *cis*.

While β and γ turns have been extensively studied and are frequently observed in model and naturally occurring peptides,¹¹

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[†] Present address: Department of Pharmacology, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, TX 75235-9041.

^{*} Present address: Central Research and Development, Experimental Station, E. I. du Pont de Nemours & Co., Wilmington, DE 19898.