Conformational Studies on 1,2-Di- and 1,2,3-Trisubstituted Heterocycles. A Spectroscopic and Theoretical Study of 3-Acylaminopicolinic Acid Derivatives and Their *N*-Oxides

Ivoneide de C. L. Barros,[†] Claudia C. C. Bejan,[‡] João Bosco P. da Silva,*[,‡] F. W. Joachim Demnitz,*[,‡] Fernando Hallwass,[‡] and Hans-Ulrich Gremlich[§]

Departamento de Química Fundamental, Universidade Federal de Pernambuco, Cidade Universitária, 50.670-901 Recife-PE, Brazil, Departamento de Química, Universidade Federal do Amazonas, Manaus-AM, Brazil, and Novartis Pharma AG, WSJ-503.1001, Lichtstrasse, CH-4002 Basel, Switzerland

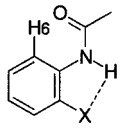
jdemnitz@npd.ufpe.br

Received June 30, 2000

Theoretical studies involving minimization of model 3-propanoylaminopicolinic acids (**10d-*trans***, **10d-*cis***), methyl ester (**10a**), and corresponding -*N*-oxide derivatives (**10b**, **10c-*trans***, **10c-*cis***) using AM1 gave conformations contrary to both sound chemical intuition and experimental data. RHF ab initio calculations using the 6-31G and 6-31G** basis sets on the other hand corroborated spectroscopic data. 3-Amidopicolinic acid derivatives (**7a**−**9a**, **7b**−**9b**, **7c**−**9c**, **9d**) were prepared and studied by NMR and IR spectroscopy. The results show that a strong intramolecular hydrogen bond between amide-H and the 2-carboxyl substituent results in a planar molecular conformation. This is particularly profound in the 3-acylaminopicolinic acid *N*-oxides (**c**-series). When the 2-substituent is a methyl ester on the other hand, repulsion between *N*-oxide and ester functions induces twisting of the carbomethoxy group out of the plane of the aromatic ring. The type of method used in molecular modeling can have profound impact on the final theoretical result in the case of the above-mentioned class of compounds. Our results indicate, that it is advisable to employ ab initio methods for modeling these types of compounds, and further, that the choice of basis set used for such calculations should depend on the type of information required. Thus, for most purposes pertaining to molecular conformation the 6-31G basis set provides sufficiently sound data in relatively short CPU time. For data related to electronic properties such as involvement of the *N*-oxide function or spectroscopic information such as IR frequencies or ^{1}H or ^{15}N NMR chemical shifts, the use of polarization functions as contained in the 6-31G** basis set seems to be a must.

Introduction

The conformation of ortho-disubstituted aromatics is greatly influenced by the mutual interaction between the substituents in question.[1,2h] In particular, hydrogen bonding may induce the molecule to assume a conformation different from that which purely steric considerations would otherwise dictate. Secondary aromatic amides with hydrogen bond acceptors disposed in a 1,2-fashion have been extensively studied, especially by NMR[2] and IR.[4] For example, the large downfield "acetylation shifts" observed for H6 in acetanilides carrying hydrogen bond acceptors in the 2-position have been attributed to conformation **1**.[2c,3] In this conformation, a hydrogen bond between amide-H and the C2 substituent forces the amide carbonyl into a position able to deshield H6, and the molecule assumes a planar conformation. In fact, the magnitude of the downfield "acetylation shift" of H6 in 2-substituted acetanilides (**1**) after acetylation of the respective aniline precursor has been deemed sufficiently reliable so as to be used as a diagnostic tool to estimate the extent of coplanarity in such molecules.[2c,d]



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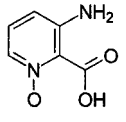

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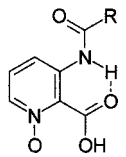

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We have recently become involved in an endeavor to synthesize *N*-oxide derivatives of 3-aminopicolinic acid (**2**) as new bidentate ligands for lanthanide ions. Such ligands coordinating through the *N*-O and carboxyl functions act as antennas[5] in light conversion devices.[5,6,7] The amino group serves as a point of attachment for the introduction of appropriate substituents with a view to modifying the physicochemical and/or electronic characteristics of the respective lanthanide complexes. With

* To whom correspondence should be addressed. Fax: +55 81 3271 8442. E-mail: (J.B.P.d.S.) paraiso@npd.ufpe.br.
[†] Universidade Federal do Amazonas.
[‡] Universidade Federal de Pernambuco.
[§] Novartis Pharma AG.

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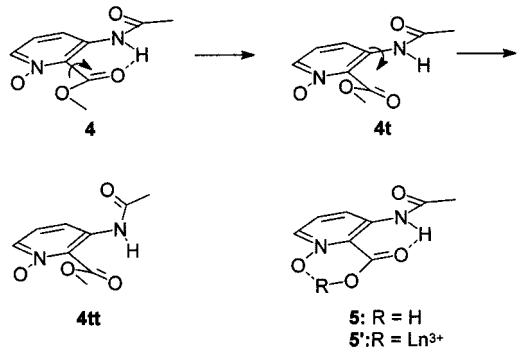
10.1021/jo000993j CCC: $22.00
Published on Web 12/29/2001

regard to the former, long-chain hydrocarbon substituents would improve the solubility[8] of such species, while in the case of the latter property, one may envisage Schiff-base or amide derivatives with the proviso, that these be coplanar with the pyridine ring in order to be able to manipulate excited state (π^*) energy levels in the ligands by variation of the substituent on nitrogen. The fulfillment of this condition can be guaranteed by the presence of an NH···*o*-COOR hydrogen bond constraining the amide in the plane of the aromatic ring (**3**), since there is no reason to believe that 3-*N*-acylaminopicolinic acids and esters will succumb to different conformational dictates as the abovementioned ortho-substituted acetanilides (**1**). Furthermore, the pyridine nitrogen introduces an additional bias not present in the acetanilides, inasmuch as the C═O dipole lies preferably anti to the pyridine nitrogen (as shown in **2** and **3**), thereby well disposed to hydrogen bond the neighboring amide proton.[9]

Thus, conformational predictions for 3-aminopicolinic acid derivatives were expected to be straightforward. We anticipated however, that the introduction of an *N*-oxide moiety producing a 1,2,3-trisubstituted aromatic system would result in additional interactions, which might perturb molecular geometry. With a methyl ester derivative in the preferred *s-cis* conformation, mutual repulsion of the alkyl-oxygen and pyridine-*N*-oxygen would oppose the stabilizing influence of the intramolecular hydrogen bond and ought to induce rotation about the C2−COOMe bond in order to relieve this steric interaction, (**4**), with concomitant departure of the 2-carbomethoxy-3-acylamino system from planarity giving a "twisted" conformation (**4t** or **4tt**). In a 2-carboxy unit on the other hand an s-trans configuration would permit an intramolecular H-bond between the acid proton and *N*-oxide,[10] a situation once again conducive to an overall planar shape for the molecule (**5**). Bidentate complexation of such a molecule through N^+-O^- and COO^- to a lanthanide metal cation (Ln^{3+}) would similarly be expected to result in an overall planar ligand geometry (**5′**).

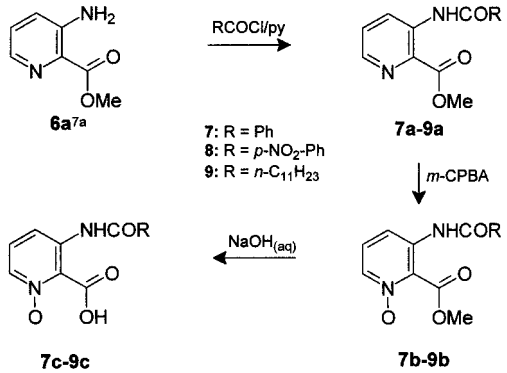


We have examined a series of substrates including both the parent 3-amino- and some 3-acylaminopicolinic esters and acids as well as the respective *N*-oxides and europium(III) complexes thereof by NMR and IR spectroscopy in order to gain insight into their conformational behavior. Furthermore, to underpin our experimental analysis, we have compared our interpretations with predictions gained from molecular modeling studies.

Spectroscopic Results

To be able to synthesize lipophilic luminescent lanthanide complexes, we prepared a series of aryl- and long-chain alkyl amide derivatives of picolinic acid-*N*-oxide to serve as appropriate ligands. The ligands (*N*-oxide acids (**c**-series)), intermediates (esters (**a**-series), *N*-oxides (**b**-series)) and complexes under study here were synthesized in standard fashion from methyl 3-aminopicolinate (**6a**),[7a] (Scheme 1). Surprisingly, of the various methods tried for N-oxidation (CH_3CO_3H, CF_3CO_3H, MMPP, *m*-CPBA) only the latter provided the *N*-oxides.[7b] The tris-Eu(III) complexes (**Eu(7c)$_3$**) and (**Eu(9c)$_3$**) of the respective *N*-oxide acids were prepared in refluxing EtOH in the presence of 0.33 equiv of $Eu(ClO_4)_3$ and 1 equiv of base[7b,c]

Scheme 1



The ^{1}H NMR chemical shifts of 3-aminopicolinic acid derivatives are depicted in Table 1. The very large downfield shifts of 2.12−2.32 ppm observed for H4 upon acylation of **6a** to **7a**−**9a** (column 4) are clearly a result of the neighboring amide C═O anisotropy and corroborate earlier results[2,3] obtained with ortho-substituted acetanilides. The lesser effects upon protons H5 and H6 when going from **6a** to **7a-9a** (columns 5 and 6) are almost certainly through-bond effects.[2b] The large chemical shifts of the amide NH protons (column 7, cf. *o*-carbomethoxy-

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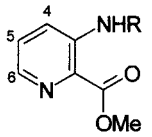
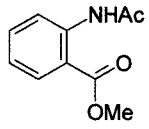
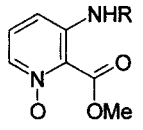
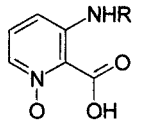
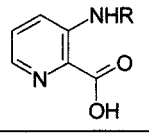
(8) The parent complex tris(3-aminopyridine-2-carboxylato)-diaquaeuropium(III)[7a] is difficult to purify and handle and, therefore, has limited utility due to its extremely low solubility in all common solvents.

(9) Gandolfo, C.; Favini, G. *Gazz. Chim. Ital.* **1970**, *100*, 534. Gandolfo, C.; Bueni, G.; Favini, G. *Gazz. Chim. Ital.* **1972**, *102*, 946.

(10) Dega-Szafran, Z.; Grundwald-Wyspianska, M.; Szafran, M. *J. Mol. Struct.* **1992**, *275*, 159.

Table 1. Experimental ^{1}H and Amide ^{15}N NMR Chemical Shifts of 3-Aminopicolinic Acid Derivatives (Series 6−9) in $CDCl_3$ and Corresponding Calculated Chemical Shifts for Model 3-Propanoylaminopicolinic Acid Derivatives (10 Series) Using ab Initio 6-31G and 6-31G Levels of Theory[f]**

		R	δ-H4	δ-H5	δ-H6	δ-NH	δ-OH	δ-N[e]
	**6a**[a]	H	7.03	7.21	8.06	5.75		
	7a	COPh	9.35	7.57	8.47	11.98		-266.28
	8a	CO-*p*-NO_2-Ph	9.30	7.60	8.52	12.20		
	9a	CO-*n*-$C_{11}H_{23}$	9.15	7.49	8.41	10.98		nd
	(10a)	CO-Et (6-31G**)	9.80	7.65	8.61	10.03		-324.18 (22%)[f]
		CO-Et (6-31G)	10.35	8.16	9.37	10.25		-431.90 (62%)[f]
	[b]		8.36[c]	7.67[c]	7.25[c]	10.65[c] 10.49[d]		
	**6b**[a]	H	6.63	6.99	7.65	5.00		
	7b	COPh	8.55	7.35	8.05	9.82		-269.40
	8b	CO-*p*-NO_2-Ph	8.55	7.38	8.12	10.24		
	9b	CO-*n*-$C_{11}H_{23}$	8.36	7.25	7.92	8.83		-264.53
	(10b)	CO-Et (6-31G**)	8.70	7.49	8.52	7.14		-328.59 (24%)[f]
		CO-Et (6-31G)	9.65	7.91	9.49	7.08		-438.48 (66%)[f]
	**6c**[a,b]	H	7.24	7.43	7.92	7.69	18.70	
	7c	COPh	9.48	7.68	8.16	13.35	20.16	-263.89
	8c	CO-*p*-NO_2-Ph	9.44	7.68	8.22	13.62		
	9c	CO-*n*-$C_{11}H_{23}$	9.28	7.55	8.10	12.34	19.98	-258.70
	(10c)	CO-Et (6-31G**)	9.85	7.67	8.65	11.11	16.27	-321.68 (24%)[f]
		CO-Et (6-31G)	10.72	8.10	9.60	10.98	14.94	-431.16 (67%)[f]
	**9d**	CO-*n*-$C_{11}H_{23}$	9.27	7.60	8.31	11.13		-259.65
	(10d)	CO-Et (6-31G**)	9.94	7.74	8.49	10.01	9.91	-324.17 (25%)[f]
		CO-Et (6-31G)	10.49	8.22	9.11	10.00	9.96	-432.68 (67%)[f]

[a] Reference 7a. [b] Spectrum in DMSO-d_6. [c] Reference 2h. [d] Reference 2f. [e] $\delta(CH_3NO_2) = 0$. [f] For ^{15}N chemical shifts, the percent deviation of the calculated from the experimental value for the corresponding alkylamide nitrogen (**9** series) is given in parentheses (except for **10a**[g]). [g] Deviation from **7a**.

acetanilide[2f,h]) imply that they are involved in hydrogen bonding. To establish additional evidence for the intramolecular nature of this hydrogen bond to the ester carbonyl, the NMR spectra of the amides (**7a**−**9a**, **7c**−**9c**, and **9d**) were determined in high dilution. As expected, the positions of the amide-H resonances suffered no alteration. The particularly large downfield resonances of the carboxylic acid protons in **7c** and **9c** (column 8) are an indication that, as anticipated, these protons are hydrogen bonded by the *N*-oxide function.

It can be argued, that oxidation of the pyridines (**6a**−**9a**) will result in mutual repulsion of the *N*-oxygen and ester alkyl-oxygen atoms in the *N*-oxide products (**6b**−**9b**). The ensuing rotation of the carbomethoxy group out of the plane (**4** → **4t**) would weaken the hydrogen bond to the amide-NH. The large upfield shifts (1.96−2.16 ppm) of the amide protons in *N*-oxides (**7b**−**9b**) as compared to (**7a**−**9a**) support this rationale. Furthermore, it is interesting to note, that in all cases the H4 aromatic protons also suffer an appreciable upfield shift upon passing from the **a**- to the **b**-series implying a concomitant change in the C=O anisotropy (column 4). Taking pyridine as a model, it is established, that *N*-oxidation results in an upfield shift of 0.29 and 0.23 ppm for the H4 and H2/6 protons respectively, while the H3/5 protons in the meta positions remain relatively unaffected.[11] A comparison with methyl 3-dodecanoylaminopicolinate (**9a**) and its *N*-oxide (**9b**) is instructive; (Figure 1).

The H5 (−0.24 ppm vs +0.08 ppm) and H6 protons (−0.49 vs. −0.23 ppm) of **9a** suffer only moderately greater upfield shifts upon *N*-oxidation than is the case in pyridine. However, H4 is considerably more affected after *N*-oxidation with an upfield shift of 0.79 ppm as compared to only 0.29 ppm in pyridine. Assuming that *N*-oxidation contributes approximately 0.30 ppm to the upfield shift of the H4 proton we conclude, that the additional effect of 0.49 ppm upon H4 comes from *reduced deshielding of this proton* by the amide carbonyl in the

(11) Hesse, M.; Meier, H.; Zeeh, B. *Spektroskopische Methoden in der organischen Chemie;* Georg Thieme Verlag: Stuttgart, 5. Aufl., 1995; p 191.

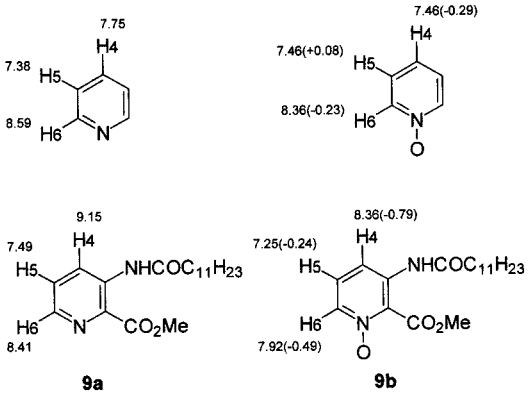


Figure 1. Comparison of ^{1}H NMR chemical shifts of pyridine and methyl 3-dodecanoylaminopicolinate (**9a**) as well as their respective *N*-oxides. Relative upfield (−) and downfield (+) shifts in *N*-oxides are given in parentheses.

N-oxide derivative (**9b**) as compared to **9a**. Indeed, it has been estimated, that anisotropic deshielding of ortho protons by a coplanar amide group in simple acetanilides does in fact contribute about +0.5 ppm to their chemical shift.[2b] One may rationalize, that the effect of N−O ↔ MeOOC repulsion is "translated" around the periphery of the molecule, resulting in twisting of both C2−CO_2-Me and C3-amide bonds. Such a rotation removes the amide carbonyl deshielding cone from proximity to H4 and diminishes its through-space effect on this proton (see **4tt** and structure **10b** in Figure 2). On the other hand, H4 in the free amine (**6a**), devoid of the anisotropic C═O group, is, upon *N*-oxidation, deshielded by only 0.40 ppm a value only half that of the acylated series and close to that for pyridine itself. Our modeling studies support this hypothesis (vide infra).

^{15}N NMR spectra were obtained in deuteriochloroform solution with an INEPT pulse sequence. Chemical shifts are quoted relative to nitromethane. The influence of hydrogen bonding upon the ^{15}N chemical shift is best seen by comparing the **b**- and **c**-series. As expected, NH····· O═COR hydrogen bonding shifts the ^{15}N resonance to lower field (column 9; **7b**/**9b** vs **7c**/**9c**). The *N*-oxide oxygen has little effect on the amide-*N* chemical shift, as shown by comparing **9c** and **9d**. Attempts to further investigate the hydrogen bonding phenomena in this class of compounds by ^{17}O NMR spectroscopy proved fruitless. No signals could be observed using a variety of sequences (single pulse, RIDE) and acquisition conditions. Thus, both in $CDCl_3$ and CD_3CN at room temperature and 70 °C only the D_2O peak was observed.

Finally, it was not possible to determine the structure of the europium complexes (**Eu(7c)$_3$**) and (**Eu(9c)$_3$**) by NMR spectroscopy. The former was virtually insoluble in all common solvents, while the ^{1}H NMR spectrum of **Eu(9c)$_3$** was largely perturbed, displaying only a prominent methylene envelope along with a series of very small humps spread over the entire spectral region.[12]

The COO−H cis configuration in carboxylic acids is favored by approximately 3 kcal mol^{-1} over the trans form.[13] However, it has been estimated that the enthalpy of H-bond formation in *o*-alkoxybenzoic acids (leading to a trans COO−H configuration) is about 3.3 kcal mol^{-1}.[14] We would expect the picolinic acid *N*-oxides (**7c**−**9c**), were they in an s-cis configuration (vide infra), to be in an overall conformation similar to that of the methyl esters (**7b**−**9b**), i.e., a "twisted carboxyl"-conformation similar to **4tt**. The presence of the *N*-oxide, however, provides a stabilizing hydrogen bond acceptor for the acidic proton. Consequently, a trans conformation such as depicted in **5** is possible and should "restore" the planarity lost in the ester (**b**) series. An inspection of the chemical shifts of both amide and aromatic H4 protons (Table 1) in acids **7c**−**9c** reveals that the deshielding "lost" in going from a pyridine (**a**-series) to an *N*-oxide (**b**-series) is, more than, restored by ester hydrolysis (**c**-series). The amide protons now resonate strongly downfield (> 12 ppm) and the chemical shifts of the H4 protons are very close to what they were in the pyridines (**7a**−**9a**). Possibly the reason the chemical shifts for H4 in *N*-oxide-acids (**7c**−**9c**) *are consistently larger by about 0.14 ppm* than in the corresponding pyridines (**7a**−**9a**) lies in the fact that the effect due to deshielding by the neighboring amide carbonyl is slightly potentiated in the **c**-series by a reduction of the *N*-oxide +M effect in view of this oxygen being compromised in a hydrogen bond.

The IR frequencies of the amide N−H, *N*-oxide as well as amide-I and carbonyl C═O stretching modes for benzoyl (**7a**−**c**) and dodecanoyl (**9a**−**c**) derivatives as well as for the complexes (**Eu(7c)$_3$**) and (**Eu(9c)$_3$**) are shown in Table 2 together with the respective theoretical values obtained from ab initio calculations using the 6-31G** basis set. For comparison, pertinent stretching frequencies for published spectra of methyl 2-acetamidobenzoate,[4] *N*-phenylacetamide[4] and methyl benzoate are included. The results corroborate our conclusions based upon NMR investigations. The positions of the N−H bands clearly imply H-bonding and in all cases the intramolecular nature of this amide-to-ester carbonyl hydrogen bond (O═CN−H·····O═C(OR)) was substantiated by solution-IR. The N−H stretching frequencies in dichloromethane solution were unaltered by dilution, and compare very well to the respective value in methyl 2-acetamidobenzoate[4] as do the amide-I and ester carbonyl stretches in **7a** and **9a**.

Our proposal, that the *N*-oxide esters have a "twisted-COOMe" conformation (**4tt**) implies a weaker H-bond in the **b**-series. Insights into the relative strengths of the hydrogen bond were gained from the respective peak frequencies. Thus in both the benzoyl- (**7**) and dodecanoyl- (**9**) amides a weakening of the H-bond in going from the **a**- to the **b**-series was observed in dichloromethane solution, (**7a**: $\nu_{max(N-H)}$ 3311 → **7b**: $\nu_{max(N-H)}$ 3398 cm^{-1} and **9a**: $\nu_{max(N-H)}$ 3318 → **9b**: $\nu_{max(N-H)}$ 3401 cm^{-1}) as would be expected as a result of rotation about the pyridine(C2)-carbomethoxyl bond and concomitant

(12) These complexes were prepared according to the procedure given in ref 7a. All attempts to obtain single crystals suitable for X-ray structure determination proved fruitless in the case of these compounds. **Eu(7c)$_3$** could not be dissolved in any suitable solvent, and those small quantities of material separating from large volumes of very dilute methanol solutions were irregular and microcrystalline at best. **Eu(9c)$_3$**, on the other hand, provided an amorphous solid from several different solvents. A more detailed discussion of these compounds and their characteristics is being submitted elsewhere. The limited solubility of similar types of europium complexes is well documented. Typically they are obtained as powders. See ref 7a as well as: de Sá, G. F.; Barros Neto, B. d. B.; Ferreira, R. *Inorg. Chim. Acta* **1977**, *23*, 249. de Sá, G. F.; Nunes, L. H. A.; Wang, Z.-M.; Choppin, G. R. *J. Alloys Compd.* **1993**, *196*, 17. Boyd, S. A.; Kohrman, R. E.; West, D. X. *Inorg. Nucl. Chem. Lett.* **1976**, *12*, 603.

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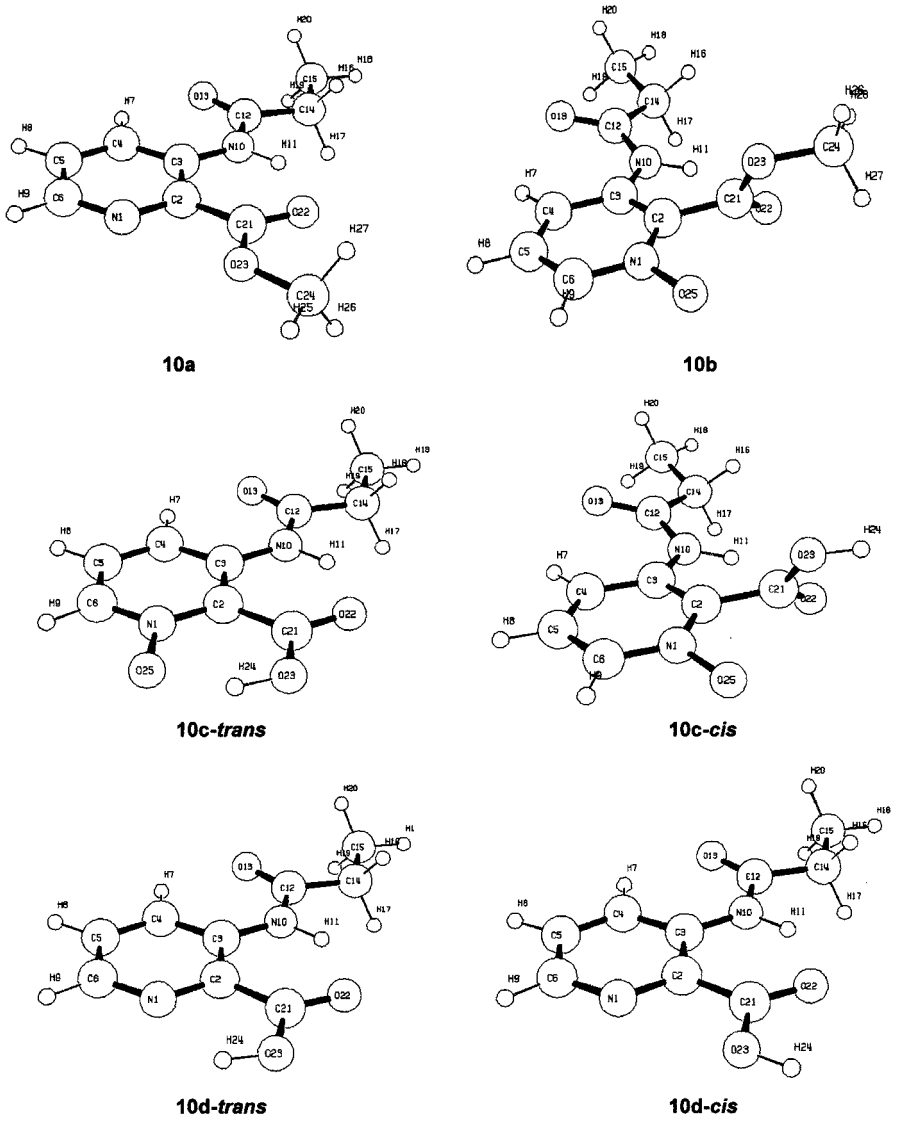

Figure 2. Minimized conformations for selected 3-propanoylaminopicolinic acid derivatives using ab initio calculation in the RHF/6-31G basis set. Gaussian numbering.

increase of the amide(H)-to-carboxyl(O) distance in the *N*-oxides (**7b**/**9b**). *Complete loss* of intramolecular amide-(H)-to-ester(O) hydrogen bonding would result in a slightly greater shift to higher frequency as shown by the N−H stretches of methyl 2-acetamidobenzoate and *N*-phenylacetamide[4] ($\Delta\nu_{max(N-H)}$ = 121 cm^{-1};[4] Table 2, column 4). The loss in H-bonding incurred between the **a**- and **b**-series is regained in the planar *N*-oxide carboxylic acids (**c**-series), which display a particularly strong hydrogen bond as shown by the low values for the N−H stretch; (**7c**: $\nu_{max(N-H)}$ 3114 cm^{-1}, **9c**: $\nu_{max(N-H)}$ 3161 cm^{-1}). This observation lends additional support to the already mentioned very low field chemical shift of the amide protons observed in these compounds, lower still than in the similarly intramolecularly H-bonded precursors **7a** and **9a**; (Table 1; compare also the calculated H11O22 distances for **10a** and **10c-*trans*** in Table 4: entry 33). A peculiar exception to this general trend is observed in the KBr solid state IR spectra. In this case, the surprisingly low amide N−H stretching frequency in the *N*-oxides **7b** and **9b** (column 5) imply (contrary to expectations) the presence of a strong hydrogen bond. We attribute this to the presence of dimers[4,15] in the KBr matrix. Evidently, as the carbomethoxyl moiety rotates from planarity in the **b**-series, the thus "liberated" amide function is able to participate in intermolecular amide association. The corresponding ester carbonyl stretching vibrations in this case therefore suffer shifts to higher wavenumbers (column 9) in accordance with this groups' departure from involvement in a hydrogen bond to the neighboring amide. Thus in all cases an increase in the ester C═O stretching frequency in KBr upon going from pyridine (**a**) to *N*-oxide (**b**) implies the absence of an intramolecular hydrogen bond in the latter species.

In fact, the IR spectra of the *N*-oxide esters **7b**/**9b** are particularly intriguing. While a comparison of the characteristic functional group frequencies for the **a**- and **c**-series reveals very good agreement between KBr and solution spectra, this is not so in the case of the intermediate esters **7b**/**9b**. Apart from the abovementioned discrepancy in the N−H stretches, the ester C═O stretching frequencies differed substantially depending

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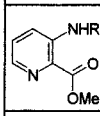
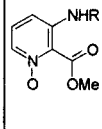
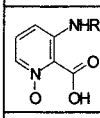
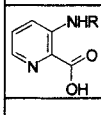
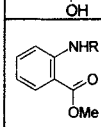
Table 2. Selected Peak Frequencies of IR Spectra of 3-Aminopicolinic Acid Derivatives (7a−c, 9a−d) in KBr Matrix and 0.5% CH_2Cl_2 Solution and of Europium(III) Complexes ($Eu(7c)_3$, $Eu(9c)_3$) in KBr[h]

		R	$\nu_{max(N-H)}$		$\nu_{max(NC=O)}$ *Amide-I*		$\nu_{max(C=O)}$ *Ester / Acid*		$\nu_{max(N-O)}$
			CH_2Cl_2	KBr	CH_2Cl_2	KBr	CH_2Cl_2	KBr	KBr[a]
	**7a**	COPh	3311(*m*)	3299(*m*)	1681(*s*)	1671(*s*)	1700(*s*)	1684(*s*)	
	9a	CO-*n*$C_{11}H_{23}$	3318(*m*)	3309(*m*)	1693(*s*)	1690(*s*)	1703(sh,*s*)	1710(*s*)	
	10a	CO-Et (6-31G**)	3822		1973		1944		
	**7b**	COPh	3398(w)	3168(m)	1693(br,s)	1673(s)	1693(br,s) 1754(sh)	1749(s)	1244(s)[b]
	9b	CO-*n*$C_{11}H_{23}$	3401(w)	3234(m)	1709(br,s)	1658(s)	1709(s) 1751(sh)	1744(s)	1253(s)[b]
	10b	CO-Et (6-31G**)	3855		1982		1975		1371
	**7c**	COPh	3114(w)[c]	3101(m)	1685(m)[c]	1652(m)	1685(m)[c]	1688(s)	1221(m)
	9c	CO-*n*$C_{11}H_{23}$	3161(w)	3109(m)	1667(m)	1675(m)	1706(m)	1701(s)	1274(s)
	10c	CO-Et (6-31G**)	3764		1980		1989		1310
	**9d**	CO-*n*$C_{11}H_{23}$	3307(w)	3109(w)	1700(m)	1658(s)	1741(s)	1694(s)	
	10d	CO-Et (6-31G**)	3804		1975		2010		
		COMe[d]	3325[e]		1687[e]		1700[e]		
N-phenyl-acetamide[d]			3446[f]		1688[e] 1706[f]				
methyl benzoate[g]							1709[e]		
pyridine-*N*-oxide		(6-31G**)							1368
	$Eu(7c)_3$			3113		1629		1710	1220
	$Eu(9c)_3$			3100		1648		1688	1218

[a] Assignment of N−O stretching frequencies in CH_2Cl_2 not possible. [b] Assignment tentative (see text). [c] Assignment tentative due to low solubility. [d] Reference 4. [e] Spectrum in $CHCl_3$. [f] Spectrum in CCl_4. [g] *Aldrich Library of IR Spectra*; Aldrich Chemical Co.: Milwaukee, WI. [h] Calculated ab initio 6-31G** values for model 3-propanoylaminopicolinic acid derivatives (**10a**−**d**) and experimental peak frequencies of pertinent reference compounds are given for comparison purposes. Values in cm^{-1}.

Table 3. Comparison of Selected Molecular Coordinates for Optimized AM1, RHF/6-31G, and RHF/6-31G Conformations of 3-Propanoylaminopicolinic Acid *N*-Oxides (10c-*trans* and 10c-*cis*)[a]**

		10c-*trans*			10c-*cis*		
entry	coordinate	AM1	6-31G	6-31G**	AM1	6-31G	6-31G**
8	C21O23	1.3535	1.3127 (+1.89)	1.2883	1.3568	1.3303 (+1.60)	1.3094
9	C21O22	1.2382	1.2213 (+1.94)	1.1981	1.2404	1.2171 (+1.99)	1.1933
22	C12O13	1.2406	1.2244 (+2.33)	1.1965	1.2407	1.2234 (+2.34)	1.1954
23	N1O25	1.2275	1.3828 (+6.16)	1.3026	1.2163	1.3561 (+6.81)	1.2696
31	C2C21O23	122.54	118.75 (+0.90)	117.85	115.71	113.97 (−0.05)	114.02
47	C21O23H24	113.15	113.65 (+4.43)	109.22	109.13	114.59 (+5.71)	108.88
54	N1C2C21O22	148.18	179.99 (+0.00)	179.99	145.48	128.15 (+0.55)	128.70
58	C4C3N10H11	−166.14	−180.00 (+0.04)	−179.96	−166.04	−158.38 (+0.54)	−157.84
70	H7O13	2.1254	2.0893 (−1.23)	2.1153	2.1393	2.2198 (−1.62)	2.2564
71	H11O22	2.0340	1.7881 (+0.02)	1.7877	2.0711	2.1371 (+1.12)	2.1135
72	H24O25	2.0211	1.5918 (+3.89)	1.5322			
73	O23O25				2.5941	2.8077 (+1.79)	2.7607

[a] Bond lengths in angstroms, angles in degrees. In parentheses: deviation of RHF/6-31G values from corresponding RHF/6-31G** values: in percent for bond lengths; in degrees for angles. Entry numbers correspond to the entries in the full Table S2 in the Supporting Information.

on the medium in which the spectra were run. While the KBr spectra for both compounds **7b**/**9b** revealed single strong absorptions in the expected regions (1749 and 1744 cm^{-1} respectively, column 9), the dichloromethane spectra (column 8) show broad strong bands in the carbonyl region (encompassing both amide-I and ester C═O), with a weak shoulder at about 1750 cm^{-1}, suggesting the presence of two different conformations. As before, one can rationalize these results in terms of the twisting about the C2-ester bond in these compounds. As already mentioned, in the solid-state intermolecular amide association results in a hydrogen bond-free ester twisted from coplanarity, with an appropriate high-frequency C═O stretching vibration (≈1750 cm^{-1}) as a

Table 4. Comparison of Selected Values for Optimized RHF/6-31G and AM1 Conformations of 3-Propanoylamino Picolinates[a]

		10a	10b	10c-*trans*	10c-*cis*	10d-*trans*	10d-*cis*
1	total energy	−718.869 352 2	−793.605 134 9	−754.617 711	−754.597 069 3	−679.869 828 4	−679.862 972
9	C2C21	1.4799	1.4866	1.5072	1.4841	1.4862	1.4745
		1.4879 (+0.54)	1.4797 (−0.46)	1.4880 (−1.27)	1.4761 (−0.54)	1.4907 (+0.30)	1.4850 (+0.71)
23	N1C2C21O23	−0.01	−59.86	0.00	−59.09	−0.01	−0.01
		−42.05 (+42.04)	−40.96 (−18.90)	−33.91 (+33.91)	−36.54 (−22.55)	−22.08 (+22.07)	−38.49 (+38.48)
24	C2C3N10H11	0.00	20.93	0.00	20.88	0.00	0.00
		15.57 (+15.57)	14.06 (−6.87)	13.36 (+13.36)	13.46 (−7.42)	11.27 (+11.27)	15.14 (+15.14)
26	C4C3N10C12	0.04	18.86	0.01	18.57	0.00	0.01
		16.26 (+16.22)	14.62 (−4.24)	13.69 (+13.69)	14.19 (−4.38)	13.04 (+13.04)	15.96 (+15.95)
32	H7O13	2.1393	2.2264	2.0893	2.2198	2.1479	2.1382
		2.1556 (+0.76)	2.1441 (−3.70)	2.1254 (+1.73)	2.1393 (−3.63)	2.1263 (−1.01)	2.1511 (+0.60)
33	H11O22	1.8565	2.1442	1.7881	2.1371	1.9032	1.8672
		2.1193 (+14.16)	2.0874 (−2.64)	2.0340 (+13.75)	2.0711 (−3.09)	2.0376 (+7.06)	2.1047 (+12.72)
34	O23O25		2.8129		2.8077		
			2.6378 (−6.22)		2.5941 (−7.61)		
35	H24O25			1.5918			
				2.0211 (+26.97)			

[a] Total energy in hartrees, Bond lengths in angstroms, dihedral angles in degrees. For each entry: first line: RHF/6-31G values. Second line: AM1 values. In parentheses: deviation of AM1 value from RHF/6-31G value in percent for bond lengths, in degrees for angles. Entry numbers correspond to the entries in the full Table S1 in the Supporting Information.

result of lower conjugation with the aromatic ring. In dichloromethane an equilibrium exists between the intermolecular "amide-association" and intramolecular "amide-to-ester H-bond" species with high frequency and low-frequency ester C═O stretching bands, respectively. This hypothesis was tested by measuring the IR spectrum of **9b** in CH_2Cl_2 solution at different concentrations. At concentrations of 0.5, 2 and 8%, the ratio of the peak intensities at 1751 and 1709 cm^{-1} were 0.25, 0.31 and 0.68 respectively, thereby corroborating our conclusion that at higher concentrations dimer formation is increased.

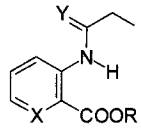
In the **c**-series there is once again very good agreement when comparing KBr spectra with those obtained in dichloromethane solution. We reason, that in **7c**/**9c** the *N*-oxide effectively "freezes" the acid function into a single orientation by means of an additional hydrogen bond. An equilibrium between two different conformations, which can only reasonably be rotamers about C2−COOH can be ruled out in this case, the entire molecule being effectively locked into place by two intramolecular hydrogen bonds on its' periphery (**5**). Thus a single conformation is observed irrespective of whether the IR-spectrum is run in KBr or dichloromethane. Similar agreement between solid state and solution spectra is noted for **7a**/**9a**, which is to be expected in view of the absence of the *N*-oxide function and presence of an intramolecular hydrogen bond.

Finally, the N−O stretch in the *N*-oxides (**7b**/**9b**) ought to be shifted to lower frequency upon ester saponification, as would be expected from the formation of a hydrogen bond to N−O in derivatives **7c** and **9c**. Unfortunately the preponderance of bands between 1200 and 1300 cm^{-1} precludes any unambiguous identification of the band in question.

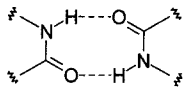
Complexation of the *N*-oxide acids (**7c**/**9c**) to Eu^{3+} occurs at the N^+-O^-/COO^- site,[7b,c] providing **Eu(7c)$_3$** and **Eu(9c)$_3$** respectively. That coplanarity of the pyridine and amide moieties was maintained in these complexes follows from the N−H stretching vibrations, which indicate strong hydrogen bonding comparable to that in the precursors (**7c**/**9c**) (Table 2). The complexes were highly luminescent, showing improved optical properties over their unsubstituted, free amine predecessors.[7,16] Molecular modeling using the *Sparkle* Program developed in this Department[17] furnished planar ligand geometries in all cases upon minimization.[16]

Molecular Modeling

A. Conformational Studies. Having thus interpreted our spectroscopic findings in terms of a convincing conformational rationale we proceeded to underpin our conclusions with an investigation of these molecules by molecular modeling. To this end we subjected a model series of 3-*N*-propanoylaminopicolinic acid derivatives (**10a**−**d**) as well as the propylamine (**11**) to a series of semiempirical and ab initio calculations at different levels of theory, performing an extensive conformational analysis to study energetic, geometric and electronic density aspects.



10a: X = N, R = Me, Y = O
10b: X = N-O, R = Me, Y = O
10c: X = N-O, R = H, Y = O
10d: X = N, R = H, Y = O
11: X = N-O, R = H, Y = H_2



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To guarantee the best compromise between the theoretical analysis of the molecules and our real computational availability, we decided to model the alkyl-amide series. Beyond that, we used 3-*N*-propanoylaminopicolinyl- as a prototype system for representing the 3-*N*-dodecanoylaminopicolinate series. For the semiempirical calculations the AM1 method implemented in the Mopac 6.0 package[18] was used, whereas the ab initio calculations at the Restricted Hartree−Fock (RHF) level using 6-31G and 6-31G** basis sets[19] were performed in the Gaussian

(16) Unpublished results; manuscript in preparation.

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(19) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.

94 program.[20] Both programs were run on Risc 6000 workstations in the Molecular Architecture Laboratory of the Universidade Federal de Pernambuco.

Intriguingly, the AM1 models provided some highly improbable structural results (see Table 4 and the Supporting Information) contrary not only to sound chemical intuition but, more importantly, to experimental data. Indeed, Perni et al.[21] recently disclosed that in a theoretical study of pyridine-*N*-oxide at 10 different theory levels, semiempirical calculations, including AM1, gave unsatisfactory bond lengths when compared to experimentally derived values, especially as regards the N−O bond. The best method found in those studies was the 6-31G** basis set. At this level of theory, the calculated N−O bond length in pyridine-*N*-oxide was 1.16% lower than the experimentally derived one, while 6-31G provided a value 6.01% higher. There was thus a discrepancy of 7.25% between the 6-31G** and 6-31G derived N−O bond length values. In view of those results, we ran the isomers (**10c-*trans***) and (**10c-*cis***) (Figure 2) through a series of different calculations. The semiempirical AM1 method was clearly unsatisfactory, but we found little overall difference between ab initio RHF results obtained using STO-3G, 3-21G, 6-31G or 6-31G** basis sets. The principal molecular geometrical parameters for AM1, 6-31G and 6-31G** pertinent to the discussion at hand are depicted in Table 3 (a full table is given in the Supporting Information). From an electronic point of view, similar qualitative agreement between **10c-*trans*** and **10c-*cis*** was also found for Mulliken atomic charges derived from 6-31G and 6-31G** basis sets.

In good agreement with Perni's results,[21] the N−O bond lengths in the two conformers studied were between 6 and 7% higher in the 6-31G as compared to the 6-31G** basis set (entry 23). This gives a slightly more open C21O23H24 bond angle in the carboxyl group of **10c-*trans*** as the longer N−O bond "pushes" the bound hydrogen outward, (6-31G: 113.65° vs 6-31G**: 109.22°, entry 47). Other differences in molecular coordinates between the two ab initio basis sets were generally less than 1% for bond lengths or less than 1° for angles in both conformers (see the Supporting Information), with the only exceptions being the polar C21O23 and C21O22 bonds in the carboxyl group and the amide carbonyl, C12O13 (6-31G bond lengths 1.60−2.34% higher, entries 8, 9, and 22, respectively). These discrepancies, although not as profound, are in accord with the trend observed by Perni[21] for the *N*-O function inasmuch as the 6-31G basis set, devoid of polarization functions, gives rise to an overestimation for the bond length in such (polar) cases. Satisfyingly, the values of the molecular coordinates most important to the main thrust of the discussions herein were essentially immune to which of the two basis sets was used to obtain them. As such, both the acid and the amide functions in **10c-*trans*** were predicted as being completely coplanar with the pyridine ring, with no difference between the calculated 6-31G and 6-31G** N1C2C21O22 (entry 54) and C4C3N10H11 (entry 58) dihedral angles. Furthermore, the H7O13, H11O22 and O23O25 nonbonding interatomic distances (entries 70, 71, and 73) predicted by the two basis sets also showed acceptable agreement. The difference in the H11O22 hydrogen bond length for **10c-*trans*** was only 0.0004 Å (0.02%) for these two calculations. Due to the discrepancy in the predicted N−O bond lengths as well as C2C21O23 (entry 31) and C21O23H24 (entry 47) bond angles, both of which are larger for 6-31G, there is a difference of almost 4% in the predicted H24O25 hydrogen bond lengths of **10c-*trans*** (entry 72). Significantly though, this result does not perturb the overall planar molecular conformation. In view of these results the 6-31G basis set was considered adequate for the conformational studies at hand, so that, to economize on computer time, other ab initio calculations can be carried out with this basis set only. It is quite clear on the other hand however, that AM1 results were inadequate (see, for example, entries 54, 58, 71, and 72). These are discussed at length in the Supporting Information.

In Figure 2, we show the optimized RHF/6-31G structures for all the 3-*N*-propanoylaminopicolinate derivatives modeled (**10**-series), while Table 4 depicts selected geometric parameters together with the total energies for the completely optimized structures at both ab initio and AM1 levels of theory. A comparison of AM1 and 6-31G derived values quickly shows considerable differences between the two. (A more thorough discussion of the differences between ab initio and AM1 results is given as Supporting Information.)

As can be seen, the conformational predictions gleaned from our spectroscopic results are corroborated by the optimized RHF/6-31G structures for the compounds shown in Figure 2. In particular, the starting pyridine ester (**10a**) as well as the *N*-oxide acid (**10c-*trans***) are completely planar as borne out by the N1C2C21O23 and C2C3N10H11 angles (entries 23 and 24). The H11O22 distances of 1.857 and 1.788 Å respectively (Entry 33), clearly indicate a strong intramolecular hydrogen bond in these substrates. Furthermore, the C4C3N10C12 zero dihedral angles (Entry 26) show that the amide carbonyl function is in the plane of the aromatic ring with the NC═O group strongly deshielding H7 (Gaussian numbering) (H7O13 = 2.139 (**10a**) and 2.089 Å (**10c-*trans***), entry 32), in agreement with the ^{1}H NMR chemical shifts in Table 1 for **9a** and **9c**. Our spectral data discussed above indicate that the *N*-oxide esters (**b**-series) have significantly weaker intramolecular hydrogen bonds than the **a**- and **c**-series. As can be seen from the optimized conformation of the **9b**-model (the propanoylamino analogue (**10b**) having the methyl ester in a preferred *s-cis* conformation), the introduction of an *N*-oxide group obliges the central carbomethoxyl to rotate from coplanarity. We rationalize this observation as a result of repulsion between the oxygen atoms O23 and O25. In the optimized conformation the C2C21 bond (entry 9) is slightly longer in **10b** than in **10a** (1.487 vs 1.480 Å) reflecting a reduction in bond order as the carbomethoxyl group is twisted by as much as −60 degrees (N1C2C21-O23, entry 23) from the aromatic plane. O23 and O25 are thus 2.813 Å apart (entry 34). That this is so, and that for example the methyl group in the ester has no bearing upon this torsion was underlined by performing the ab initio calculation on a hypothetical analogue with

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(21) Perni, R. B.; Kowalczyk, P. J.; Treasurywala, A. M.; Tracy, M *Tetrahedron Lett.* **1995**, *36*, 699.

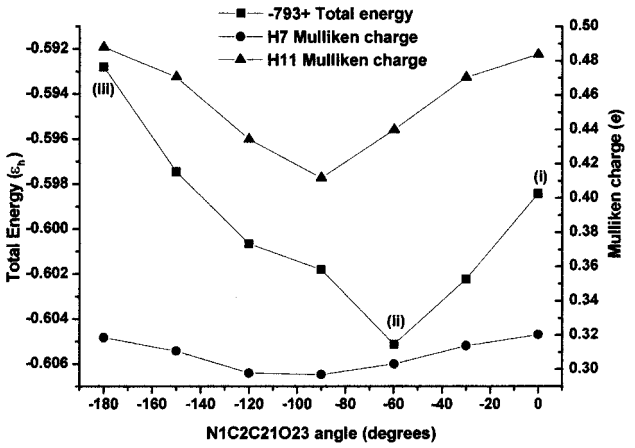


Figure 3. Variation of total energy and H7- and H11 Mulliken charges as a function of N1C2C21O23 dihedral angle for *N*-oxide ester **10b**.

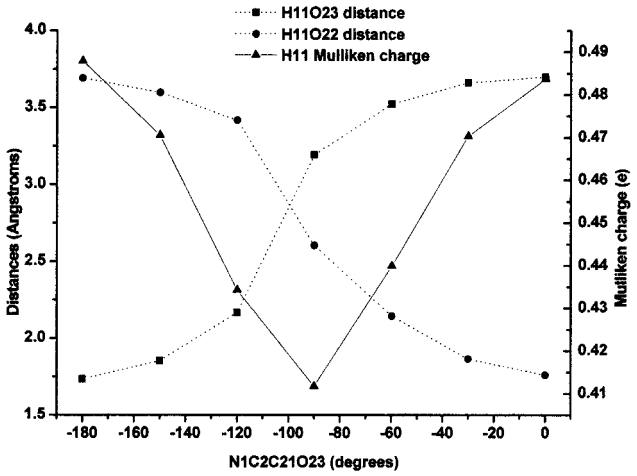


Figure 4. Variation of H11-Mulliken charge, H11O22 and H11O23 interatomic distances as a function of N1C2C21O23 dihedral angle for *N*-oxide ester **10b**.

the acid constrained in the *s-cis* conformation (**10c-*cis***). In this case, the central carboxyl group twists from coplanarity by the same amount (−59.09°, entry 23; O23O25 = 2.808 Å, entry 34) as in the *s-cis* ester (**10b**). The twisting of the carbomethoxyl group in **10b** necessarily increases the H11O22 distance resulting in a significantly weakened hydrogen bond (2.144 Å) as compared to **10a** (1.857 Å, entry 33). This is corroborated by the infrared N−H stretching frequencies for the corresponding dodecanoylamides **9a** and **9b** ($\nu_{max(N-H)}$ 3318 and 3401 cm^{-1} respectively) as well as by the amide proton NMR chemical shifts ($\delta_{(N-H)}$ 10.98 and 8.83 ppm respectively), the NH in the former substrate being significantly less shielded.

In a simulated full rotation of the carbomethoxyl group in **10b** about C2C21 we have investigated the change in total energy as well as the electronic Mulliken charges on the para and amide protons, H7 and H11 respectively, as functions of dihedral angle. To this end the molecule was optimized for a series of fixed dihedral angle conformations at 30° intervals around the C2C21 bond. The results are depicted in Figure 3.

Starting from a planar situation (i), the lowest energy conformation (ii) for **10b** is reached after a carbomethoxyl rotation of −60 degrees (see structure **10b** in Figure 2) resulting in a slightly longer C2C21 bond as conjugation is disrupted. Continuation to complete inversion (−180°), placing *N*-oxide and ester carbonyl dipoles in parallel, results in appreciable destabilization, (iii). The total Mulliken electronic charge at the para proton (H7) varies little during this rotation. Significantly though, the charge is highest for planar conformations (i) and (iii) in which hydrogen bonding to the amide, and therefore H7-deshielding, are strongest. As anticipated, the variation in Mulliken charge at the amide proton (H11) on the other hand roughly parallels the change in total energy as a function of the N1C2C21O23 dihedral angle. This is to be expected because the rotation of the carbomethoxy group resulting in total energy lowering with departure from planarity and relief of strain, also weakens hydrogen bonding to H11, thereby decreasing the Mulliken charge.

Figure 4 depicts the variation in Mulliken charge of H11 as a function of the N1C2C21O23 dihedral angle, and at the same time the H11O23 (alkyl-O) and H11O22-(acyl-O) interatomic distances for each of the abovementioned minimized fixed angle conformations of compound **10b**.

At the extremities of 0° and 180° H11····O22 or H11·····O23 hydrogen bonds respectively result in higher charges at H11, while a Mulliken charge minimum is observed at the center, corresponding to an orthogonal orientation of the COOMe group with respect to the NH-bond, with no possibility for hydrogen bonding to either oxygen. As the N1C2C21O23 angle increases past −100°, the H11O23 (amide(H)-to-(O)alkyl) distance falls below H11O22 and an inversion of the C2C3N10H11 dihedral angle takes place (data not shown) as H11 and O23 approach each other.

The twisting at hand of the ester group in **10b** is accompanied by a similar departure from planarity of the amide function. Inspection of the minimized conformation of **10b** reveals that *N*-oxidation of **10a** induces a disrotatory twisting about C2C21 and C3N10 so as to place the H-bonding partners H11 and O22 on the same side of the aromatic plane (cf. **4** → **4tt**). Significantly, the amide group is twisted at only about 20° (entries 24 and 26, Table 4) to the pyridine ring reflecting this groups' reluctance to sacrifice delocalization energy. This amide rotation however manifests itself in the considerable upfield NMR shift for the *para* proton (H4 in **9b**) in the **b**-series (as compared to the **a**-series), for which the +M effect of the *N*-oxygen is only partly responsible. In addition, the rotation of the amide group necessarily modifies the anisotropy exerted upon this proton—the distance between H7 and the amide carbonyl oxygen O13 is increased from 2.139 Å in **10a** to 2.226 Å in **10b** (entry 32) and the mutual orientation of these atoms is modified resulting in a further upfield shift of the NMR resonances.

The calculated RHF/6-31G energy difference between the *N*-oxide acid (**10c-*trans***) and its hypothetical *s-cis* carboxyl isomer (**10c-*cis***) is 12.95 kcal·mol^{-1}, with the former more stable. While the *s-cis* conformer (**10c-*cis***) would have an almost identical conformation to **10b** (cf. Table 4, columns 4 and 6), the *N*-oxide acid actually exists preferably in the **10c-*trans*** form attaining coplanarity upon ester saponification of the twisted precursor (**10b**). This state of affairs obviously results out of increased conjugation coupled with the formation of two strong

intramolecular hydrogen bonds (H11O22: 1.788 Å, H24O25: 1.592 Å, entries 33 and 35) effectively locking the molecule into a planar conformation. This regaining of coplanarity in going from the **b-** to the **c**-series was previously inferred both from infrared (Table 2, shift to lower N−H stretch frequencies) as well as NMR data (Table 1, lowfield shifts for **9c**) pointing to increased amide-to-acid hydrogen bonding. The modeling results at hand clearly substantiate this interpretation.

We also indirectly investigated the subtle conformational influences upon the H7 NMR chemical shifts by virtue of calculation of H7 Mulliken electronic charges. The H7 chemical shifts observed for compounds of the **c**-series are a compromise between neighboring amide carbonyl deshielding and *N*-oxide shielding, which in its turn can be attenuated by hydrogen bonding to the carboxyl-OH in the carboxylic acid (**10c-*trans***). The electronic Mulliken charge on H7 as a function of rotation of the amide and acid-OH groups in **10c-*trans*** and **11** was calculated, to obtain its' variation as a function of dihedral angle. The results are depicted in Figure 5.

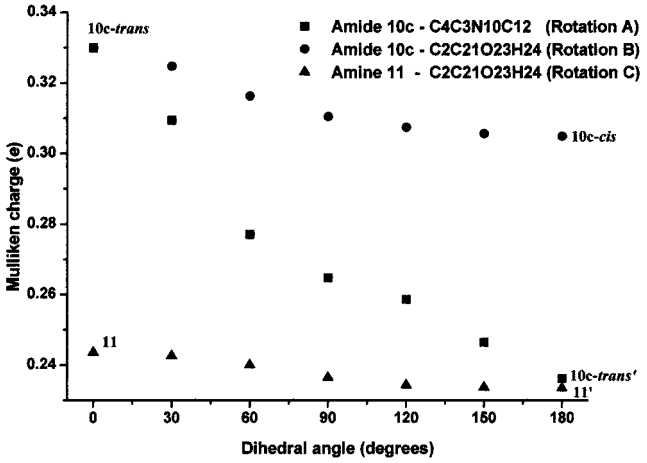
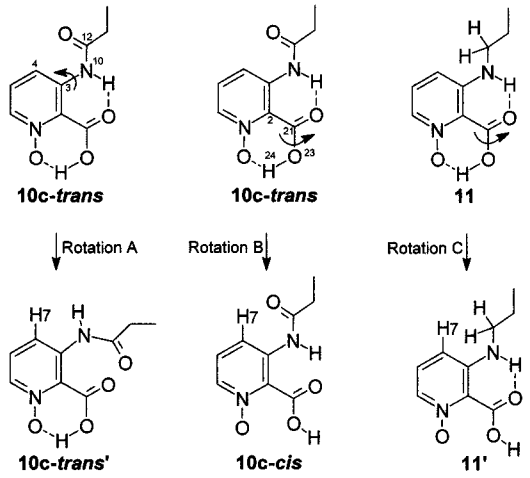


Figure 5. Variation of H7-Mulliken charge, as a function of dihedral angles C4C3N10C12 and C2C21O23H24 in *N*-oxide acid (**10c-*trans***) and as a function of C2C21O23H24 dihedral angle in *N*-oxide propylamine (**11**).



The striking effect of removing the amide C═O deshielding cone is apparent in a large drop in the H7 electronic Mulliken charge in **10c-*trans*** on rotating the C═O group away from this proton (rotation A). As anticipated above, the *N*-oxide function para to H7 can hydrogen bond to the neighboring acid OH. As this group is rotated from the s-trans to the s-cis conformation in **10c** (**10c-*trans*** → **10c-*cis***, rotation B), hydrogen bonding is gradually weakened and eventually lost, with a concomitant, albeit small, decrease in the positive electronic Mulliken charge on H7 as the *N*-oxide +M effect increases. That it is largely the amide group (and not *N*-oxide hydrogen bonding) which is responsible for the exceptional H7-downfield shift is supported not only by comparing the H7 chemical shifts in the free amine **6c** with those for amides **7c**−**9c**, but also by performing a similar rotational simulation (rotation C) of the acid OH group on the propylamine derivative **11** devoid of amide C═O anisotropy. In this case the electronic Mulliken charge on H7 is not only much lower but a similar effect of only a small(!) H7-charge lowering in going from a hydrogen-bonded *N*-oxide (**11**) to a free one (**11′**) is seen. The convergence of the amide group rotation curve for **10c-*trans*** (rotation A) with that for OH rotation in amine **11** (rotation C) is interesting because it suggests a similar environment for H7 in the two resulting conformers (**10c-*trans′*** and **11′**). In conclusion it can be said, that the deshielding due to amide anisotropy outweighs the *N*-oxide (+M) shielding effect in determining the NMR chemical shift of the H7 proton in the *para* position, and that reduction of the latter effect by H-bonding a neighboring carboxyl-H results in minimal charge elevation at the para hydrogen (H7).

As opposed to the *N*-oxides, the minimized conformations of the pyridine analogues **10d-*trans*** and **10d-*cis*** (methyl picolinates) are both planar, with the former more stable by 4.30 kcal.mol^{-1}. Devoid of the destabilizing *N*-oxide ↔ alkyloxy repulsion, **10d-*trans*** would assume a planar shape and take full advantage of the amide-to-carbomethoxyl hydrogen bond.

Cyclic dimers of the type (**12**) are common for secondary amides.[15] In the case of *N*-oxide-ester (**10b**), possessing twisted C2-carbomethoxyl and C3-amide bonds and thus devoid of stabilizing intramolecular hydrogen bond interactions, we entertained the possibility of amide dimer formation both in CH_2Cl_2 solution and KBr matrix during IR-studies (vide supra). With this in mind we performed an ab initio RHF geometry optimization of the dimer of **10b** using the 6-31G basis set. To this end we used a modified starting conformation in which the amide configuration was set as trans. The optimized dimeric arrangement is shown in Figure 6. The H11O41/O13H39 interatomic distances of 1.876 Å indicate moderately strong hydrogen bonding, while the N1C2C21O22 and C2C3N10C12 dihedral angles of −93.39 and 91.46° respectively show that both carbomethoxyl and amide groups are orthogonal to the pyridine ring. The total energy of the dimer was calculated as −1587.967496 au, a value 3.36 kcal·mol^{-1} less than twice the calculated energy of the monomeric *cis*-amide (**10b**), thereby indicating that some gain is to be had from dimer formation compensating the loss of intramolecular hydrogen bonding to the ester carbonyl. However, we also performed the RHF calculation with the 6-31G** basis set. The geometric parameters were very similar (H11O41/O13H39, N1C2C21O22 and C2C3N10C12 = 1.976 Å, −95.92 and 94.95°, respectively), although the energy of the dimer was only 0.32 kcal·mol^{-1} less than that of twice the monomer energy. Despite the fact, that these values satisfyingly support our idea of dimer formation, the results suggest that thus determined H-bond energies

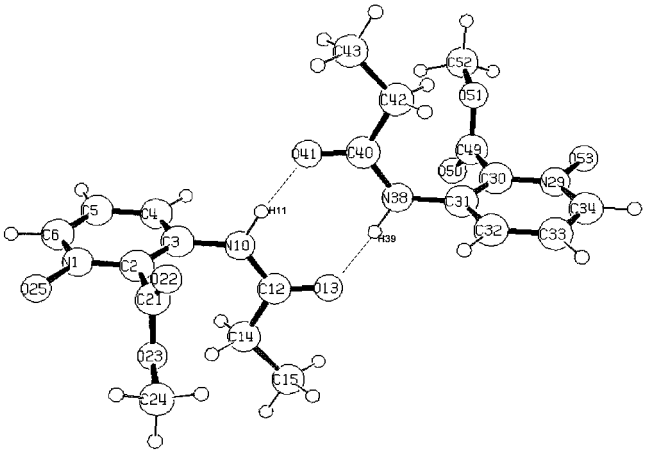


Figure 6. Minimized RHF/6-31G structure of the dimer of *N*-oxide ester **10b**.

strongly depend on the basis set employed. Such differences are well recorded,[22] and consequently undue importance should not be imparted upon these values.

B. Spectroscopic Studies. Selected calculated[23] GIAO ^{1}H and ^{15}N NMR chemical shifts for the model 3-propanoylaminopicolinates (**10a**−**d**) using both 6-31G and 6-31G** basis sets are shown in Table 1. When comparing with **9a**−**d**, the data show two important trends. First, 6-31G**-derived chemical shifts are uniformly more reliable than 6-31G-derived ones. Thus, in the 6-31G** basis set the calculated chemical shifts for the three aromatic protons are, on average, about 4% higher than the experimentally determined values, while 6-31G calculations provide an average over-estimate of 12.5% for these protons. Second, taking the aromatic protons individually over all the derivatives (**10a**−**d**), the estimates for H5 are clearly the most accurate with an average deviation from the experimental spectroscopic values of +2.2% and +8.4% for 6-31G** and 6-31G, respectively. H4- and H6-estimates are slightly less accurate with 6-31G calculated chemical shifts deviating about 2 to 3 times as much (in percent) as the 6-31G** values. The larger deviations of calculated H4 and H6 shifts from experimental values are consistent with the fact that these hydrogens are closer than H5 to electronic perturbation originating in the polar pyridine nitrogen/*N*-oxide and amide moieties. It is therefore to be expected, that, as compared to 6-31G, employment of the 6-31G** basis set will improve all three, but especially, as indeed borne out, the chemical shift estimates for H4 and H6.

Although, strangely the 6-31G** basis set provides no improvement over 6-31G with regard to accuracy in predicting amide hydrogen chemical shifts, the deviations from the experimentally derived values are of the same order of magnitude in the case of the planar molecules (**10a**), (**10c**) and (**10d**) (≈6−11%) as was seen with the aromatic protons. The sole outlier was the "twisted" derivative (**10b**), for which both basis sets resulted in a 20% overestimation of the true N−H chemical shift.

In the case of ^{15}N NMR, 6-31G based ab initio calculations grossly over-estimate the absolute value of the chemical shifts of the amide nitrogen in the compounds investigated. 6-31G** was much better. It is interesting to note, that there were well-defined, almost fixed deviations of calculated ^{15}N chemical shifts from experimental ones of 24% for 6-31G**- and 66% for 6-31G basis sets. Comparing **7b/c** and **9b/c** it can be seen, that the amide C═O substituent has only a small effect on the ^{15}N chemical shift ($\Delta(\delta\text{-}^{15}N_{\mathbf{7b/9b}}) = 1.8\%$; $\Delta(\delta\text{-}^{15}N_{\mathbf{7c/9c}}) = 1.97\%$), so that model-(**10**)-based δ-^{15}N calculations provide good predictability for arylamides as well, provided a +24% correction is taken into account. Although the calculated nitrogen chemical shifts are significantly less accurate than the proton shifts, a coherent trend of these values in accordance with hydrogen bonding can be discerned. Thus, in the same way that involvement of amide-H in hydrogen bonding in **9c** leads to a 5.8 ppm downfield shift of the ^{15}N resonance with respect to precursor **9b**, there is a similar shift of 6.9 ppm in the corresponding calculated resonances for the model compounds (**10b**) and (**10c**).

The IR-spectra of model compounds (**10a**−**d**) were calculated with both 6-31G and 6-31G** basis sets. The unambiguous attribution of calculated peak frequencies in the former case was much more difficult, especially for carbonyl stretches, which were often weak in intensity as well as apparently coupled to more complex vibrational modes. For this reason, Table 2 shows only the theoretical peak values obtained from the 6-31G** basis set. The calculated peak frequencies were on average uniformly 15−20% higher in model compounds (**10a**−**d**) when compared to the respective experimentally investigated dodecanoyl analogues (**9a**−**d**).

Despite the deviation of calculated values from experimental ones, it was gratifying to observe that the shift tendencies were always in the same direction (albeit generally smaller) upon passing along the series **a** → **b** → **c** → **d**. Thus, disruption of hydrogen bonding causes an increase in (KBr)ν_{N-H} (**7a** → **7b**: +2.6%, **9a** → **9b**: +2.5%, **10a** → **10b**: +0.9%) and subsequent renewed H-bonding results in a decrease (**7b** → **7c**: −8.4%, **9b** → **9c**: −7.1%, **10b** → **10c**: −2.4%). Similar trends were observed for the Amide-I bands. The ester C═O stretch for **10b** on the other hand is an interesting point. The calculated $\nu_{C=O}$ stretch for this *N*-oxide ester (1975 cm^{-1}) can only be one corresponding to the twisted, weakly intramolecular hydrogen bonded nondimerized conformer (as shown in **10b**), and as such must be compared to the peak at 1709 cm^{-1} for **9b**. To further investigate this point, we submitted the **10b**-dimer to an ab initio calculation, to obtain the calculated peak frequency for ester $\nu_{C=O}$ in this species in the expectation that this value would be higher than the calculated $\nu_{C=O}$ value for **10b**. Unfortunately however, this calculation greatly exceeded our computational possibilities.

Finally, as in the experimental series, the N−O stretches were difficult to attribute, being coupled to breathing of the pyridine ring. To aid in peak assignment, we calculated the IR-spectrum of pyridine-*N*-oxide using both basis sets. Indeed, as expected in view of Perni's[21] and our own results presented herein, 6-31G did not provide an unambiguously attributable N-O stretch, while the 6-31G** basis set yielded a value of 1368 cm^{-1}, which compares well to the corresponding calculated frequencies for **10b** and **10c**.

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Conclusion

3-Amidopicolinic acids and their *N*-oxides exist in a planar conformation due to strong intramolecular NH··· ·O═C and N−O···H−O hydrogen bonds. In the case of methyl 3-acylaminopicolinate-*N*-oxides, repulsion between *N*-O and alkyl oxygens results in twisting of the carbomethoxyl and amide functions from the aromatic plane. The conformation of such compounds can be investigated theoretically, but care must be exercised in choosing the molecular modeling approach for *N*-oxides, since AM1 gives highly improbable results. The best method found for pyridine *N*-oxide itself involves use of ab initio RHF calculations with the 6-31G** basis set,[21] although we have found that 6-31G works equally well for determining molecular geometry. Discrepancies between 6-31G and 6-31G** derived results are found for polar groups, especially the *N*-oxide bond. It seems probable, that the former basis set is satisfactory for modeling *N*-oxides, if a correction factor of −7% is used for the estimation of the *N*-oxide bond length. Molecular modeling studies of 3-propanoylaminopicolinic acid derivatives show that the ^{1}H NMR resonances of the proton in the pyridine 4-position in such substrates are shifted downfield as a result of deshielding by the neighboring amide carbonyl group. For more reliable predictions particularly with regard to ir and NMR spectroscopic parameters the 6-31G** basis set is a must. ^{1}H and ^{15}N chemical shifts for this method are on average overestimated by about 4% and 24% respectively, while 6-31G gives an almost three times larger average deviation.

Experimental Section

Melting points are corrected. Flash chromatography was carried out using silica gel (Merck, Kieselgel 60, 230−400 mesh) and analytical TLC was done on precoated plastic sheets (Macherey-Nagel, Polygram SIL G/UV$_{254}$). Commercial AR grade solvents and reagents (Fluka, Aldrich) were used directly unless, where necessary, purified using standard published procedures.[24] The starting material, methyl 3-aminopicolinate (**6a**) as well as analogues (**6b**) and (**6c**) were prepared according to ref 7a. NMR spectra were obtained on a Varian Unity Plus 300 spectrometer in the Departamento de Química Fundamental. Samples were dissolved in $CDCl_3$. Chemical shifts are quoted relative to TMS ($\delta = 0$) for ^{1}H and nitromethane ($\delta = 0$) for ^{15}N.

Methyl 3-Benzoylaminopicolinate (7a). To a stirred, refluxing solution of the amine **6a**[7a] (2 g, 13.2 mmol) in $CHCl_3$ (20 mL) were added pyridine (2.1 mL, 2 equiv), DMAP (50 mg), and a solution of benzoyl chloride (2.2 mL, 19.8 mmol, 1.5 equiv) in $CHCl_3$ (10 mL). After 22 h at reflux, the solution was cooled and washed sequentially with saturated aqueous $CuSO_4$, dilute NaOH, and brine, dried (Na_2SO_4), filtered, and concentrated. Recrystallization of the residue from cyclohexane/EtOAc provided a white powder (2.9 g, 86%): mp 134−136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.98 (s, 1H), 9.35 (dd, J = 8.5, 1.2 Hz, 1H), 8.47 (dd, J = 4.5, 1.2 Hz, 1H), 8.06 (dd, J = 8, 1.5 Hz, 2H), 7.57 (m, 4H), 4.10 (s, 3H); IR (KBr) see Table 2; MS *m*/*z* (rel intensity) 256 (M^+, 28).

Methyl 3-*p*-Nitrobenzoylaminopicolinate (8a). This compound was prepared in a fashion similar to that of **7a**, employing *p*-nitrobenzoyl chloride. Reflux for 4 h, workup, and recrystallization from cyclohexane/EtOAc provided fine, off-white crystals (46%): mp 201−204 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.20 (s, 1H), 9.30 (dd, J = 8.7, 1.5 Hz, 1H), 8.52 (dd, J = 4.5, 1.5 Hz, 1H), 8.40 (dd, J = 7, 2 Hz, 2H), 8.21 (d, J = 7 Hz, 2H), 7.60 (dd, J = 8.7, 4.5 Hz, 1H), 4.10 (s, 3H); IR (KBr) ν_{max} 3300, 1688 cm^{-1}; MS *m*/*z* (rel intensity) 301 (M^+, 1).

Methyl 3-Dodecanoylaminopicolinate (9a). This material was prepared in a fashion similar to that for **7a** using CH_2Cl_2 at room temperature instead of refluxing $CHCl_3$. Recrystallization from MeCN provided a white, amorphous solid (100%): mp 68−71 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.98 (br s, 1H), 9.15 (dd, J = 8.7, 1.5 Hz, 1H), 8.41 (dd, J = 4.5, 1.5 Hz, 1H), 7.49 (dd, J = 8.7, 4.5 Hz, 1H), 4.04 (s, 3H), 2.47 (t, J = 7.5 Hz, 2H), 1.75 (m, 2H), 1.44−1.20 (m, 16H), 0.87 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 168.0, 143.3, 139.5, 131.4, 128.4, 128.2, 96.2, 53.0, 38.6, 31.9, 29.7, 29.5, 29.4, 29.2, 25.4, 22.7, 14.2; IR (KBr) see Table 2; MS *m*/*z* (rel intensity) 334 (M^+, 13).

Methyl 3-Benzoylaminopicolinate *N*-Oxide (7b). To a stirred solution of the amide **7a** (2 g, 7.8 mmol) in MeCN (50 mL) was added ≈85% *m*-CPBA (3.37 g, ≈16.8 mmol, ≈2.2 equiv). After 2 h, filtration and evaporation gave a white solid. Two cycles of slurrying in cold MeCN, filtration, and evaporation removed most of the remaining *m*-CPBA and *m*-CBA. Chromatography of the residue (EtOAc/MeOH) followed by crystallization from cyclohexane/EtOAc furnished a white powder (710 mg, 33%): mp 153−155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1 H), 8.55 (dd, J = 8.7, 1.0 Hz, 1 H), 8.05 (dd, J = 6.0, 1.0 Hz, 1H), 7.91 (m, 2H), 7.60 (m, 1H), 7.54 (m, 3H), 7.35 (dd, J = 8.7, 6.0 Hz, 1H), 4.09 (s, 3H); IR (KBr) see Table 2; MS *m*/*z* (rel intensity) 272 (M^+, 6).

Methyl 3-*p*-Nitrobenzoylaminopicolinate *N*-Oxide (8b). A procedure similar to that for **7b** employing *m*-CPBA (≈4 equiv) for 2 days provided, after chromatography with EtOAc/MeOH and crystallization from EtOAc, off-white needles (35%): mp 159−160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.55 (br d, J = 8.4 Hz, 1H), 8.39 (m, 2H), 8.12 (m, 3H), 7.38 (dd, J = 8.4, 6.5 Hz, 1H), 4.10 (s, 3H); IR (KBr) ν_{max} 3096, 1757, 1693 cm^{-1}; MS *m*/*z* (rel intensity) 317 (M^+, 5).

Methyl 3-Dodecanoylaminopicolinate *N*-Oxide (9b). A solution of the pyridine ester (**9a**) (1.08 g, 3.23 mmol) in $CHCl_3$ (25 mL) was treated with ≈70% *m*-CPBA (980 mg, ≈5.68 mmol, ≈1.8 equiv) and heated to 50 °C for 1 h. Solvent evaporation and flash chromatography (eluent: EtOAc/MeOH) of the residue gave recovered starting material (360 mg, 33%) followed by the desired *N*-oxide (**9b**) as a light yellow powder (450 mg, 60% based on recovered starting material) which could be recrystallized from *i*-Pr$_2$O to provide pure material: mp 91−92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (br s, 1H), 8.36 (br d, J = 8.7 Hz, 1H), 7.92 (br d, J = 6.3 Hz, 1H), 7.25 (dd, J = 8.7, 6.3 Hz, 1H), 4.04 (s, 3H), 2.36 (t, J = 7.5 Hz, 2H), 1.68 (m, 2H), 1.42−1.20 (m, 16H), 0.89 (t, J = 6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 163.4, 137.7, 134.8, 130.8, 126.3, 116.7, 96.0, 53.0, 37.7, 31.7, 29.4, 29.3, 29.2, 28.9, 24.9, 22.5, 14.0; IR (KBr) see Table 2; MS *m*/*z* (rel intensity) 351 (MH^+, 31).

3-Benzoylaminopicolinic Acid *N*-Oxide (7c). The methyl ester **7b** (90 mg, 0.33 mmol) dissolved in MeOH (5 mL) was treated with 0.2 M aqueous NaOH (1.8 mL, 1.1 equiv) and stirred at room temperature for 4 days. The solution was diluted with water and carefully acidified with dil HCl to pH ≈5 to precipitate the product. After being stirred for an additional 2 h, the mixture was cooled and filtered, and the white precipitate was washed with cold water. Drying and recrystallization from MeOH furnished a white flocculent solid (32 mg, 38%): mp 185−186 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 20.16 (s, 1H), 13.35 (s, 1H), 9.48 (br d, J = 9 Hz, 1H), 8.16 (m, 1H), 8.09 (m, 2H), 7.68−7.53 (m, 4H); IR (KBr) see Table 2; MS *m*/*z* (rel intensity) 258 (M^+, 1).

3-*p*-Nitrobenzoylaminopicolinic Acid *N*-Oxide (8c). This product was prepared from the ester in the same way as **7c** with a reaction time of 6 days. Recrystallization from MeOH furnished a fine, white powder (23%): mp 276−279 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.62 (s, 1H), 9.44 (br d, J = 9 Hz, 1H), 8.39 (d, J = 9 Hz, 2H), 8.24 (d, J = 9 Hz, 2H), 8.22 (br d, J = 6.6 Hz, 1H), 7.68 (dd, J = 9, 6.6 Hz, 1H); IR (KBr) ν_{max} 3106, 1695, 1671 cm^{-1}; MS *m*/*z* (rel intensity) 258 ($MH^+ - CO_2$, 25).

(24) Perrin, D. D.; Armarego, W. L. F., Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: Oxford, 1980.

3-Dodecanoylaminopicolinic Acid *N*-Oxide (9c). This product was prepared from the ester in the same way as **7c** with a reaction time of 8 h. Recrystallization from MeOH/water gave a white powder (66%): mp 103−104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 19.98 (br s, 1H), 12.34 (br s, 1H), 9.28 (dd, J = 9, 1 Hz, 1H), 8.10 (dd, J = 6.3, 1 Hz, 1H), 7.55 (dd, J = 9, 6.3 Hz, 1H), 2.50 (t, J = 7.5 Hz, 2H), 1.74 (m, 2H), 1.42−1.20 (m, 16H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8, 173.6, 165.0, 142.9, 131.4, 127.7, 124.1, 123.3, 38.7, 31.9, 29.6, 29.4, 29.3, 29.2, 29.1, 25.1, 22.7, 14.1; IR (KBr) see Table 2; MS *m*/*z* (rel intensity) 336 (M^+, 1).

3-Dodecanoylaminopicolinic Acid (9d). This product was prepared from the ester (**9a**) in the same way as **7c** (from **7b**) with a reaction time of 34 h. Recrystallization from MeOH/water gave the free acid **9d** as a white microcrystals (88%): mp 134−135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.13 (br s, 1H), 9.27 (br d, J = 8.7 Hz, 1H), 8.31 (m, 1H), 7.60 (dd, J = 8.7, 4.5 Hz, 1H), 2.49 (t, J = 7 Hz, 2H), 1.76 (m, 2H), 1.46−1.16 (m, 16H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 166.0, 139.8, 139.5, 130.7, 130.2, 129.3, 38.5, 31.9, 29.6, 29.4, 29.3, 29.1, 25.2, 22.7, 14.1; IR (KBr) see Table 2; MS *m*/*z* (rel intensity) 320 (M^+, 18).

Acknowledgment. Financial support was obtained from CNPq (Conselho Nacional de Pesquisa e Desenvolvimento, Brazilian Agency). We are indebted to the analytical laboratories of Novartis S.A., Basel, Switzerland, for obtaining IR spectra. I.d.C.L.B., C.C.C.B., and F.H. thank the Brazilian Agencies CAPES and CNPq for scholarships. We are indebted to Professor Katia Zaccur Leal/Universidade Federal Fluminense for help with the NMR studies.

Supporting Information Available: Discussion of AM1, RHF/6-31G, and RHF/6-31G** molecular modeling results for **10a**, **10b**, **10c-*trans***, **10c-*cis***, **10d-*trans***, and **10d-*cis*** and full molecular coordinate tables for **10c-*trans*** and **10c-*cis***. RHF/6-31G results for 3-benzoylaminopicolinic acid *N*-oxide (**7c-*cis***). Full experimental characterization as well as ^{1}H NMR spectra for compounds **8b**, **8c**, and **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000993J