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Gas phase versus solution chemistry: on the reversal of regiochemistry of methylation of sp^2- and sp^3-nitrogens

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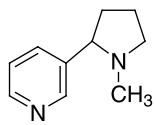
Abstract—The nicotine analogue 3-(*N*,*N*-dimethylaminomethyl)pyridine **2**, which reacts with methyl iodide in acetonitrile exclusively on the sp^3-nitrogen, methylates exclusively on the pyridine nitrogen with trimethyloxonium in the gas phase. Calculations at the RHF/6-31G**//6-31G** level suggest that there is an interaction between the side chain nitrogen and hydrogens on the aromatic ring. This interaction affects both the conformation of **2** as well as the relative basicity of its two nitrogens. Calculations also indicate that, in the gas phase, the pyridine methylated product (no counterion) is more stable than the pyrrolidine methylated product.

The nicotine **1** analogue 3-(*N*,*N*-dimethylaminomethyl)-pyridine **2** reacts exclusively at the sp^3-nitrogen with methyl iodide in acetonitrile solution to give exclusively the quaternary salt **3** (Scheme 1; counterion, not shown, is I^-).[1] This regiochemistry is due to two well known factors: (1) that the rate of the Menschutkin reaction is strongly correlated to the basicity of the nitrogen atom; and (2) that sp^3-amines are significantly more basic than sp^2-pyridine nitrogens.[2,3] We herein report that the gas phase methylation of **2** with trimethyloxonium **5** results exclusively in the formation of **4**, a reversal of methylation regiochemistry. We also report the results of calculations at the RHF/6-31G**//6-31G** level which demonstrate weak hydrogen bonding between the sp^3-nitrogen of **2** and two of its pyridine ring hydrogens [C(2)–H and C(4)–H], thereby decreasing its sp^3-nitrogen nucleophilicity. Calculations demonstrate that, in the isodesmic reaction between **3** and **4**, **4** is the thermodynamically more stable isomer. These two theoretical results suggest an explanation for the shift to pyridine methylation in the gas phase.



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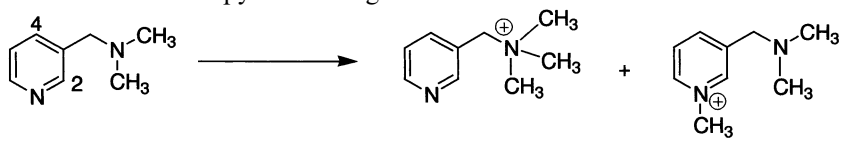
All experiments were performed in a Finnigan MAT quadrupole ion trap mass spectrometer (ITMS). Samples were introduced into the vacuum chamber through a heated leak valve at a static nominal pressure of



2 **3** **4**

Reagent	Product	
CH_3I in acetonitrile (Ref. 1)	Exclusive product (as the iodide)	Not observed
$(CH_3)_3O^+$ (**5**) (This work)	Not observed	Exclusive product

Scheme 1.

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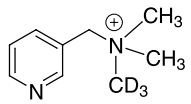
1–2×10^{-6} torr. Dimethyl ether was added to nominally 1–2×10^{-5} torr. Helium buffer gas was added to increase the pressure to one millitorr. Solids were introduced to the chamber via a heated direct insertion probe. Trimethyloxonium and trimethyloxonium-d_6, generated from dimethyl ether and dimethyl ether-d_6 ions, respectively, was isolated and permitted to react with the neutral analyte for ca. 100 ms. The $(M+CH_3)^+$ and $(M+CD_3)^+$ product ions were isolated using the apex isolation method[4] and subjected to resonance collisionally activated dissociation (CAD), typically at a q_z of 0.3.

When **2** is methylated with trimethyloxonium, the only fragment observed from $(M+CH_3)^+$ is m/z 108, due to loss of 43 u. The loss of 43 u is best rationalized as the loss of CH_3–N=CH_2, which can readily occur from the dimethylamino portion of the molecule (see Scheme 2). The $(M+CD_3)^+$ ion also dissociated exclusively by loss of 43 u to form m/z 111, which means the same loss of CH_3–N=CH_2 occurs.

The loss of 43 u from either the $(M+CH_3)^+$ or $(M+CD_3)^+$ ions of **2** cannot be readily rationalized if deuteriomethylation had occurred on the sp^3-nitrogen to form **6**. In that case, a mixture of CH_3–N=CH_2, CD_3–N=CH_2 and CH_3N=CD_2 fragments would have resulted from the $(M+CD_3)^+$ ion, corresponding to loss of 43, 46, and 45 u, because the two methyl and one deuteriomethyl groups have equivalent chances of being eliminated when all are bound to the same nitrogen. The alkylating methyl group is not directly involved in the fragmentation process.



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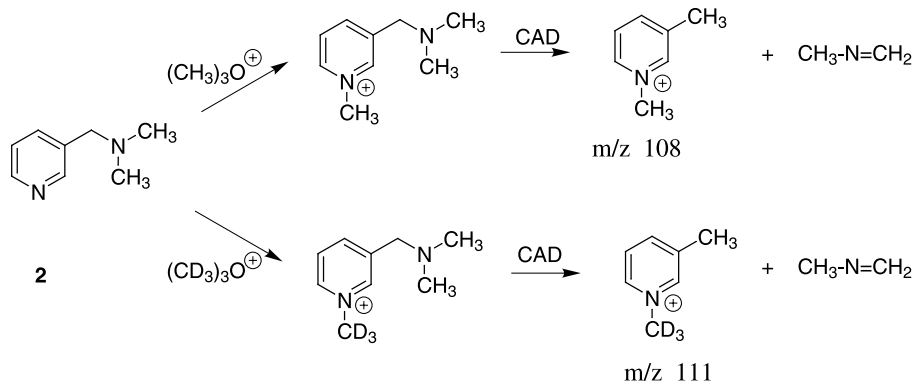
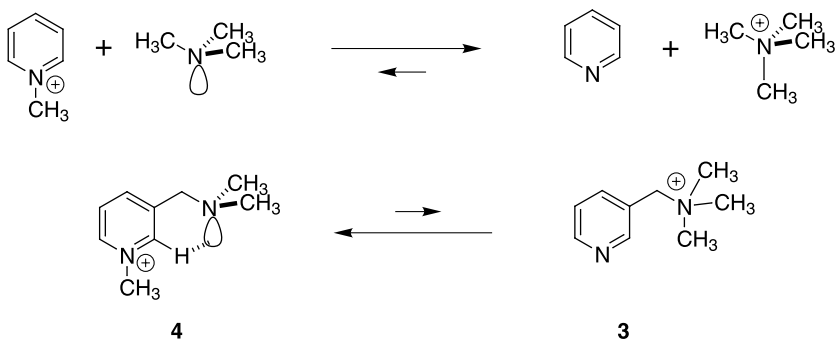
To evaluate the dichotomy between the gas phase and solution methylation reactions of **2**, we consider in turn gas phase and solution methylation reactions.

The isodesmic reactions shown in Scheme 3 were examined at the RHF/6-31G**//6-31G** level using Cadpac.[5] The reaction between methylpyridinium and trimethylamine is found to favor tetramethylammonium and pyridine by 12.2 kJ mol^{-1}, corresponding to a ratio of more than 100:1 at room temperature in the gas phase. In contrast, ion **4** is calculated to be more stable than **3** by 21.4 kJ mol^{-1}, corresponding to a room temperature/gas phase ratio of over 5000:1 in favor of **4**.

This contrast may in part be explained by the decrease in the basicity of the sp^3-amine in **2** and **4**, because of the presence of the electron withdrawing properties of the pyridine ring. In addition, calculations reveal a weak hydrogen bond between the sp^3-amine's lone pair of electrons and the C(2)–H and C(4)–H of the pyridine ring in **2** and **4**. This is seen by examining the preferred conformations of these and related model compounds, as determined by theory. The side chain of **3** is perpendicular to the plane of the pyridine ring, i.e. τ_1[C(2 or 4)–C(ipso)–C_α–N] = ca. 90°, similar to that found for ethylbenzene,[6] propylbenzene,[6] and isobutylbenzene[7] **7**



Scheme 2.



4 **3**

Scheme 3.

and the monoprotonated **8** (see Fig. 1). However, in the pyridine ring methylated **4** and 3-(dimethylamino)-methylpyridine **2**, a very different conformation is found. Here, the lone pair on the side chain nitrogen points towards either the C(2)– or C(4)–hydrogen (see data in Fig. 1). The torsional angle found for *N*,*N*-dimethylbenzylamine **9** in this work is consistent with the literature experimental data and the highest level of theory in the earlier calculations.[12] The sp^3-nitrogen lone pair is within hydrogen bonding distance to the C(2)– and C(4)–hydrogens. This is reminiscent of the formyl hydrogen bond recently identified by Corey et al.[8,9] and investigated computationally by one of us (J.G.).[10,11]

If this analysis is correct, the strength of the nitrogen lone pair–aromatic ring hydrogen interaction would increase as the polarization of the C(aromatic)–H bond increases. This would lead to a decrease in the torsional angle, as the acyclic nitrogen lone-pair–ring hydrogen interaction would be more able to counteract the steric effects pushing the side chain out of the plane. The calculated geometries are consistent with this interpretation. As the *ortho* aromatic-hydrogen increases its positive charge, the torsional angle shifts from perpendicular toward the plane of the aromatic ring, indicating an increased nitrogen lone pair–hydrogen bond. This trend is shown in Fig. 1. The nitrogen lone pairs in **4**, **2** and **9** are oriented to point in the direction of an aromatic hydrogen. The calculations show that for **4**, the nitrogen lone pair prefers to interact with the C(2)–H by ca. 5 kJ/mol. For **2**, it prefers the C(4)–H by ca. 2 kJ/mol. This switch in orientation is consistent with a polarization phenomenon, the interaction increasing with C(2)–H as the pyridine nitrogen becomes more positively charged.

The regiochemistry of the gas phase methylation of **2** may now be explained based on both kinetic and thermodynamic features: the sp^3-amine's nucleophilicity is decreased by virtue of its weak hydrogen bonding to the C(2)–H and presumably C(4)–H. In addition, as **4** is significantly more stable than **3**, thermodynamic considerations also favor pyridine methylation.

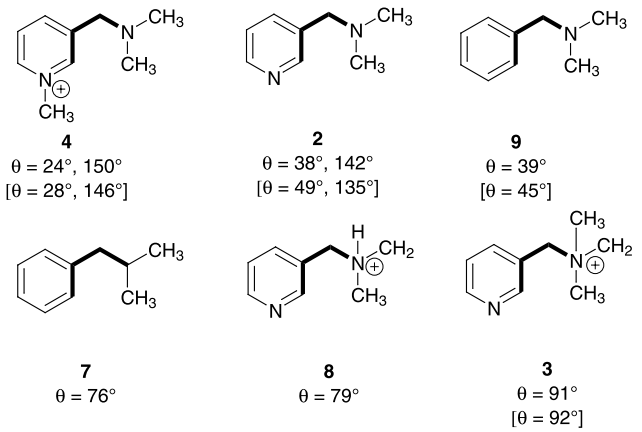


Figure 1. Torsion angles $\tau_1(C_{aromatic}–C_{ipso}–C_\alpha–N)$ or $\tau_1(C_{aromatic}–C_{ipso}–C_\alpha–C_\beta)$ from RHF/3-21G calculations and [in brackets] RHF/6-31G** calculations.

Acetonitrile is known to more effectively solvate pyridine than either ammonia or trimethylamine.[7] By analogy, acetonitrile would more effectively solvate the pyridine ring nitrogen than the dimethylaminomethyl nitrogen in **2**. In acetonitrile, pyridine methylation may be energetically less favored in part because pyridine desolvation must occur first.

In conclusion, a reversal in regiochemistry is observed for gas-phase[13] and condensed methylations: A counterbalancing of effects explain the results.[14] In the gas phase, sp^2-nitrogen methylation is explained by a weak hydrogen bonding interaction between the sp^3-nitrogen lone pair and the C(2)- and C(4)-hydrogen atoms which acts against sp^3-methylation. In acetonitrile, preferential pyridine solvation acts against sp^2-nitrogen methylation.

Acknowledgements

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References

1. Seeman, J. I.; Whidby, J. F. *J. Org. Chem.* **1976**, *41*, 3824–3826.
2. Seeman, J. I. *Pure Appl. Chem.* **1987**, *59*, 1661–1672.
3. Abboud, J.-L.; Notario, R.; Bertran, J.; Sola, M. *Prog. Phys. Org. Chem.* **1993**, *19*, 1–182.
4. Weber-Grabau, M.; Kelley, P. E.; Syka, J. E. P.; Bradshaw, S. C.; Brodbelt, J. S. *Proceedings of the 35th ASMS Conference of the American Society for Mass Spectrometry*; Denver, CO, May 24–29, 1987; p. 1114.
5. CADPAC: The Cambridge Analytic Derivatives Package Issue 6, Cambridge, 1995. A suite of quantum chemistry programs developed by R. D. Amos with contributions from I. L. Alberts, J. S. Andrews, S. M. Colwell, N. C. Handy, D. Jayatilaka, P. J. Knowles, R. Kobayashi, K. E. Laidig, G. Laming, A. M. Lee, P. E. Maslen, C. W. Murray, J. E. Rice, E. D. Simandiras, A. J. Stone, M.-D. Su, and D. J. Tozer.
6. Breen, P. J.; Warren, J. A.; Bernstein, E. R.; Seeman, J. I. *J. Am. Chem. Soc.* **1987**, *109*, 3453–3455.
7. Seeman, J. I.; Secor, H. V.; Breen, P. J.; Grassian, V. H.; Bernstein, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 3140–3150.
8. Corey, E. J.; Rohde, J. J.; Fischer, A.; Azimioara, M. D. *Tetrahedron Lett.* **1997**, *38*, 33–36.
9. Corey, E. J.; Rohde, J. J. *Tetrahedron Lett.* **1997**, *38*, 37–40.
10. Goodman, J. M. *Tetrahedron Lett.* **1992**, *33*, 7219–7222.

11. Mackey, M. D.; Goodman, J. M. *Chem. Commun.* **1997**, 2383–2384.
12. Li, S.; Bernstein, E. R.; Seeman, J. I. *J. Phys. Chem.* **1991**, *96*, 8808–8813.
13. For a leading discussion of related gas phase reactions, see: Zhong, M.; Brauman, J. I. *J. Am. Chem. Soc.* **1996**, *118*, 636–641.
14. The two reactions being compared herein (Scheme 1) differ not only in terms of the reaction medium, but also in terms of alkylating reagent and reaction type (i.e. formation of a salt from two neutral molecules versus reaction of one neutral molecule with a carbocation, to form another neutral molecule and another carbocation). These additional issues will be discussed in detail in our full paper.