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Citation for published version (APA):

DOI:
10.1021/jo00001a005

Document status and date:
Published: 01/01/1991

Document Version:
Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

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Conformational Interlocking in Axially Chiral Methyl N-(2',4'-Dimethylnicotinoyl)-N-methylphenylalaninates

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Received February 22, 1990

Axially chiral 2,4-dimethylnicotinamides incorporating a protected N-methylphenylalanine moiety (1; 2) have been prepared to serve as NAD* model precursors. Starting from L- or d-methyl N-methylphenylalaninate hydrochloride (S)- or (R)-4, the M-syn diastereomer 1a or its P-syn enantiomer 2a, were isolated in fair yield by a combination of rotamerization, helical isomerization, and crystallization. Evidence is presented for a strong conformational preference in solution not only at the amide bond but also at the chiral center (C-2) and at the benzylic carbon (C-3). The conformational interdependence compares well with the spatial arrangement in crystals of analogous axially chiral nicotinamide derivatives. Due to a preferred syn orientation of the amide carbonyl and C-2-H, the phenyl ring of the less polar syn diastereomers resides near the C-2'-methyl group either at the α side of the pyridine ring in 1a or at the β side in 2a. In these syn diastereomers the S chirality in the amino acid residue (i.e., in 1a) corresponds to a CO UP or M helicity, the R chirality (i.e., in 2a) to a CO DOWN or P orientation. Conversely, the phenyl ring of the more polar syn diastereomers 1b (P conformer) and 2b (M conformer) resides preferentially in the vicinity of the C-4' methyl group.

Introduction

Transient axial chirality induced by out-of-plane rotation of the amide group in NADH-NAD* was proposed as a rationale for the high stereoselectivity of the hydride transfer in vivo.1 NADH Model studies on peralkylated, chiral 3-(aminocarbonyl)-1,4-dihydroquinoline6 and -pyridine3 have unambiguously demonstrated that in vitro hydride transfer occurs highly stereoselectively as well as with regard to the NADH model as to the carbonyl substrate. They have given support to the concept of syn chiral 3-(aminocarbonyl)-1,4-dihydr~quinoline~ as a rationale for the high stereoselectivity of the hydride enzymic cavity and via hydrogen bridge formations with C-H bond during the hydride transfer.

Methyl N-methylphenylalaninate was selected as a peptide prototype. Oligopeptide moieties were envisaged. Methyl N-methyl-formational interlocking of the pyridine ring, the amide for NAD+ models, is described in this paper. Their spectral formation in the presence of an HCl scavenger (Et,N) gives rise to the syn-anti rotamerism about the amide bond and the consequence of two types of conformational isomerism, Le., (1c,d → 1a,b) and (2a,b → 2c,d), which can be considered as immediate precursors for NAD* models, is described in this paper. Their spectral characteristics in solution are discussed in terms of conformational interlocking of the pyridine ring, the amide group, the chiral center at C-2, and the phenyl ring at C-3.

Results and Discussion

1. Isolation of 1a,b and 2a,b. Treatment of 2,4-dimethylnicotinoyl chloride hydrochloride (3) with methyl N-methyl-l-phenylalaninate hydrochloride ((S)-4) at 0 °C in the presence of an HCl scavenger (Et,N) gives rise to the formation of four diastereomeric amides 1a-d as a consequence of two types of conformational isomerism, i.e., the syn-anti rotamerism about the amide bond and the axial chirality around the C-3'-C amide axis.

In CDCl3 a 1'H NMR spectrum of the mixture, taken immediately after the reaction, revealed the presence of eight distinct singlets ranging from 1.45 to 2.50 ppm and corresponding to the C-2' and C-4' methyl protons of 1a-d (Table I). Typical doublet of doublets were observed for C-2-H, centered around 5.85 ppm for the two major isomers (~75%, ratio 1:1) and around 4.25 ppm for the minor ones (~25%, ratio 1:1). The latter featured an N-methyl proton absorption at lower field (~3.25 ppm) than the former (~2.65 ppm). Interestingly, the signals belonging to the major isomers gradually increased in intensity at the expense of those belonging to the minor conformers, finally reaching a 96:4 ratio at equilibrium. Obviously a relatively slow conformational inversion around the amide C-N bond was responsible for this phenomenon. The preference for the formation of the major isomers 1a,b was apparently less pronounced than the thermodynamic preference. Taking into account the relative bulkiness of the 1-carbomethoxy-2-phenylethyl group and the behavior of other tertiary nicotinamides (vide infra), an anti → syn transformation (1c,d → 1a,b) was assumed. A 1'H NMR spectrum of a mixture of 1a,b in CDCl3 featured strikingly selective shieldings exerted on H-5' (δ 6.94 vs 6.82) and on the C-2' and C-4' methyl protons (δ 2.50 and 2.28 vs 1.70 and 1.45). The downfield signals were almost superimpos-able on those found in the N,N-dimethyl analogue 5 (Table I). Fortunately we were able to isolate the less polar diastereomer (R, 0.17, SiO2, CHCl3-MeOH, 98:2) by crystallization and demonstrated it to contain considerably shielded C-2' methyl protons (δ 1.70 vs 2.44 for the corresponding protons in 5). Structure 1a was assigned to this compound, based on evidence that is described subsequently. The mother liquor were enriched in the more polar diastereomer (R, 0.12). The relative (vs 5) shielding of both H-5' (δ 0.1 ppm) and the C-4' methyl protons (Δ 0.83 ppm) in 1'H NMR offered partial evidence for the assignment of structure 1b to this compound.

Conformational Interlocking in Chiral Phenylalaninates

Table I. Relevant 1H NMR Spectral Data of syn- and anti-2,4-Dimethylnicotinamides.a,b

<table>
<thead>
<tr>
<th>entry</th>
<th>R1 (syn)</th>
<th>R2 (anti)</th>
<th>C-4 Me</th>
<th>C-2 Me</th>
<th>NCH2 syn</th>
<th>NCH2 anti</th>
<th>H-5</th>
<th>H-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>CH(CH2Ph)CO2Me (S)</td>
<td>Me</td>
<td>2.28</td>
<td>1.70</td>
<td>5.96</td>
<td>2.65</td>
<td>6.94</td>
<td>8.29</td>
</tr>
<tr>
<td>1b</td>
<td>CH(CH2Ph)CO2Me (S)</td>
<td>Me</td>
<td>2.15</td>
<td>2.50</td>
<td>5.98</td>
<td>2.65</td>
<td>6.82</td>
<td>8.29</td>
</tr>
<tr>
<td>1c</td>
<td>Me</td>
<td>CH(CH2Ph)CO2Me (S)</td>
<td>1.56</td>
<td>2.36</td>
<td>3.27</td>
<td>4.26</td>
<td>6.86</td>
<td>8.34d</td>
</tr>
<tr>
<td>1d</td>
<td>Me</td>
<td>CH(CH2Ph)CO2Me (S)</td>
<td>2.18</td>
<td>1.96</td>
<td>3.25</td>
<td>4.23</td>
<td>7.00</td>
<td>8.36</td>
</tr>
<tr>
<td>2a</td>
<td>CHMe2</td>
<td>Me</td>
<td>2.23</td>
<td>2.44</td>
<td>3.15</td>
<td>2.61</td>
<td>6.92</td>
<td>8.28</td>
</tr>
<tr>
<td>2b</td>
<td>CHMe2</td>
<td>Me</td>
<td>2.24</td>
<td>2.46</td>
<td>5.11</td>
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<td>2.48</td>
<td>3.02</td>
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<td>2.49</td>
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<td>3.56</td>
<td>6.96</td>
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</tr>
<tr>
<td>5</td>
<td>CHMe2</td>
<td>H</td>
<td>2.29</td>
<td>2.50</td>
<td>4.32</td>
<td>4.32</td>
<td>6.92</td>
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<tr>
<td>6</td>
<td>CH(CH2Ph)CO2Me (S)</td>
<td>H</td>
<td>2.08</td>
<td>2.30</td>
<td>5.15</td>
<td>5.15</td>
<td>6.85</td>
<td>8.22</td>
</tr>
</tbody>
</table>

*In CDCl3 in ppm. In N,N-dimethylacetamide the syn N-methyl protons are found at higher field than the corresponding anti protons (2.9 vs 3.1 ppm), while in N,N-disopropylacetamide the same holds for the methine protons (3.52 vs 3.93 ppm). In N-methyl-N-isopropylacetamide, however, the methine proton of the syn isomer resonates at lower field than that of the anti isomer (4.52 vs 3.92 ppm).† In compounds 1a-d and 9 the protons are numbered: C-2' and C-4'. Me, H-5 and H-6.‡ Structures 1c and 1d are assigned tentatively.

Moreover, and comparable to the behavior of optically active 5,a rotational isomerism around the C-3'-CO bond in the diastereomers 1a and 1b took place slowly at room temperature in CDCl3 or C6D6 (t1/2 ~ 14 days). In CF3CO2D no appreciable isomerization occurred within a month.ub Upon heating at reflux temperature in CD3CN, however, fast isomerization occurred to afford a 1:1 mixture of 1a and 1b (30 min). On the basis of these observations, a procedure was developed for the high yield conversion of the mixture 1a-d into pure 1a. After amide formation, the reaction mixture was taken up in boiling diethyl ether to remove insoluble Et3N.HCl and to complete concomitantly the anti → syn rotamerization. The resultant 1:1 mixture of 1a and 1b was concentrated and subsequently crystallized from diisopropyl ether to afford a solid 9:1 mixture of 1a and 1b from which pure 1a could finally be obtained upon crystallization from diethyl ether at 0 °C. The mother liquors were recycled by using gradually diminishing quantities of diisopropyl ether as solvent. Thus, at a 1-g scale, pure amide 1a was recovered in more than 60% yield from 3. With the aid of HPLC also diastereomer 1b could be isolated in high diastereomeric purity (98:2).

The nicotinamides 2a,b derived accordingly from (R)-4 and 3. The next section deals with the conformational analysis of 1a and its syn stereoisomers in solution.

2. Conformational Analysis of 1a and Its Syn Stereoisomers. Axial Chirality. The severe steric crowding around the C-3'-CO axis forces the pyridine and amide planes in 1 (and 2) into a perpendicular arrangement and so induces atropisomerism.1 The syn amides 1a and 1b are helical isomers with the CO UP around the C-3'-CO bond (M) and CO DOWN (P) conformation, respectively. Judged from 1H NMR data (i.e., relative integrations), in solution no appreciable energy difference exists between conformers 1a and 1b.

Figure 1. CD spectra of methyl N-(2',4'-dimethylnicotinoyl)-L-phenylalaninates 1a, 1b and 9 in MeOH.

However, the former crystallized preferentially and featured the higher melting point and lower polarity. Secondary amide 9 (Table I), lacking the anti N-methyl substituent of 1, by contrast, behaves at room temperature as a single molecule devoid of axial chirality.

The absolute conformation (M or P) of the amide dipole in 1a and 1b was determined by comparison with 2,4-dimethylnicotinamide derivatives of known helicity and containing a common anti N-methyl group but differing syn N substituent e.g., 5, 10, 11, 12. A positive Cotton effect was in every case associated with a CO DOWN or P conformation, a negative Cotton effect with a CO UP or M conformation.5 Pure, crystalline diastereomer 1a exhibited a negative Cotton effect [Δe (265 nm) = -3.3 (MeOH)], while 1b featured a positive Cotton effect [Δe ≈ +2.1]. The difference in absolute magnitude of these Cotton effects may be explained by the small contribution to Δe of the S chirality at C-2. Indeed, for compound 9 (Table I), lacking stable axial chirality, a Δe (260 nm) ≈ -0.6 was measured (Figure 1). Therefore, amide 1a was assigned the M helicity and its more polar diastereomer

(6) (a) Van Lier, P. M.; Meulendijska, G. H. W. H.; Buck, H. M. Recl. Trav. Chim. Payse-Bas 1983, 102, 327. (b) It has been established previously that, at room temperature, optically active 5,a 3.2 fast racemization in n-hexane (t1/2 < 1 h), while it loses its optical purity only slowly in water (t1/2 > 1 month) (ref 6a). The more important contribution of the dipolar mesomeric form of the amide in polar solvents lowers the rate of racemization (Jackman, L. M.; Kavanagh, T. E.; Haddan, R. C. Org. Magn. Reson. 1969, 1, 109). This may also diminish the probability for P → M interconversion of dimethylnicotinamides 1, and 2, if one assumes—for steric reasons—that the latter is accompanied by rotation around the amide C-N bond. Moreover, the volume of the amide group may be affected in protic solvents by hydrogen bonding. Additional N-1 protonation in the presence of the strong proton donor CF3CO2H may ultimately prevent helical isomerization of 1a,b (2a,b).
1b the P helicity. Evidently 2a, being enantiomeric to 1a, exhibited the positive Cotton effect ($\Delta\varepsilon \approx +3.3$) required for a CO DOWN or P conformation.

Syn-Anti Rotamerism. Hindered rotation in amides, brought about by the contribution of the dipolar, mesomorphic structure, has been studied extensively by $^1$H NMR spectroscopy.$^9$ In tertiary 2,4-dimethylnicotinamides (e.g., 1, 2, 5, 6, 7), the barrier to rotation about the C-N axis is enhanced by the presence of two locking ortho substituents$^{10}$ on the aromatic ring and the absence of cross conjugation between perpendicularly arranged amide and aromatic rings.$^9$ In the case of nonsymmetric tertiary amides, e.g., 6a,b (Table I), a complete set of signals for each rotamer becomes visible in $^1$H NMR. The thermodynamic preference for a particular isomer is—except for formamide—inversely proportional to the degree of steric interaction between the carbonyl substituent and the amide anti N substituent.$^{3,11}$ Inspection of the molecular models leaves no doubt that in the anti isomers the C-3'40 bond and any deviation therefrom by rotation around the N-C bonds, the relative position of syn and anti N-methyl protons cannot be used as an a priori criterion for the assignment of the conformation in which the methine proton is directed to the pyridine ring enhances the van der Waals interaction between the N-methyl group and the aromatic ring and the N-methyl group. The diastereoselective synthesis of 3-deuterophenylalanines and N-

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Figure 2. Preferred N-C-H orientations in nicotinamides 1c, 1a, 6a, and 7.

Figure 3. Staggered conformations along the C-2-C-3 axis in 1a.

in the 2,4-dimethylnicotinamide series (1a-d, 5, 6a,b). In N-methyl-N-isopropyl (6a,b) or N-methyl-N-(1-carboxymethoxy-2-phenylethyl) derivatives (1), the syn isomers have their methine group orientated preferentially syn and coplanar to the amide carbonyl, resulting in a marked deshielding ($\delta$ 5.11 and ~5.95, respectively)$^{12}$ (Figure 2). In the anti isomers, the methine protons are preferentially directed to the pyridine ring and are therefore subjected to additional shielding ($\delta$ 3.63 and ~4.25 in 6b and 1c,d, respectively). These considerations explain why the syn and anti N-methyl protons are only separated by ~0.55-0.6 ppm while the methine protons differ by ~1.5 and 1.7 ppm in 6b and 1a-d, respectively. In disisopropyl derivative 7 the conformational preferences for the syn and anti substituents cannot be reconciled and the anti substituent dominates since any deviation from a conformation in which the methine proton is directed to the pyridine ring enhances the van der Waals interaction between the C-2 or C-4 methyl and one of the anti N-isopropyl methyl groups. The syn methine proton cannot, therefore, occupy a position similar to that in 6 or 1 without causing two unfavorable syn 1,3-diaxial ( eclipsed) interactions. All four methyl groups are accommodated in a 1,3-staggered disposition by turning the syn isopropyl group over 120$^\circ$. The overall result is that both methine protons in 7 are coinciding at 3.56 ppm.

From all these data it can safely be concluded that the isomers to which we assigned structures 1a and 1b are indeed syn rotamers and that in these isomers a strong preference exists for the syn orientation of the C-2-H bond and the amide carbonyl. This has far-reaching consequences for defining the preferred molecular conformation of 1a,b and 2a,b.

Conformation around C-3. At last we will discuss the rotational preference around the benzylidene C-3, considering three staggered conformers F (folded), E$_Q$ (extended to oxygen), and E$_N$ (extended to nitrogen)$^{13}$ (Figure 3). The marked nonequivalence of H-3a and H-3P in $^1$H NMR (Table II, $\Delta\delta = 0.57$ ppm) and the exceptionally high difference in coupling constant ($^3J_{2,3a} = 4.8$, $^3J_{2,3m} = 12.4$ Hz) suggest a strong preference for one conformer. The sum of both vicinal coupling constants (17.2 Hz) is indicative for the unimportance of the folded conformation (two gauche couplings). This is presumably due to an unfavorable syn 1,3-diaxial interaction between the phenyl ring and the N-methyl group. The diastereoselective synthesis of 3-deuterophenylalanines and N-

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benzoyl derivatives) allowed the unambiguous assignment of the diastereotopic methylene protons in unlabeled material. In the L isomers the upfield methylene proton were calculated. The introduction of slightly enhanced populations of >80% for the EN, Eo, and F conformers. The large preference for the EN conformation can partly be rationalized by assuming some attractive inter- as compared to Pachler’s parameters gave calculated larger vicinal coupling constant (J = 8 ± 1 Hz vs 5.5 ± 1 Hz for H-3α). This means that the EN rotamer predominates in solution. All aforementioned data together allow the assignment of the high-field signal in 1a,b (H-3β) to the pro-R proton and features the (2-2' methyl group. Conversely indeed corresponds to the (2-2' methyl group. Conversely, the introduction of slightly enhanced values for J2 (14.43 vs 13.56 Hz) and J2 (2.77 vs 2.60 Hz), as compared to Pachler’s parameters, gave calculated populations of 82, 18, and 0% for the EN, Eo, and F conformers. The large preference for the EN conformation can partly be rationalized by assuming some attractive interactions between the amide N+ and either the phenyl ring or an ester oxygen or both. In itself it provides a rationale for the selective and large shielding effect that either the C-2' methyl protons feature deshielded signals, in accordance with their close vicinity to the negative side of the pyridine dipole. In 1a, the replacement of CDCl3 by C6D6 shows that in the N,N-dimethyl derivative, only the C-2 methyl protons feature deshielded signals, in accordance with their close vicinity to the negative side of the pyridine dipole. In 1a, the replacement of CDCl3 by C6D6 causes the C-4' and C-2' methyl protons to approach each other ppm), proving that the original signal at 2.50 ppm belongs to the C-2' methyl protons of 1a (2a) or the C-4' methyl protons in 1b (2b) (Table I).

3. Molecular Conformation of 1a,b and 2a,b. 1H NMR Data. On the basis of all preceding conformational data gathered for 1a,b (2a,b), the introduction of a phenyl ring is directed preferentially toward the pyridine ring (Figure 4) and is so responsible for the selective and large shielding effect that either the C-2' (1a, 2a) or the C-4' (1b, 2b) methyl protons undergo. As clarified in section 2, in all compounds the proton at the chiral center C-2 is located nearly coplanar and syn with the amide carbonyl dipole. Having determined the conformational preferences at C-2 and C-3, it follows that further proof is given for the absolute helical conformation

\begin{table}
\centering
\caption{Restricted Rotational Freedom around C-3 in Some \textit{syn}-N-Acylphenylalanine Derivatives\textsuperscript{a}}
\begin{tabular}{cccccccc}
\hline
entry & solvent & H-3α & H-3β & \(\Delta\delta\) & J2,2α & J2,2β & \(\Delta J\) & \(\Sigma J\) \\
\hline
1a & CDCl\textsubscript{3} & 3.61 & 3.04 & 0.57 & 4.8 & 12.4 & 7.6 & 17.2 \\
1b & CDCl\textsubscript{3} & 3.61 & 3.03 & 0.58 & 4.8 & 12.4 & 7.6 & 17.2 \\
9 & \textit{MeCONCH(CH\textsubscript{2}Ph)CO\textsubscript{2}Me}\textsuperscript{b} (L) & 3.37 & 3.05 & 0.32 & 5.3 & 11.1 & 5.8 & 16.4 \\
5 & \textit{MeCONCH(CH\textsubscript{2}Ph)CO\textsubscript{2}Me}\textsuperscript{e} (L) & 2.97 & 2.82 & 0.15 & 5.9 & 8.8 & 2.9 & 14.7 \\
10 & \textit{CF\textsubscript{2}CONCH(CH\textsubscript{2}Ph)CON(Me)CH(Me)CO\textsubscript{2}Me}\textsuperscript{d} (L-\textit{syn}) & 3.18 & 3.02 & 0.16 & 6.0 & 6.9 & 0.9 & 12.9 \\
& (DL-\textit{anti}) & 3.20 & 3.06 & 0.14 & 6.0 & 6.9 & 0.9 & 12.9 \\
\hline
\end{tabular}
\textsuperscript{a}In CDCl\textsubscript{3} (\textit{H} NMR data). Chemical shifts are in ppm; \(\Delta J\) values are in hertz. \textsuperscript{b}Reference 21. \textsuperscript{c}Reference 22. \textsuperscript{d}Reference 16.
\end{table}

\begin{table}
\centering
\caption{Comparative ASIS Data for 2,4-Dimethylisoxinolinamides 1a,b and 5\textsuperscript{a,b}}
\begin{tabular}{cccccccc}
\hline
entry & solvent & C-2 Me & C-4 Me & \(\Delta\delta\) & NMe \textit{anti} & NCH syn & H-5 & H-6 \textsuperscript{a} \\
\hline
1a & CDCl\textsubscript{3} & 1.70 & 2.28 & -0.58 & 2.65 & 5.96 & 6.94 & 8.29 \\
& C\textsubscript{6}D\textsubscript{6} & 1.95 & 2.13 & -0.14 & 2.24 & 5.98 & 6.47 & 8.30 \\
1b & CDCl\textsubscript{3} & 2.50 & 1.45 & 1.05 & 2.65 & 5.98 & 6.82 & 8.29 \\
& C\textsubscript{6}D\textsubscript{6} & 2.70 & 1.35 & 1.35 & 2.23 & 5.98 & 6.41 & 8.30 \\
5 & CDCl\textsubscript{3} & 2.44 & 2.23 & 0.21 & 2.81 & 3.15 & 6.92 & 8.28 \\
& C\textsubscript{6}D\textsubscript{6} & 2.47 & 1.91 & 0.58 & 2.07 & 2.70 & 6.41 & 8.24 \\
\hline
\end{tabular}
\textsuperscript{a}Expressed in ppm. \textsuperscript{b}Concentration 0.2 M. \textsuperscript{c}In compounds 1a,b the protons are indicated as C-2' and C-4' Me, H-5', and H-6'.
\end{table}

\section*{Figure 4}

Preferred molecular conformations of 1a and 1b. in 1a,b and 2a,b as it was deduced earlier from the sign of the Cotton effect (vide supra). Also ASIS (anisotropic solvent induced shift) measurements in C\textsubscript{6}D\textsubscript{6} corroborate the foregoing results. Indeed, as depicted in Table III, the replacement of CDCl\textsubscript{3} by C\textsubscript{6}D\textsubscript{6} shows that in the N,N-dimethyl derivative, only the C-2 methyl protons feature deshielded signals, in accordance with their close vicinity to the negative side of the pyridine dipole. In 1a, the replacement of CDCl\textsubscript{3} by C\textsubscript{6}D\textsubscript{6} causes the C-4' and C-2' methyl proton signals to approach each other (\(\Delta \delta \) 0.58 – 0.18 ppm), indicating that the original signal at 1.70 ppm indeed corresponds to the C-2' methyl group. Conversely in 1b, the singlets corresponding to the C-2' and C-4' methyl groups are more remote in C\textsubscript{6}D\textsubscript{6} (\(\Delta \delta \) 1.05 – 1.35 ppm), proving that the original signal at 2.50 ppm belongs to the C-2' methyl protons of 1b. Interestingly, it was also observed that the C-2''H absorptions in 1a,b (2a,b) were barely affected by replacement of CDCl\textsubscript{3} through C\textsubscript{6}D\textsubscript{6} in contrast to the usual moderate to large shieldings of other amide N substituents (cf. the N-methyl groups in Table III). An orientation as proposed by our conformational considerations counterbalances the shielding effect of C\textsubscript{6}D\textsubscript{6} by positioning C-2'-H at the negative side of the carbonyl dipole.

\section*{13C NMR Data of 1a and 1b. Also 13C NMR spectra of 1a and 1b reveal straightforward differences between both diastereomers. Especially relevant are the relative positions of the signals attributed to the C-2' and C-4' methyl carbons: while, with respect to 5, the C-2' methyl carbon in 1a is shielded by 0.8 ppm (\(\delta \) 21.4 vs 22.2), the same shielding is observed for the C-4' methyl carbon in 1b (\(\delta \) 17.5 vs 18.6). No difference exists between the C-4' (C-4) methyl carbons of 1a and 5 or the C-2' (C-2) methyl carbons of 1b and 5. Transmission of the shielding effect

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Preferred molecular conformations of 1a and 1b.}
\end{figure}
to C-2' and C-4' is also observed: whereas \( \Delta \delta \) C-2-C-4 amounts to 10.2 ppm in 5, differences of 9.75 ppm in 1a and 10.4 ppm in 1b were found for the corresponding signals. The degree of shielding at the methyl carbons is of equal magnitude as that observed in \(^1\)H NMR for the corresponding protons.

**Difference in Polarity between 1a (2a) and 1b (2b).** The difference in polarity between the less polar syn N-methyl group in 3J,2,3e

N-methyl group in

nicotinoyl group is locked, and two stable helical isomers pyridine ring and toward the ester function in the phenyl ring near C-4' at the \( \beta \) side of the pyridine ring. Behaves differently toward sodium dithionite or other reductants than that derived from 1a, where the phenyl ring resides in the vicinity of C-2' and at the \( \alpha \) side of the pyridine ring. Ultimately, the design of a NAD*-NADH model, provided with a high, reversible, and stereoselective activity, may be facilitated by taking advantage of restricted conformational freedom in solution.

**Experimental Section**

**General Methods.** Column chromatographic separations were performed on silica gel (63–200 \( \mu \)m) and TLC analyses on aluminum sheets precoated with silica gel. Preparative HPLC was realized on a column (120 \( \times \)16 mm) loaded with Lichrosorb 5A and eluted at a rate of 15 mL/min. Melting points are uncorrected.

**2,4-Dimethylnicotinoyl Chloride Hydrochloride (3).** Acid chloride 3 was obtained from crotonaldehyde and ethyl \( \beta \)-aminocrotonate in four steps.

**Methyl N-Methyl-1-phenylalaninate Hydrochloride ((S)-4).** The title compound was prepared from N-methyl-1-phenylalanine according to the description of Warnke and Young\(^ {8a} \) on a 10-mm scale. The crude reaction mixture was triturated with diethyl ether–2-propanol (9:1, 10 mL) to afford white, solid (S)-4 (1.65 g, 72%). Recrystallization from disopropyl ether-acetone (1:1, 20 mL) gave analytically pure (S)-4 (1.46 g, 84%); mp 116–117°C (lit.\(^ {3a} \) mp 86–87°C (MeOH); lit.\(^ {8b} \) mp 136°C (acetone)). [\( \alpha \)]: +56° (c 1, CHCl\(_3\)); [\( \alpha \)]: +59° (CHCl\(_3\)); lit.\(^ {8b} \) +19° (CHCl\(_3\)). \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 2.67 (s, 3 H, NMe), 3.03 (dd, \( J \) = 13.75 and 5.1 Hz, 1 H, H-3a), 3.26 (dd, \( J \) = 15.0 and 5.1 Hz, 1 H, H-3b), 3.68 (s, 3 H, CO\(_2\)Me), 3.94 (dd, \( J \) = 5.4 and 9.1 Hz, 1 H, H-2), 7.2–7.35 (m, 5 H, Ar H), 9.9 (bs, 1 H, NH,). \(^13\)C NMR (CDCl\(_3\)): \( \delta \) 134.0 (C-1'), 134.0 (C-16), 128.3 (C-3', C-5' Ar), 128.8 (C-2', C-4', C-6' Ar), 134.0 (C-1' Ar), 167.8 (CO). Analy. Calcd for C\(_{16}\)H\(_{15}\)ClN\(_2\)O: C, 57.5; H, 7.0; N, 6.1. Found: C, 57.8; H, 7.4; N, 6.1.

**Methyl N-Methyl-d-phenylalaninate Hydrochloride ((R)-4).** Compound (R)-4 was prepared and purified in the same way as described for its enantiomer (S)-4 (vide supra). Analytically pure (R)-4 was obtained in 62% yield, mp 115–117°C. \( \delta \) [\( \alpha \)]: −58° (c 1, CHCl\(_3\)). The \(^1\)H NMR and \(^13\)C NMR spectra were superimposable with those of (S)-4. Anal. Found: For C\(_{16}\)H\(_{15}\)ClN\(_2\)O: C, 57.5; H, 6.9; N, 6.1.

**Methyl 2-(2',4'-Dimethyl nicotinoyl)-N-methyl-1-phenylalaninate 1a–d.** A suspension of (S)-4 (600 mg, 2.61 mmol) in cold dichloromethane (24 mL) was brought to dissolution with triethylamine (1.12 mL, 792 mg, 7.83 mmol). Then, while cooling in an ice bath and stirring, acid chloride 3 (558 mg, 2.61 mmol) was added portionwise. After 2 h of reaction, 3 volumes of ice-cold diethyl ether were added, triethylammonium chloride was removed by extraction with ice-water, and the dried (MgSO\(_4\)) organic phase was concentrated in vacuo at 0°C. The residue (0.81 g, 95%) was then subjected to \(^1\)H NMR spectroscopy, showing the presence of four components: 1a, (syn isomers) and 1b, (anti isomers) in a 1:1 ratio. \(^1\)H NMR and \(^13\)C NMR spectra were superimposable with those of (S)-4. Anal. Found: For C\(_{25}\)H\(_{23}\)ClNO\(_2\): C, 57.5; H, 6.9; N, 6.1.

**Methyl 2-(2',4'-Dimethyl nicotinoyl)-N-methyl-1-phenylalaninate 1a–d.** A suspension of (S)-4 (600 mg, 2.61 mmol) in cold dichloromethane (24 mL) was brought to dissolution with triethylamine (1.12 mL, 792 mg, 7.83 mmol). Then, while cooling in an ice bath and stirring, acid chloride 3 (558 mg, 2.61 mmol) was added portionwise. After 2 h of reaction, 3 volumes of ice-cold diethyl ether were added, triethylammonium chloride was removed by extraction with ice-water, and the dried (MgSO\(_4\)) organic phase was concentrated in vacuo at 0°C. The residue (0.81 g, 95%) was then subjected to \(^1\)H NMR spectroscopy, showing the presence of four components: 1a, (syn isomers) and 1b, (anti isomers) in a 1:1 ratio. \(^1\)H NMR and \(^13\)C NMR spectra were superimposable with those of (S)-4. Anal. Found: For C\(_{25}\)H\(_{23}\)ClNO\(_2\): C, 57.5; H, 6.9; N, 6.1.

**Concluding Remarks**

It has been shown that the syn-N-(2',4'-dimethyl-nicotinoyl)-N-methylphenylalaninates 1a, 2a, and 2b possess at room temperature a strongly preferred molecular conformation in solution and could be obtained as pure, crystalline materials. The behavior of these compounds in solution provides a clear example of the major influence

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(19) Recent solid-phase \(^{13}\)C NMR data corroborate the results found for 1a (2a) and 1b (2b) in solution. The diastereomers differ markedly in the chemical shifts of their C-2', C-4', C-2' methyl, and C-4' methyl carbons, respectively. Conversely, secondary amide 9, which behaves as a single compound in solution, shows axial chirality in the solid phase, as judged from the splitting of both the C-2' and C-4' methyl carbon signals.


(21) Obtained as major (\( \sim 65\% \)) together with the corresponding enol tautomers (\( \sim 20\% \)) and the anti keto tautomers (\( \sim 15\% \)).

room temperature an anti — syn rotamerization occurred as indicated by the disappearance within a few hours of the NMR signals attributed to 1c and 1d. Ultimately a 1:1 mixture occurred as

**Methyl (3'S)-syn-(2',4'-Dimethylphenylalaninyl)-N-methyl-L-phenylalaninate (1a).** The mixture of 1a,b (810 mg, 2.48 mmol, vide supra) was dissolved in boiling diethyl ether (>15 mL) and then allowed to crystallize at 0°C. Transparent needles (210 mg, 27%, 1a:1b = 1:10) were isolated. The concentrated mother liquor (1a:1b ~ 1.2) was taken up in diisopropyl ether (15 mL) and heated under reflux for 30 min. Upon cooling solid material precipitated (141 mg, 17% 1a:1b = 9:1). After filtration, the remaining solution was repeatedly subjected to the same procedure with gradually diminishing quantities of diisopropyl ether (12, 9, and 6 mL) to afford more solid material enriched in 1a (254 mg, 31%, 1a:1b = 9:1). A final recrystallization of the combined precipitates (614 mg, 76%) from diethyl ether gave analytically pure 1a (366 mg, 45%, 1a:1b ≥ 99): mp 132–133°C. 

$$\Delta (265 \text{ nm, MeOH}) = -3.34. [\alpha]_D^{22} = -84^\circ \text{ (c 1, CHCl}_3).$$

**1H NMR (CDCl)_3, Tables 1–III and foregoing modus; (C6D_6) (Table III), 8 22.1 (3-Me), 22.2 (C-2'), 33.5 (NMe syn), 37.6 (NMe anti), 123.4 (C-5), 133.5 (C-3), 143.7 (C-4), 149.4 (C-6), 154.25 (C-2), 169.7 (CO). Anal. Calcd for C_{26}H_{31}NO_3 (MW 393.51): C, 69.9; H, 6.8; N, 8.4.

**2a** (2',4'-Dimethylnicotinoyl)-N-methyl-Dphee (2a).

A stirred solution of methyl-L-phenylalaninate (309 mg, 1.50 mmol) in dichloromethane (10 mL) was cooled in an ice bath and consecutively treated with triethylamine (0.64 mL, 455 mg, 4.50 mmol) and acid chloride = 30 mL, -300 mmol), the aqueous phase was extracted with dichloromethane (4 × 40 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to leave a brown oily residue. The latter was extracted with boiling hexane to afford—after concentration—pure, slightly yellow 7 (2.59 g, 55%).

**N,N-Diisopropyl-2,4-dimethylphenylalaninamide (6).** To a stirred, cooled (~20°C) solution of acid chloride 3 (4.12 g, 20 mmol) in dichloromethane (16 mL) were consecutively added solutions of triethylamine (0.45 g, 4.04 g, 40 mmol) in dichloromethane (8 mL) and of isopropanol (2.36 g, 40 mmol) in dichloromethane (8 mL). Then, the reaction was continued at room temperature for 2 h. Evaporation of the reaction mixture under reduced pressure and column chromatography of the residue (CH_2Cl_2-MeOH, 95:5, R_f = 0.16) gave a viscous oil, which solidified on standing (3.50 g, 91%). Analytically pure 8 was obtained by recrystallization from diethyl ether (50%, 99%).

**Methyl syn-(2',4'-Dimethylphenylalaninyl)-L-phenylalaninate (9).** A cooled (0°C) suspension of methyl L-phenylalaninate hydrochloride (1.08 g, 5.0 mmol) and diisopropylamine (30 mL) was brought to dissolution by adding ethylamine (2.14 mL, 151 g, 15 mmol). Subsequently solid acid chloride 3 (1.03 g, 5.0 mmol) was introduced portionwise (15 min) under stirring. The reaction was then continued at room temperature for 1.5 h. The resultant mixture was evaporated to dryness and the residue thoroughly extracted with diethyl ether.
Among commercially available resolved compounds having the bicyclo[3.1.1] framework, (+)- or (-)-α-pinene (1a, X = H) has been of exceptional importance in syntheses of chiral compounds. Its hydroboration product, diisopinocampheylborane, has been developed by Brown’s group as a crystalline, readily prepared reagent, which hydroborates some cis-alkenes with high enantiomeric excess.2 Boronate esters of pinanediol, obtained from hydroborates some cis-alkenes with high enantiomeric excess.3 Among commercially available resolved compounds having the bicyclo[3.1.1] framework, (+)- or (-)-α-pinene (1a, X = H) has been of exceptional importance in the synthesis of chiral compounds. Its hydroboration product, diisopinocampheylborane, has been developed by Brown’s group as a crystalline, readily prepared reagent, which hydroborates some cis-alkenes with high enantiomeric excess.2 Boronate esters of pinanediol, obtained from hydroborates some cis-alkenes with high enantiomeric excess.3

Preparation of Chiral Inducers Having the Bicyclo[3.1.1]heptane Framework. Assignment of Diastereomer Configuration by NMR and Comparison of Calculated and Observed Coupling Constants

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Received December 28, 1989

Several bicyclo[3.1.1] compounds have been prepared for possible uses in asymmetric synthesis, including 10-phenyl-α-pinene and the diastereomeric (1S,2S,5S)-10-phenylmyrtenols. The geometry and NMR properties of bicyclo[3.1.1] compounds have been investigated by using molecular mechanics and NMR coupling constants.

Among commercially available resolved compounds having the bicyclo[3.1.1] framework, (+)- or (-)-α-pinene (1a, X = H) has been of exceptional importance in syntheses of chiral compounds. Its hydroboration product, diisopinocampheylborane, has been developed by Brown’s group as a crystalline, readily prepared reagent, which hydroborates some cis-alkenes with high enantiomeric excess.2 Boronate esters of pinanediol, obtained from hydroborates some cis-alkenes with high enantiomeric excess.3 Among commercially available resolved compounds having the bicyclo[3.1.1] framework, (+)- or (-)-α-pinene (1a, X = H) has been of exceptional importance in syntheses of chiral compounds. Its hydroboration product, diisopinocampheylborane, has been developed by Brown’s group as a crystalline, readily prepared reagent, which hydroborates some cis-alkenes with high enantiomeric excess.2 Boronate esters of pinanediol, obtained from hydroborates some cis-alkenes with high enantiomeric excess.3 Among commercially available resolved compounds having the bicyclo[3.1.1] framework, (+)- or (-)-α-pinene (1a, X = H) has been of exceptional importance in syntheses of chiral compounds. Its hydroboration product, diisopinocampheylborane, has been developed by Brown’s group as a crystalline, readily prepared reagent, which hydroborates some cis-alkenes with high enantiomeric excess.2 Boronate esters of pinanediol, obtained from hydroborates some cis-alkenes with high enantiomeric excess.3