Gas-Phase Basicity and Site of Protonation of Polyfunctional Molecules of Biological Interest: FT-ICR Experiments and AM1 Calculations on Nicotines, Nicotinic Acid Derivatives, and Related Compounds

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Received December 27, 1990

The proton affinities (PAs) of nornicotine, nicotine, nicotinamide, *N,N*-diethylnicotinamide, 3-acetylpyridine, 3-benzoylpyridine, and methyl nicotinate have been obtained by FT-ICR. Comparisons of these experimental PAs with those calculated for the different possible sites of protonation by using the AM1 method, or estimated from substituent effects on model compounds, lead to the conclusion that nornicotine and nicotine protonate preferentially on the five membered ring amino nitrogen. Considering the accuracy of the calculations concerning *N,N*-diethylnicotinamide, it was not possible to decide whether the pyridine nitrogen or the carbonyl oxygen is the most basic site. For the other four derivatives studied, the pyridine nitrogen appears to be the prefered site of protonation.

Introduction

Molecules containing the pyridine ring are of major interest with regard to the prominent role they play in biological systems. Nicotines and nicotinic acid derivatives, which are meta-substituted pyridines, are active as insecticides, vitamins, or stimulants. Even in the case of these relatively simple molecules the question still remains whether the basic site interacting with the biological medium is always the pyridine nitrogen, whatever the substituent may be. In this regard the case of *N,N*-diethylnicotinamide (DENA) is striking. Though DENA is protonated by strong acids on the aza nitrogen in apolar solvents and in water, hydrogen bonding with weak acids such as phenols takes place on the oxygen of the amide group in apolar media.[1]

Studies devoted to gas-phase interactions, free from medium effects, are expected to shed light on the factors governing the acid-base behavior.[2] The present article is the first step of a comparative study of proton transfer in the gas phase and of proton sharing (hydrogen bonding) in an apolar solvent. We report here gas-phase basicities, measured by Fourier Transform Ion Cyclotron Resonance (FT-ICR) mass spectrometry, of nornicotine (**1**), nicotine (**2**), 3-acetylpyridine (**3**), 3-benzoylpyridine (**4**), and the nicotinic acid derivatives methyl nicotinate (**5**), nicotinamide (**6**), and *N,N*-diethylnicotinamide (**7**) (Scheme I). AM1 molecular orbital calculations are used to calculate the proton affinities (PAs) of the potential basic sites, with the aim to assign the more stable form of protonated **1-7** by comparison with experimental PAs. Independent estimations of the basicity, based on substituent effects on pyridine and amino or carbonyl functions, are also confronted to the experimental and theoretical results.

Methods

FT-ICR Measurements. One of the techniques commonly used for the study of gas-phase proton transfer equilibria is ICR.[3] Its latest computerized form, FT-ICR,[4] has several advantages such as high sensitivity, rapidity, high resolution, and possibility of complex sequences of ion manipulation (acceleration, collision, ejection). Gas-phase basicities (as GBs) were determined using the FT-ICR mass spectrometer constructed at the University of Nice-Sophia Antipolis.[5] The equilibrium constants for proton transfer between the base under study (B) and the reference base (Ref), as given in eq 1

$$\mathrm{Ref} + \mathrm{BH}^+ \rightleftharpoons \mathrm{RefH}^+ + \mathrm{B} \qquad (1)$$

were calculated according to eq 2

$$K_1 = \frac{I(\mathrm{RefH}^+)}{I(\mathrm{BH}^+)} \frac{P_{\mathrm{BA}}(\mathrm{B})}{P_{\mathrm{BA}}(\mathrm{Ref})} \frac{S_r(\mathrm{Ref})}{S_r(\mathrm{B})} \qquad (2)$$

where $I(\mathrm{RefH}^+)$ and $I(\mathrm{BH}^+)$ are the intensities of signals for ions RefH^+ and BH^+, respectively, $P_{\mathrm{BA}}(\mathrm{B})$ and $P_{\mathrm{BA}}(\mathrm{Ref})$ are the pressures measured with a Bayard-Alpert (BA) ionization gauge (Alcatel BN 111). $S_r(\mathrm{Ref})$ and $S_r(\mathrm{B})$ are the sensitivities (relative to N_2) of the BA gauge estimated according to Bartmess and Georgiadis (BG).[6] The BA gauge sensitivities of pyridine and compounds **2** and **5** were measured using a spinning rotor gauge (Leybold, Viscovac

Scheme I

R = H	1	X = Me	3
Me	2	Ph	4
		OMe	5
		NH_2	6
		NEt_2	7

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0022-3263/91/1956-4490$02.50/0

Table I. Relative and Absolute Gas-Phase Basicities and Proton Affinities for 1-7 (kcal·mol^{-1})

entry	base (B)	reference (Ref)	$\Delta_1G°$ [a]	GB(B)[b]	PA(B)[c]
1	nornicotine	pyrrolidine	3.36 ± 0.08	220.3[d]	228.1
		N-methylpyrrolidine	−0.60 ● 0.01		
2	nicotine	$(n\text{-Pr})_2NH$	0.75 ± 0.03	220.5 ● 0.1	228.3
		N-methylpyrrolidine	−0.39 ± 0.04		
3	3-acetylpyridine	$MeCON(Me)_2$	1.62 ± 0.02	210.4 ± 0.4	218.2
		$n\text{-BuNH}_2$	0.23 ± 0.02		217.2[f]
4	3-benzoylpyridine	$sBuNH_2$	1.64 ● 0.01	214.1 ± 0.1	221.9
		pyridine	0.98 ± 0.04		
		cyclohexylamine	0.71 ± 0.05		
5	methyl nicotinate	$n\text{-PrNH}_2$	2.35 ± 0.06	211.9 ± 0.1	219.7
					219.5[g]
		morpholine	0.24 ● 0.10		
		pyridine	−1.16 ± 0.14		
6	nicotinamide	$MeCON(Me)_2$	1.39 ● 0.02	210.4 ± 0.6	218.2
		$iBuNH_2$	−0.18 ● 0.04		
7	*N,N*-diethylnicotinamide	pyridine	2.69 ± 0.31	215.4 ± 0.1	223.2
		$tBuNH_2$	≈1.8[e]		
		N,N-dimethylaniline	0.00 ± 0.02		
		4-methylpyridine	≈−1.2[e]		

[a] Gibbs free energy change for eq 1. Uncertainties are calculated from the standard deviation on 3-5 equilibrium constant values obtained for different partial pressures ratio of B and Ref. [b] Absolute Gibbs free energy of deprotonation of BH^+. Quoted errors correspond to the goodness of the overlap between the different references used. They are an indication of the uncertainties of the *relative* basicities. The absolute GBs are in fact accurate to about 2.0-2.5 kcal·mol^{-1} due the uncertainties commonly encountered in the anchoring data. In the absolute anchoring scale used here GB (pyridine) = 213.1 kcal·mol^{-1}.[18,19] [c] PA = GB + $T\Delta S°$. For 1-7 $\Delta S°$ is taken as the translational entropy of the proton at 298.15 K (standard state: 0.1 MPa). [d] Only the closest reference was considered, pyrrolidine gives 220.7 kcal·mol^{-1}. [e] Less reliable values due to the difficulties encountered in stabilizing the pressure. [f] References 17 and 18. [g] Reference 19.

VM 210)[7] and were found to be 3.89 ± 0.05, 7.20 ± 0.20, and 5.25 ± 0.17, respectively. For comparison, the S_r values, estimated from the BG equation,[6] using the average molecular polarizability (α_{ahc} calculated according to Miller and Savchik),[8] are equal to 3.71, 7.29, and 5.31, respectively for pyridine and 2 and 5. The BG equation estimates quite accurately the S_r values for these compounds. For the amines used as reference bases a small underestimation was noted,[9] but no significant bias is introduced by the systematic use of calculated S_r values in eq 2. Ion intensities were followed as a function of the reaction delay introduced between the ionization pulse and the ion detection pulse. Typically 10 spectra in the mass range 15-200 u were taken for delays 0, 1, 2, ..., 9 s. Each spectrum corresponds to 3-10 scans of 16 K data points, zero-filled to 64 K prior to Fourier transformation. GB(B) is obtained from the equilibrium constant K_1:

$$\Delta_1G° = -RT \ln K_1$$

$$\text{and } GB(B) = GB(Ref) + \Delta_1G°$$

All measurements were carried out at a FT-ICR cell temperature of 338 K.[10] All the compounds studied have low vapor pressures and necessitate heating to reach a workable pressure with a reasonable delay. The introduction system and the vacuum chamber are heated at 45-80 °C (318-353 K). Within this range, it was found that the effect of the vacuum chamber temperature on the cell temperature is negligible. Cell temperature depends only on the filament current used for electron ionization, usually 2.8 A.

All the chemicals 1-7 and the reference bases used in the FT-ICR measurements were commercially available: nornicotine (1) (Sigma) has been used without further purification; compounds 2-7 (Aldrich) have been distilled under vacuum or recrystallized. The compounds were degassed by freeze-pump-thaw cycles before introduction in the spectrometer. They were checked for the conformity of their 70-eV electron ionization mass spectra with reference spectra from the literature at the beginning of the FT-ICR measurements.

MO Calculations. Molecular orbital calculations have proved to be useful tools for the interpretation of the experimental gas-phase basicity,[11] in particular in the case of the substituent effects on PA of amines[12] and aza heterocycles.[13] Theoretical approaches have been extensively used to assign the favored site of protonation in polyfunctional molecules.[14] It is worth noting that the protonated forms of the molecules under study cannot undergo intramolecular hydrogen bonding. The large size of the investigated systems does not allow ab initio calculations, and we have chosen to use the less expensive semiempirical AM1 method.[15] The predictive power of this method was thoroughly evaluated for the PA of various classes of bases.[16] All computations were carried out

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by using the standard AM1 program from the AMPAC package (QCPE number 523). Neutral species and their most probable conjugate acids were considered. For the purpose of comparison, *N,N*-diethylacetamide and *N,N*-dimethylbenzamide were also submitted to calculations. In the amide series, Dewar et al.[16] have only considered formamide. The geometries of the neutrals were fully optimized by minimizing the energy with respect to all internal coordinates and without any symmetry constraint. These geometries were used as initial imputs to optimize the energy of the protonated species. We have checked that conformational effects do not affect significantly PAs. For example, in the case of 4 and 7 we calculated changes of enthalpy of formation of less than 0.2 kcal·mol^{-1} when various stable conformations of the carbonyl in the neutrals were considered. For the protonated forms, the changes are less than 0.7 kcal·mol^{-1}. Similar observations have been reported by Voets et al.[13c] for 3-formylpyridine. Considering the level of the various approximations used in this work such small conformational effects have been no longer investigated. Detailed geometrical parameters of neutral and charged species (bond lengths, bond and dihedral angles, cartesian coordinates) are available as supplementary material.

Results and Discussion

For each base 1–7, at least two reference compounds were used in order to obtain a good overlap with the existing basicity scale.[17-19] The results are given in Table I. In general a good agreement is observed for the measurements done with various references (see footnote *b*). For 1, we have given more weight to the data relative to the closest reference. The other reference being ≥3 kcal·mol^{-1} less basic than 1, the equilibrium conditions are probably not met, and this measurement was considered as approximate, though giving a basicity value for 1 rather close to that reported in the table. As compared to the other bases, we observe for 3 and 6 a less accurate overlap between the measurements relative to the different references. This may be attributed in part to the GB value for $MeCONMe_2$, which appears not to be well settled and was recently revised.[19] The other references are amines or pyridines, and their GBs seem to be more consistent. It will also be noted that nicotinamide (6) has a very low volatility, rendering the pressure measurements less accurate. The goodness of the overlap for the determination of GB values given in Table I (see footnote *b*) is an indication of the precision on the *relative* basicities. Uncertainties on absolute GBs taken individually are much larger, due to the lack of a precise anchor within the range of compounds studied.[18]

Proton affinities, also reported in Table I, were calculated from the experimental GBs by assuming all entropy effects were negligible except for the translational entropy of the free proton (26.04 cal·mol^{-1}·K^{-1} at 298.15 K and 0.1 MPa). Usually, only the change in symmetry number upon deprotonation of BH^+ is considered to bring a significant additional contribution to the entropy term. Due to the structures of 1–7 there is no such a change in the series and a constant $T\Delta S°$ = 7.8 kcal·mol^{-1} term was used. It should be noted that this practice, as followed here, neglects the possible changes in rotational barriers. This change may contribute to the entropy of deprotonation and consequently may introduce a small bias in the estimation of PAs.[20]

Table II. AM1 Calculations of the Enthalpies of Formation of Neutrals and Protonated Forms Together with the Calculated Proton Affinities (PA_{AM1}) (kcal·mol^{-1})

entry	base (B)	$\Delta_f H°$(B)	protonated atom	$\Delta_f H°$(BH$^+$)	PA_{AM1}[a]
1	nornicotine	28.4	pyridine N	178.4	217.2
			amino N	176.5	219.1
2	nicotine	35.7	pyridine N	184.9	218.0
			amino N	183.8	219.1
3	3-acetyl-pyridine	−3.7	pyridine N	152.0	211.5
			carbonyl O	163.8	199.7
4	3-benzoyl-pyridine	30.3	pyridine N	184.8	212.7
			carbonyl O	192.4	205.1
5	methyl nicotinate	−51.0	pyridine N	106.5	209.7
			carbonyl O	118.0	198.2
6	nicotinamide	−6.0	pyridine N	151.6	209.6
			carbonyl O	153.1	208.1
			amide N	164.1	197.1
7	*N,N*-diethyl-nicotin-amide	−6.5	pyridine N	147.8	212.9
			carbonyl O	145.0	215.7
			amide N	154.7	206.0

[a] $PA_{AM1} = \Delta_f H°(B) + \Delta_f H°(H^+) - \Delta_f H°(BH^+)$; $\Delta_f H°(H^+)$ = 367.2 kcal·mol^{-1} (ref 21). This value corresponds to the "electron in thermal motion" convention, as implicitly adopted in ref 16.

We report AM1 calculations performed on the most stable conformation of the neutrals 1–7 (for the carbonyl compounds, the carbonyl group is opposite to the pyridine nitrogen) and on the corresponding protonated structures. Table II shows the calculated enthalpies of formation of these species as well as the derived PA_{AM1}s. For compounds 3–5, the pyridine nitrogen appears to be significantly more basic (7–12 kcal·mol^{-1}) than the carbonyl functions. Nevertheless the PA_{AM1}s calculated for the pyridine nitrogen are lower than the experimental proton affinities, PA_{exptl}, by 8–10 kcal·mol^{-1}. This is to be compared to $PA_{AM1} - PA_{exptl}$ = −7.4 kcal·mol^{-1} found by Dewar and Dieter for 3-methylpyridine.[16] For a large majority of compounds studied by Dewar and Dieter, the AM1 method leads to an underestimation of the PAs. Of interest for the present study is the case of pyrrolidine and *N*-methylpyrrolidine for which the PA is underestimated by 8.3 and 10.8 kcal·mol^{-1}, respectively.[16] For compounds 1 and 2 the PA_{AM1} for the pyrrolidino nitrogen is lower than PA_{exptl} by 9.0 and 9.2 kcal·mol^{-1}, respectively.

These observations lead us to correct the calculated values by an amount corresponding to the difference $PA_{AM1} - PA_{exptl}$ found for monofunctional model compounds. The corrected values, $PA_{AM1corr}$, are reported in Table III. The models used for error calculations are given in footnotes *c–j*. For the carbonyl protonation of the amides 6 and 7, the only error model available in the Dewar and Dieter's paper[16] is formamide. We have preferred to base our corrections on amides of structure closer to that of target compounds. PA_{AM1} for *N,N*-diethylacetamide and *N,N*-dimethylbenzamide, for which experimental PAs are known (220.0 and 221.6 kcal·mol^{-1}, respectively),[19] were calculated (214.6 and 217.6 kcal·mol^{-1}, respectively). The average $PA_{AM1} - PA_{exptl}$ error (−4.7 kcal·mol^{-1}) was used as correction.

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(20) For example, if deprotonation reduces a given rotational barrier from 10 to 5 kcal·mol^{-1}, the corresponding entropy increase is 0.8 cal·K^{-1}·mol^{-1} (giving $T\Delta S_{rot}$ = 0.24 kcal·mol^{-1} correction on PA); see: Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley: New York, 1976.

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Table III. Comparison between Experimental PAs, Corrected AM1 Results, and Estimations Using Substituent-Effect Models (kcal·mol^{-1})

entry	base (B)	PA_{expt}[a]	protonated atom	$PA_{AM1corr}$[b]	PA_{est}[i]
1	nornicotine		pyridine N	224.6[c]	223.2
		228.1	amino N	227.4[d]	224.3
2	nicotine		pyridine N	225.4[c]	223.7
		228.3	amino N	229.9[e]	227.9
3	3-acetylpyridine	218.2	pyridine N	218.9[c]	216.9
			carbonyl O	199.2[f]	199.0
4	3-benzoyl-pyridine	221.9	pyridine N	220.1[c]	217.2
			carbonyl O	204.6[f]	205.0
5	methyl nicotinate	219.7	pyridine N	217.1[c]	217.2
			carbonyl O	201.2[g]	198.6
6	nicotinamide	218.2	pyridine N	217.0[c]	216.7
			carbonyl O	212.8[h]	≈209[j]
7	*N,N*-diethyl-nicotinamide	223.2	pyridine N	220.3[c]	219.9
			carbonyl O	220.4[h]	219.3

[a] From Table I [b] PA_{AM1} corrected for the error calculated[16] (PA_{AM1} − PA_{expt}) for model compounds given in the following footnotes. [c] 3-Methylpyridine. [d] Pyrrolidine. [e] *N*-Methylpyrrolidine. [f] Formaldehyde and acetaldehyde. [g] Methyl acetate. [h] *N,N*-Dialkylamides. [i] Estimated from substituent effects on model systems, see text. [j] No reliable model system available.

Independent estimates of the PA for each potential site of protonation can be obtained by using the methodology developed by Taft and Topsom[22] for the interpretation and prevision of gas-phase basicities. The linear additive model separates field/inductive (F), resonance (R), and polarizability (P) substituent effects in model structures. Each effect is represented by a $\rho\sigma$ product in which σ is a substituent parameter and ρ a sensitivity coefficient to a given effect characteristic of the reacting function. Concerning the protonation of the pyridine site we have used the experimental ρ values obtained for the 3-substituted pyridines.[22] When the necessary σ values were not known, they were evaluated by using an additivity attenuation scheme, based on σ of closely related substituents.[23] For the protonation of the other possible sites, we have considered the effect of the 3-aza pseudosubstituent on the various functionalities. It appears that the 3-aza global effect is comparable to the F effect of the CF_3 substituent.[24] The sensitivity to the F effect ρ_F, is known for the meta position of acetophenones, methyl benzoates, and *N,N*-dimethylbenzamides,[22] and these values were used to evaluate the 3-aza effect on carbonyl basicity. For **4**, **6**, and **7** we considered experimental data to correct for the change in substitution close to the carbonyl.[25] The evaluation of the basicity of the amino nitrogen of nicotine is not straightforward. Starting from the basicity of *N*-methylpyrrolidine it is necessary to calculate the effect of the 3-pyridinyl substituent α to the amino nitrogen. This effect may be decomposed in two components, a phenyl effect and then a 3-aza effect. The phenyl effect is calculated from the ρ values pertaining to the XCH_2NMe_2 series.[22] There is no model system to evaluate directly the 3-aza effect. We used the ρ_F value obtained for the 3-$XC_6H_5NMe_2$ series[22] attenuated by a factor of 2.0 for the interposition of a carbon atom between the benzene ring and the basic center (the calculated ρ_F = 7.6 kcal·mol^{-1} corresponds to the 3-$XC_6H_5CH_2NMe_2$ series, not known). At this step the 3-aza effect was evaluated as above. The nornicotine amino nitrogen basicity was obtained by considering the effect of methyl removal on the basicity of *N*-methylpyrrolidine.

The uncertainty of this "back of the envelope" methodology is difficult to assess. On the basis of the standard deviations of ρ_F values, and the approximations made in evaluating the various σ and increments, uncertainties of 1–2 kcal·mol^{-1} on substituent effects seem a reasonable estimate. The $\rho\sigma$ products or increments are added to the absolute PA of the appropriate parent compounds, which are of relatively close basicity (203.7–228.7 kcal·mol^{-1} from methyl benzoate to *N*-methylpyrrolidine). Though each absolute PA bears an inherent uncertainty of about ±2 kcal·mol^{-1}, the *relative* values within a restricted range are much less uncertain (cf. the above discussion on GBs). Therefore the estimated PA values may be compared each others for a significant discrimination of the protonation site provided the difference will be greater than 1–2 kcal·mol^{-1}. The same remark applies to the comparison between experimental and estimated PAs, as the reference bases (equilibrium measurements, Table I) and the parent compounds (substituent effect approach) belong to the same range of basicity.

The results of these estimations, PA_{est}, are also reported in Table III, together with corrected AM1 and experimental values. Our empirical method leads to values systematically lower than $PA_{AM1corr}$. This may be attributed to the fact that conformational effects are not taken into account by the present substituent effect approach, which refers only to the connectivity of the substituent–framework–function system. Although conformational aspects of substituent effects have been adressed theoretically,[26] we know only one experimental paper dealing with the problem of the variability of electronic substituent constants with conformation.[27] On the other hand the consideration of the favored conformation of the neutrals in our AM1 calculations may lead to a small increase of the PA_{AM1} as compared to a method which freezes the substituent, or consider it as anisotropic. There is an excellent correlation $PA_{AM1corr}$ vs PA_{est} (R = 0.9934; 13 data points; slope, 1.036 ± 0.036). The maximum deviation of 1.9 kcal·mol^{-1} is less than the sum of the expected uncertainties of both methods.

Notably, the two independent approaches, corrected AM1 and substituent effects, give a coherent picture of the potential basicity of the various functions. For compounds **3**–**6**, the pyridine nitrogen appears clearly as the favored site of protonation. This is confirmed by the experimental

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(23) The list of σ constants given in ref 22 has been recently enlarged to 74 substituents (R. W. Taft, personal communication, 1989). The unpublished and estimated values relevant to the present study are given below. The method of estimation for the polarizability constant σ_α has been described.[22] For the field effect constant σ_F, an attenuation factor of 2 when intercalating a carbon atom between the substituent and the framework was used. The resonance effect constant to be used in the pyridine series is σ^+_R (electron deficient reacting center). 2-Pyrrolidino: σ_α = −0.69 (model: CHEtNHMe), σ_F = 0.06 (model: CH_2NHMe); 2-(*N*-methylpyrrolidino): σ_α = −0.75 (model: $CHEtNMe_2$), σ_F = 0.05 (model: CH_2NMe_2); for these two substituents σ^+_R = −0.07 (model: iPr). COMe and CO_2Me: see ref 22; COPh: σ_α = −0.75, σ_F = 0.28; $CONH_2$: σ_α = −0.44, σ_F = 0.25 (estimated from σ_α = −0.59, σ_F = 0.19 for $CONMe_2$); $CONEt_2$: σ_α = −0.65, σ_F = 0.25 (as for $CONH_2$); for all carbonyl substituents: σ^+_R = 0.

(24) The PA of pyrimidine is smaller than that of pyridine by 10.1 kcal·mol^{-1}.[18] This compares well to the F effect of the 3-CF_3 in pyridine[22] (10.3 kcal·mol^{-1}). In water carboxylic acid pKs lead to σ_m values for the 3-aza substituent close to, or slightly larger than, the σ_m value for CF_3, see: Johnson, C. D. *The Hammett Equation*; Cambridge University Press: London, 1973; p 101.

(25) For **4** the effect of substituting a methyl by a phenyl on the carbonyl was evaluated from the difference in PA between acetophenone and benzophenone.[18] Similar reasonings were applied to evaluate the effect of N substitution in **6** and **7** by considering experimental PAs of various acetamides and formamides.[18]

(26) Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 125–191.

(27) Arnold, Z.; Krchňák, V.; Trška, P. *Tetrahedron Lett.* **1975**, 347–348.

PAs, which are close to the values calculated for this site. In the case of 7 an equal basic strength is forecasted for the carbonyl oxygen and for the pyridine nitrogen by either method of calculation. However, both methods fail to reproduce accurately the experimental PA. This lack of fit precludes any reasonable assignment of the preferred site of protonation. The amino nitrogen of nornicotine (1) seems to be the favored site of protonation (about 3 kcal·mol^{-1}, stronger than the pyridine nitrogen) when one compare the $PA_{AM1corr}$ and PA_{exp}. However the empirical substituent effect model gives a difference of only 1 kcal·mol^{-1} in favor of the amino nitrogen. Though the gas-phase basicity order of the two sites seems to be established, we maintain a reserve on the quantitative difference. The case of nicotine (2) is more clear-cut. The amino nitrogen appears as more basic than the pyridine nitrogen by at least 4 kcal·mol^{-1}. This is confirmed by the agreement between the PAs calculated for the amino site and the experimental PA.

Conclusion

The two basic sites present in nicotines 1 and 2, and in nicotinamides 6 and 7 are of close strength in the gas phase. Comparisons between experimental PAs and the results of AM1 calculations and empirical substituent effect estimations enabled us to assign the favored site of protonation for all the compounds included in this study, except in the case of *N,N*-diethylnicotinamide (7). For this molecule, calculated PAs obtained for each potential site of protonation are very close. This is not the case for nicotinamide (6) for which the preferred site of protonation is undoubtly the pyridine nitrogen. The same conclusion applies for the other carbonyl derivatives 3–5. On the contrary, nornicotine (1) and nicotine (2) appear to be preferentially protonated on the five membered ring amino nitrogen in the gas phase. The relevance of the present results to the behavior of bases 1–7 in solution will be discussed in a future paper.

Acknowledgment. We wish to thank Prs. O. Exner and R. W. Taft for their valuable comments.

Registry No. 1, 494-97-3; 1·H$^+$, 133777-61-4; 2, 54-11-5; 2·H$^+$, 19527-02-7; 3, 350-03-8; 3·H$^+$, 17548-86-6; 4, 5424-19-1; 4·H$^+$, 17548-92-4; 5, 93-60-7; 5·H$^+$, 76137-41-2; 6, 98-92-0; 6·H$^+$, 38719-50-5; 7, 59-26-7; 7·H$^+$, 133777-62-5.

Supplementary Material Available: Atomic coordinates, bond lengths, and bond and dihedral angles calculated by the AM1 method are given for molecules 1–7, for the protonated structures indicated in Table II, and for *N,N*-diethylacetamide (DEAC) and *N,N*-dimethylbenzamide (DMBZ) (neutral molecules and carbonyl protonated) (46 pages). Ordering information is given on any current masthead page.

Intramolecular Cyclopropanation–Ring Fragmentation Leading to Spirocyclic Ring Construction: A Stereoselective Synthesis of β-Chamigrene

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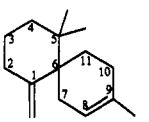
Received August 7, 1990

The transannular cyclopropanation of a keto carbene generated by $Rh_2(OAc)_4$ catalysis on a bicyclic dihydropyran nucleus provided a key oxatricyclic ketone intermediate for the synthesis of the [6.6] spirocyclic ring construction. Selective fragmentation of the cyclopropane followed by hydrolytic cleavage of the C–O bond provided the spirocyclic skeleton. Functional group manipulations to adjust oxidation states led to a total synthesis of (±)-β-chamigrene in 14 steps without the use of protection/deprotection schemes.

Introduction

Several years ago we described methodology for intramolecular cyclopropanation of dihydropyrans to form strained oxatricyclic ketones.[1] The cyclopropanation reaction was mediated by a $Rh_2(OAc)_4$-catalyzed decomposition of an α-diazo ketone. This reaction proceeded in high yield and proved to be generally reliable for the formation of small- and medium-sized tricyclic compounds. Regioselective ring fragmentation of the cyclopropane produced oxabicyclic ketones and eventually 6-, 7-, 8-, or 9-membered ring carbocycles as summarized in Scheme I. We wish to report a total synthesis of the spirocyclic sesquiterpene (±)-β-chamigrene (1) by this cyclopropanation–fragmentation strategy using a more highly substituted dihydropyran.



(±)- β-chamigrene 1

β-Chamigrene was first isolated in 1967 from the leaves of *Chamaecyparis taiwanensis*.[2] This rather simple molecule presents the synthetic challenge of constructing two contiguous quaternary carbon centers. Earlier syntheses successfully addressed this problem, using different strategies.[3a-c] We benefitted from these published

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(2) Ito, S.; Endo, K.; Yoshida, T.; Yatagai, M.; Kodama, M. *J. Chem. Soc., Chem. Commun.* **1967**, 186.

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0022-3263/91/1956-4494$02.50/0