

Crystal Structure of 1-(2-Indol-3-ylethyl)-3-carbamidopyridinium Chloride, an Intramolecular Model of the Nicotinamide Adenine Dinucleotide-Tryptophan Charge-Transfer Complex

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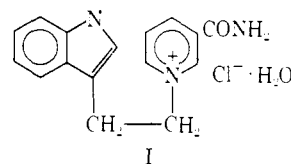
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Abstract: Yellow crystals of 1-(2-indol-3-ylethyl)-3-carbamidopyridinium chloride, an intramolecular model of charge transfer complexes between the nicotinamide (acceptor) moiety of NAD⁺ and a surface available tryptophanyl (donor) residue in proteins, were subjected to X-ray analysis. The structure solution of C₁₆H₁₆N₃O⁺Cl⁻·H₂O was obtained by standard methods (final *R* = 0.054), following determination of the approximate coordinates of the Cl atoms from a three-dimensional Patterson function. The molecules are in the extended trans configuration, with the nicotinamide ring plane rotated at approximately right angles to the plane containing the indole ring and the ethylene bridge carbon atoms. The donor and acceptor of any particular molecule are interleaved between corresponding acceptors and donors of adjacent molecules, such that the crystal consists of long columns or stacks of alternating donors and acceptors in *intermolecular* contact. Two sets of such columns are formed at roughly right angles to each other, corresponding to the perpendicular arrangement of the donor and acceptor of a given molecule. Within a column, the donors and acceptors are approximately coplanar and separated by an average distance of 3.7 Å. The π -orbital overlap between adjacent donor-acceptor "pairs" appears to be close to the maximum possible, and the permanent dipole moments are strongly coupled. The crystal conformation is substantially different from the conformation proposed for the substance in dilute solution (*gauche*, with highly overlapping rings in *intramolecular* contact and strongly coupled dipole moments). The structure is discussed in terms of the probable forces governing its conformation, and the possible biological consequences of the operation of similar forces in enzyme-coenzyme complexes. It is suggested that specific three-dimensional orientations can result from coplanar ring interactions, if at least one ring face of one molecule of a nonidentical pair is sterically blocked and the orbital shapes and charge distributions of the pair are not symmetric.

The uv or visible light-mediated charge transfer from the indolyl group to the 1-alkylnicotinamide positive ion in π -molecular complexes of these compounds has been shown to be useful in a variety of biochemical investigations.³⁻⁷ Kosower³ was the first to realize that the moderately intense long wavelength absorption band appearing in the mixtures of NAD⁺⁸ and 3-phosphoglyceraldehyde dehydrogenase⁹ could be ascribed to charge transfer from a donor to the pyridine cation. Cilento and Guisti⁴ correctly reasoned that the donor had to be an amino acid side chain, and found that tryptophan, alone among all the amino acids tested, gave rise to a charge-transfer band with 1-benzyl-nicotinamide (a model for NAD⁺) which was similar in both intensity and spectral distribution to the NAD⁺-enzyme absorption band. Almost simultaneously Isenberg and Szent-Györgyi¹⁰—acting on a study by

Pullman and Pullman¹¹ showing that the indole moiety of tryptophan would be a better electron donor than any of the other amino acids—presented evidence for charge transfer in complexes of NAD⁺ and tryptophan.

Later Shifrin¹² showed that the long wavelength absorption band observed in an equimolar mixture of tryptamine and 1-methylnicotinamide chloride was also present in the intramolecular complex 1-(2-indol-3-ylethyl)-3-carbamidopyridinium chloride (indolylethyl-nicotinamide chloride, I). The absorbance of



the inter- and intramolecular complexes are of the same order of magnitude, and since significant overlap of the donor and acceptor rings appears to be required for efficient charge transfer,¹³ a folded conformation was suggested for I in solution.¹²

Further support for this view has come from the nmr studies of Bosshard¹⁴ and Deranleau and Bosshard,¹⁵ which indicate that this compound exists virtually exclusively in a *gauche* conformation, and moreover, that

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(8) Abbreviations used are: NAD⁺, nicotinamide adenine dinucleotide; indolylethyl-nicotinamide, 1-(2-indol-3-ylethyl)-3-carbamidopyridinium positive ion.

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Table I. Final Atomic Parameters and Their Standard Deviations Given in Parentheses^a

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁ or <i>U</i>	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₁₂	<i>U</i> ₁₃	<i>U</i> ₂₃
C(1)	4418 (3)	5787 (3)	869 (1)	407 (12)	424 (13)	499 (16)	-25 (10)	26 (11)	-63 (11)
C(2)	3973 (3)	4621 (3)	1236 (1)	420 (13)	383 (13)	859 (21)	-29 (11)	71 (13)	19 (14)
C(3)	4160 (3)	5123 (3)	1702 (1)	486 (15)	520 (16)	679 (18)	87 (12)	151 (13)	215 (14)
C(4)	4740 (3)	6825 (3)	1827 (1)	383 (13)	659 (17)	393 (15)	95 (12)	68 (11)	63 (12)
C(5)	5202 (2)	8008 (3)	1467 (1)	301 (11)	429 (12)	363 (13)	36 (9)	26 (9)	11 (10)
C(6)	5050 (2)	7532 (2)	987 (1)	310 (11)	336 (11)	424 (13)	25 (9)	31 (9)	-58 (9)
C(7)	5638 (2)	9059 (2)	720 (1)	441 (12)	373 (11)	295 (14)	-13 (9)	55 (9)	-11 (9)
C(8)	6075 (3)	10388 (3)	1028 (1)	426 (12)	389 (12)	350 (13)	-27 (10)	64 (10)	-20 (10)
C(9)	5702 (6)	9124 (6)	195 (1)	595 (30)	439 (26)	329 (25)	-49 (24)	92 (22)	-16 (20)
C(10)	6017 (6)	10992 (5)	-8 (1)	466 (25)	448 (23)	317 (26)	71 (21)	78 (21)	-42 (21)
C(11)	7733 (5)	10306 (5)	-719 (1)	322 (22)	414 (23)	356 (26)	48 (19)	-31 (19)	8 (19)
C(12)	7902 (4)	9960 (5)	-1187 (1)	303 (20)	316 (19)	323 (24)	-2 (16)	45 (16)	19 (17)
C(13)	6412 (5)	10222 (5)	-1469 (1)	367 (22)	402 (23)	325 (24)	2 (19)	29 (18)	21 (19)
C(14)	4788 (5)	10783 (5)	-1273 (1)	331 (23)	539 (27)	437 (30)	32 (21)	-61 (21)	-5 (21)
C(15)	4672 (5)	11076 (5)	-800 (1)	279 (21)	392 (22)	537 (31)	56 (18)	74 (20)	23 (20)
C(16)	9751 (5)	9339 (5)	-1351 (1)	397 (24)	337 (22)	400 (30)	-20 (19)	77 (21)	21 (18)
N(1)	5819 (4)	9760 (4)	1478 (1)	483 (20)	441 (18)	368 (19)	-28 (17)	-23 (16)	-139 (16)
N(2)	6157 (4)	10820 (4)	-529 (1)	369 (18)	338 (18)	312 (20)	73 (15)	65 (15)	0 (14)
N(3)	9960 (5)	9112 (5)	-1814 (1)	366 (22)	595 (24)	365 (24)	14 (20)	84 (19)	-56 (18)
O(1)	10958 (3)	9084 (4)	-1067 (1)	326 (14)	741 (20)	422 (18)	65 (15)	38 (14)	25 (15)
OW(1)	7590 (5)	9120 (6)	-2626 (1)	529 (22)	1194 (32)	324 (25)	-151 (21)	1 (18)	-19 (21)
Cl-	1302 (2)	3348 (1)	0 (0)	788 (8)	433 (6)	333 (6)	46 (6)	-45 (6)	86 (5)
H(1)	4318 (37)	5502 (35)	524 (10)	518 (90)					
H(2)	3591 (40)	3400 (40)	1112 (11)	676 (100)					
H(3)	3751 (45)	4089 (49)	1977 (12)	878 (112)					
H(4)	4876 (35)	7268 (35)	2160 (9)	449 (89)					
H(8)	6648 (39)	11683 (40)	980 (11)	664 (103)					
H(11)	8640 (38)	10175 (38)	-520 (10)	227 (83)					
H(13)	6528 (40)	10031 (43)	-1826 (12)	689 (105)					
H(14)	3732 (45)	10907 (42)	-1456 (12)	593 (110)					
H(15)	3510 (40)	11418 (39)	-638 (10)	365 (83)					
H(18)	6018 (22)	10322 (21)	1702 (6)	343 (56)					
H(31)	9040 (41)	9217 (40)	-2008 (12)	312 (101)					
H(32)	11102 (47)	8858 (47)	-1911 (13)	639 (113)					
H(91)	6621 (42)	8277 (43)	103 (12)	567 (107)					
H(92)	4477 (40)	8670 (40)	83 (11)	481 (96)					
H(101)	7248 (36)	11436 (38)	118 (9)	382 (81)					
H(102)	5014 (33)	11868 (34)	84 (9)	259 (72)					
HW(1)	6505 (57)	8760 (64)	-2606 (17)	1274 (212)					
HW(2)	7769 (43)	9004 (43)	-2860 (10)	129 (105)					

^a The anisotropic temperature factors are defined by the equation $TF = \exp[-2\pi^2(U_{11}h^2a^{*2} + 2U_{12}hka^*b^* + \dots)]$.

rotational isomerism is absent. Molecular potential energy calculations reveal the existence of relatively large local energy minima centered around one of the gauche conformers of I which help to explain these observations.¹⁶ A study of the crystal structure of I should reveal some of the pertinent features of the interaction geometry, which may be important in the (presumably) highly specific interaction between NAD⁺ and the dehydrogenase enzyme and in the stabilization of the conformation of the model itself.

Experimental Section

The compound was prepared by the method of Shifrin.¹² Dissolving this material in hot aqueous ethanol followed by slow cooling resulted in well-formed yellow tetragonal bipyramids. Space group and approximate cell constants were obtained from precession photographs. Crystals were then transferred to a Picker FACS-1 four-circle diffractometer and the lattice parameters and orientation matrix refined by the methods of least squares.

Crystal Data. I (C₁₆H₁₆N₃O⁻Cl⁻·H₂O) is tetragonal, space group *P*4₁ (or *P*4₃) based on systematic absences (001) *l* = 4*n*; *a* = *b* = 7.386 (2) Å, *c* = 28.565 (5) Å, *V* = 1558 Å³; specimen size 0.3 × 0.3 × 0.4 mm.

Intensity data were collected using Nb filtered Mo K α radiation and employing the $\omega/2\theta$ scan technique. Within the sphere of reflection limited at $\sin \theta/\lambda = 0.7$, 1921 unique reflections were measured. Of these 341 were less than the threshold value of 2σ where $\sigma = [N_{pk\ scan} + (T_{scan}/T_{bkg})^2 N_{bkg} + (0.01_{pk\ net})^2]^{1/2}$. The

quantity $(0.01_{pk\ net})^2$ is added to the variance based on counting statistics to account for the observed fluctuation in the intensities of three standard reflections measured every 100 reflections. No deterioration of the crystal was observed nor was any absorption correction attempted.

Structure Solution. Approximate coordinates for the Cl atoms were obtained from a sharpened, origin-removed three-dimensional Patterson function. A structure factor calculation based on the halide atoms alone gave *R* = 0.55. Subsequent *F*_o and difference syntheses revealed the remaining non-hydrogen atoms (*R* = 0.33). The electron-density map revealed the presence of one water molecule per molecule of indolythylnicotinamide chloride. Refinement was achieved by three-dimensional full-matrix least squares. The function minimized was $\sum w(|F_o| - |(1/k)F_c|)^2$. The atomic scattering factors used for Cl⁻, N, O, and C were those given by Berghuis.¹⁷ Initially, the hydrogen scattering factors used were those of McWeeny¹⁸ but these were replaced before the final refinement cycle by those of Stewart, *et al.*¹⁹ The calculations were carried out on a CDC 6400 computer using the X-ray 70 program package.²⁰ Two cycles of isotropic refinement followed by two cycles of refinement in which the atoms were allowed to vibrate anisotropically lowered the conventional *R* value to 0.085. The hydrogen atom positions were located in a difference Fourier map and two additional cycles of anisotropic refinement for non-hydrogen atoms and isotropic refinement for H atoms reduced *R* to 0.055. Substituting scattering

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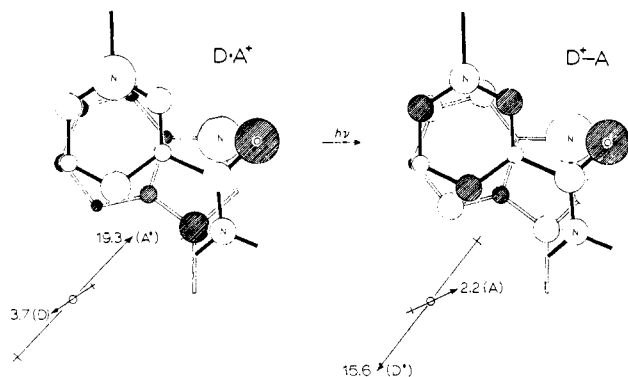


Figure 3. Approximate net charges on the atoms of the donor and acceptor in the ground ($D \cdot A^+$) and charge transfer ($D^+ \cdot A$) states. Shaded circles indicate net negative charges, and open circles net positive charges. The net atom charges are shown as being roughly proportional to the volume of an equivalent sphere of the same diameter as the circles in the diagram. (The largest net charge is about $0.5e$, on the indole ring nitrogen of the ($D^+ \cdot A$) state.)

dihydronicotinamide. The predictions were consistent with previous X-ray data on nicotinamide²² and *N*-benzyl-1,4-dihydronicotinamide.²³ The explanation²⁴ is that steric hindrance between a hydrogen of the NH_2 group and a hydrogen on the ortho ring carbon prevent the two groups from being coplanar in nicotinamide whereas in the dihydro compound, the two hydrogens on the ortho ring carbon can straddle the hydrogen from the NH_2 group. It was therefore somewhat surprising to find a planar arrangement ($\tau = 2.5^\circ$) in indolethyl-nicotinamide as this corresponds to the maximum of the conformational energy curve calculated for all values of this torsion angle. The angles about C(12) are indicative that some steric hindrance is present but by opening up angle C(13)–C(12)–C(16) (to 125.6°) and by forming 3 hydrogen bonds involving the amide group the molecule has compensated sufficiently to form a stable structure. A similar situation has recently been found in crystals of a complex of 1-methylnicotinamide and acetylacetate, a model for nicotinamide–adenine interactions.²⁵ The efficient packing and large orbital overlaps between donors and acceptors suggest that efficient charge transfer should occur in the crystal. In support of this contention, the crystals are strongly yellow colored, and very similar in apparent color to concentrated solutions of the compound in which charge transfer has been measured.

In view of the relatively good evidence for a folded (gauche) conformation in solution,^{12,14,15} the all-trans, extended conformation found in the crystal is of some interest. There is no evidence for the self-association of I in dilute solution, and the stabilization energy for the folded conformation has been estimated to be about -8 kcal/mol.¹⁶ At saturating concentrations, however, it is likely that the intermolecular forces between the (coplanar) rings of transition complexes (dimers, etc.) predominate over the intramolecular forces between the (noncoplanar) rings of the folded structure, and provide the driving force for a conformational change into the all-trans extended struc-

ture.²⁶ It is significant that no hydrogen bonds are formed between indolethylnicotinamide molecules in the crystal. Whereas such hydrogen bonds as do exist obviously contribute to the stability of the crystal as a whole, the intermolecular contacts between pairs of molecules in the crystal are confined to the rings of the donor of one pair and the acceptor of an adjacent pair. This fact strongly suggests that the van der Waals and Coulombic interactions between donors and acceptors of different molecules are mainly responsible for both the conformational change and the structural integrity of the crystal.

The relative importance of Coulombic forces in biologically significant interactions such as considered here should not be underestimated. While van der Waals forces probably comprise the larger part of the total interaction energy between the nicotinamide and indolyl moieties in the coplanar complex, Coulombic forces can have a considerable effect on the relative in-plane rotational orientation of the pair. In Figure 3 the approximate directions and magnitudes of the dipole moments of the donor and the acceptor are shown relative to the crystal conformations in both the ground and "dative" (charge transfer) states.²⁷ The dipole moments in the ground state are strongly coupled, and it is easily seen that rotation of the nicotinamide moiety by 180° in the plane of the ring would (while still satisfying the condition of maximum overlap) generate a considerable repulsion potential because of the unfavorable alignment of the dipoles.

The last point may be of more than passing interest, for many if not most biologically significant binding interactions involving planar ring structures (of which the particular complex under discussion is but one example) generally appear to exhibit two features: (1) the rings are usually highly asymmetric or at best contain a single rotation axis in the plane of the ring and (2) the charge distribution is not uniform. If the principle of maximum overlap is satisfied and the molecules both have an asymmetric electron distribution with a permanent dipole moment of any reasonable magnitude, a unique conformation (or its mirror image, viewed normal to the ring planes) can result in each case of pairing. The uniqueness of such a complex will not actually be due to the alignment of dipoles but to the specific atom-by-atom Coulombic interactions which operate at the close distances involved in the complexes. In Figure 3, rotation of the nicotinamide moiety by 180° about its *dipole* axis also satisfies the condition of maximum overlap. However, the total attractive Coulombic energy resulting from the interaction of the nearest neighbor atom charges would be smaller because of mutual repulsion of the two ring nitrogen atoms and of the carbonyl oxygen and the C_4 and C_5 carbons of the indole ring. Thus of the two possible rotational isomers of coplanar complexes in which the dipoles are strongly coupled (excluding mirror-image complexes), one should be energetically favored.

(26) Very tentative experimental evidence for such a conformational change may possibly be inferred from titration studies of the compound with 1-methylnicotinamide.

(27) Charge distributions were taken from B. Pullman and A. Pullman, "Quantum Biocoemistry," Interscience, New York, N. Y., 1963; G. Karreman, *Bull. Math. Biophys.*, **23**, 135 (1961); G. Maggiora, H. Johnson, and L. L. Ingraham, *Arch. Biochim. Biophys.*, **131**, 352 (1969).

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As an example of the application of these thoughts, let us consider the complex formed between the nicotinamide moiety of NAD⁺ and a solvent available tryptophanyl residue in 3-phosphoglyceraldehyde dehydrogenase. We can assume that virtually maximum orbital overlap occurs, since the complex exhibits an intense charge-transfer absorption for which a high degree of overlap is required. If furthermore we assume that one face of the tryptophanyl residue is blocked by the adjacent polypeptide chain of the protein (a common feature for exposed tryptophanyl residues in proteins, according to available crystallographic evidence), then a single in-plane rotational isomer should be favored for the coplanar nicotinamide-indole part of the NAD⁺-enzyme complex. Of course, the almost-equivalent complex in which the nicotinamide moiety is rotated around its dipole axis by about 180° may be close enough in *total* interaction energy so as to cause a significant fraction of complexes with this geometry to occur, in addition to those with the "best" total interaction energy. It occurs to us that nature may have been aware of this as well, and so (according to the experimental evidence²⁸) designed the coenzyme in such a fashion so as to block one face of the nicotinamide ring with an adenine ring. In this view, one of the biological functions of the adenine ring in NAD⁺ (or in NADH) may be simply to ensure that the enzyme-coenzyme complex is formed with the proper geometry for subsequent efficient enzymatic catalysis.

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In conclusion, complexes between asymmetric planar ring structures with nonzero dipole moments are inherently capable of exhibiting the same kind of stereochemical selectivity (provided that at least one of the ring faces of one molecule of the pair is blocked) that appears to operate in the more usual three-dimensional interactions between enzymes and substrates. This is most easily visualized by considering a planar surface on which three or more point charges are asymmetrically located. A second surface having opposite charges in mirror positions will exhibit minimum energy in contact with the first surface only when the charge pairs are in exact registry, all other things (degree of overlap) being equal. Furthermore, interactions between molecules with large permanent dipole moments represent a selective advantage for enzymatic efficiency over those with no permanent moment: as a molecule with a large permanent moment approaches its binding site on the enzyme, the long-range mutual interaction of the dipoles serves to orient the molecules with respect to each other until such time as the short range van der Waals and specific atom-pair Coulombic forces can act to finalize the geometry and stabilize the interaction.

Supplementary Material Available. A listing of structure factor amplitudes 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-74-1585.

Communications to the Editor

Stereodynamics of Substituted Carboranes. I. 1,2-Bis(*N,N*-dimethylcarbamoyl)-1,2-dicarba-*closo*-dodecaborane(12) and 1,7-Bis(*N,N*-dimethylcarbamoyl)-1,7-dicarba-*closo*-dodecaborane(12). Barriers to Rotation and the Aromaticity of the Carborane Cage

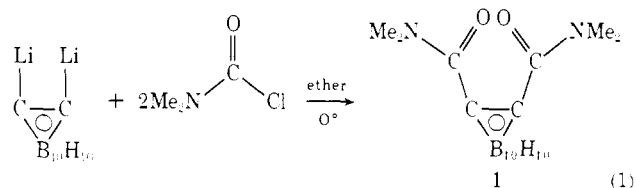
Sir:

Many recent reports have been concerned with elucidating the nature of nondestructive dynamical processes which occur in a wide variety of boron hydrides and boron hydride metal complexes.¹ There have been no papers regarding the effect of the apparently aromatic carborane cage on the conformational dynamics of attached substituents. This report concerns the observation of a dramatic acceleration in the rate of rotation about a carbonyl carbon-nitrogen bond as compared to a simple amide induced by efficient π -bonding involving the carborane cage.

The reaction of the lithium salt of the 1,2-dicarba-*closo*-dodecaborane(12) [*o*-carborane] dianion with *N,N*-dimethylcarbamoyl chloride in ether at 0° produced 1,2-bis(*N,N*-dimethylcarbamoyl)-1,2-dicarba-*closo*-dodecaborane(12) (**1**): mp 119–120°; ir, 1650 (C=O),

(1) H. Beall and C. H. Bushweller, *Chem. Rev.*, **73**, 465 (1973).

1480 and 1370 cm⁻¹ (CH₃). *Anal.* Calcd: C, 33.54; H, 7.74. Found: C, 33.82; H, 7.77 (eq 1).



Examination of the ¹H dnmr spectrum (60 MHz) of **1** (0.1 M in CHCl₃) at 56.6° (Figure 1) revealed a sharp singlet methyl resonance (δ 3.20) consistent with all methyl protons in **1** being rendered equivalent due to a rate process which is rapid on the dnmr time scale. Upon lowering the temperature, the NMe₂ dnmr spectrum broadens substantially giving evidence for the slowing of two distinct rate processes (Figure 1). For example, at -11.9°, the two sharp singlets correspond to a rate process which is slow on the dnmr time scale but these sharp peaks are superimposed on another exchange-broadened spectrum corresponding to a more rapid equilibration. At lower temperatures, the spectrum sharpens into a series of four singlet reso-