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SUPPORTING INFORMATION

Gas Phase Protonated Nicotine Is a Mixture of Pyridine- and Pyrrolidine-Protonated Conformers: Implications for Its Native Structure in the Acetylcholine Receptor

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S8. Extrapolation of the energy difference between the various NIC protomers to the MP2/CBS limit using the (4-5) polynomial: $E_{aVnZ}(n) = E_{CBS} + \frac{A}{(n+1)^4} + \frac{B}{(n+1)^5}$.

S9. Total MP2/CBS energies (E_e), zero-point corrected energies (E_o), standard state (T = 298.15 K) enthalpies ($H°$), and standard state free energies ($G°$) in au of Pyri-NIC-H$^+$ and Pyrro-NIC-H$^+$. Thermal corrections are computed at the ωB97XD/aug-cc-pVDZ level of theory. Relative energies (kcal/mol) are listed in parentheses.

S10. Structural differences between Pyri-NIC-H$^+$ / Pyrro-NIC-H$^+$ at the MP2/aug-cc-pVTZ level of theory and the crystal structure reported by Morales-Perez et.al.[1]

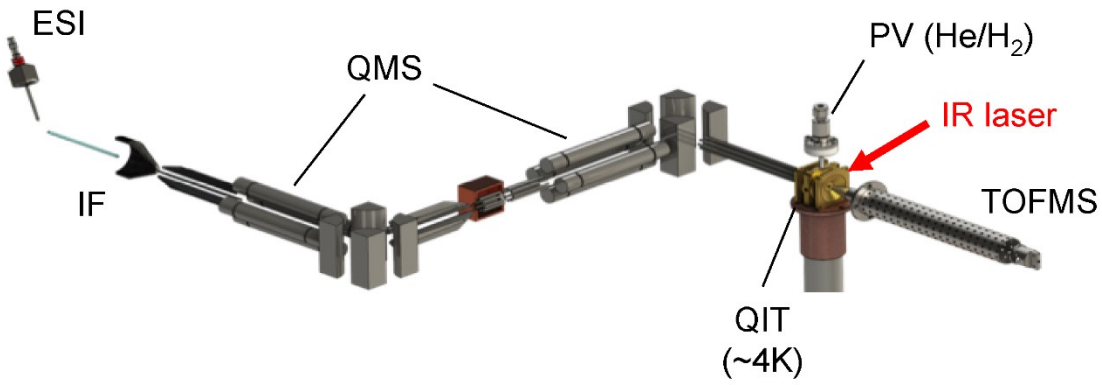


Figure S1. Experimental setup. ESI: Electrospray ion source, IF: Ion funnel, QMS: Quadrupole mass spectrometer, PV: Pulsed valve, QIT: Quadrupole ion trap, TOFMS: Time-of-flight mass spectrometer.

S2. Cartesian coordinates of Pyri-NIC-H^+ at the ωB97XD/aug-cc-pVDZ level of theory.

Pyri-NIC-H^+ S anti

C	1.38083	-1.65055	0.00638
C	0.80361	-0.35001	-0.62519
N	1.61103	0.73936	-0.09006
C	2.84921	0.16997	0.44315
C	2.38214	-1.14337	1.05360
C	-0.66460	-0.15224	-0.29885
C	-1.67308	-0.89305	-0.92729
C	-3.01329	-0.72135	-0.58256
C	-3.34212	0.20180	0.39123
N	-2.35536	0.90675	0.97507
C	-1.05206	0.76238	0.66677
C	1.79779	1.85075	-1.00614
H	0.88074	-0.41134	-1.72680
H	0.60470	-2.29815	0.43040
H	1.90054	-2.22385	-0.76984
H	1.88509	-0.95564	2.01443
H	3.19968	-1.85082	1.22499
H	3.59039	-0.01537	-0.35844
H	3.29876	0.85858	1.16854
H	-0.32408	1.37964	1.18891
H	-4.35773	0.40414	0.72144
H	-3.80147	-1.29446	-1.06516
H	-1.40526	-1.61591	-1.69905
H	0.82561	2.26892	-1.30239
H	2.33895	1.55334	-1.92441
H	2.36860	2.64443	-0.51000
H	-2.60491	1.58773	1.68572

S3. Cartesian coordinates of Pyrro-NIC-H^+ at the ωB97XD/aug-cc-pVDZ level of theory.

Pyrro-NIC-H^+ N anti

C	1.67941	0.74062	0.99061
C	0.73502	-0.05654	0.34122
C	1.18967	-0.92140	-0.66018
N	2.46021	-1.01430	-1.04146
C	3.35221	-0.24663	-0.40886
C	3.01378	0.63963	0.61493
C	-0.72858	0.02158	0.67972
N	-1.50004	0.66413	-0.47636
C	-2.90762	0.17065	-0.33891
C	-2.71671	-1.29656	0.01705
C	-1.47970	-1.30692	0.93959
C	-1.34886	2.13782	-0.56426
H	-3.45402	0.36344	-1.26742
H	-3.60854	-1.70930	0.49700
H	-2.53202	-1.88202	-0.89321
H	-1.77123	-1.35038	1.99383
H	-0.83610	-2.16949	0.74677
H	-3.36490	0.74297	0.47750
H	-0.87613	0.71202	1.51892
H	0.49371	-1.58633	-1.18444
H	4.38858	-0.34657	-0.73420
H	3.78279	1.23546	1.10313
H	1.37890	1.42345	1.78712
H	-1.75915	2.58235	0.34767
H	-1.89567	2.50203	-1.43897
H	-0.28538	2.37682	-0.65812
H	-1.11377	0.26323	-1.33628

Pyrro-NIC-H^+ N syn

N	2.93054	0.65191	0.84104
C	1.61622	0.59930	1.04753
H	1.23985	1.18818	1.88921
C	0.73406	-0.15532	0.26985
C	1.27060	-0.90094	-0.78556
H	0.64093	-1.52660	-1.42183
C	2.63851	-0.84997	-1.01426
H	3.09637	-1.41726	-1.82253
C	3.42604	-0.05945	-0.17222
H	4.50510	0.00034	-0.32184
C	-0.73773	-0.12247	0.56739
H	-0.91329	0.45128	1.48745
C	-1.49681	-1.45334	0.62288
H	-1.44232	-1.86397	1.63517
H	-1.03185	-2.18738	-0.04412
C	-2.94739	-1.14104	0.17807
H	-3.67212	-1.30754	0.98028
H	-3.24293	-1.77593	-0.66369
C	-2.94535	0.33733	-0.22916
H	-3.25354	0.99580	0.59086
H	-3.53961	0.57561	-1.11651
N	-1.50425	0.65406	-0.49957
C	-1.18788	2.10331	-0.56167
H	-1.42418	2.54910	0.40955
H	-0.12391	2.22543	-0.78291
H	-1.79476	2.56625	-1.34527
H	-1.24944	0.24044	-1.40108

S4. Total energies (E_e), zero point corrected energies (E_o), the standard state enthalpies ($H°$), and standard state free energies ($G°$) in a.u. of Pyri-NIC-H$^+$ and Pyrro-NIC-H$^+$ at the ωB97XD/aug-cc-pVDZ level of theory. Relative energies (kcal/mol) are listed in parentheses.

Conformer	E_e	E_o	$H°$	$G°$
Pyri-NIC-H$^+$	-499.26844 (0.00)	-499.02650 (0.00)	-499.01494 (0.00)	-497.69637 (0.00)
Pyrro-NIC-H$^+$ (N anti)	-499.26748 (0.61)	-499.02401 (1.56)	-499.01253 (1.51)	-497.69684 (1.50)
Pyrro-NIC-H$^+$ (N syn)	-499.26740 (0.66)	-499.02400 (1.57)	-499.01234 (1.63)	-497.69836 (0.80)

S5. Cartesian coordinates of Pyri-NIC-H^+ at the MP2/aug-cc-pV*n*Z; *n* = D, T levels of theory.

Pyri-NIC-H^+ MP2/aug-cc-pVDZ

C	1.37935	-1.65461	0.01517
C	0.80946	-0.34406	-0.62356
N	1.60444	0.75345	-0.05458
C	2.86639	0.16276	0.43099
C	2.38896	-1.14346	1.06498
C	-0.65989	-0.15324	-0.30531
C	-1.67030	-0.90207	-0.94726
C	-3.01932	-0.72878	-0.59671
C	-3.35871	0.20030	0.39173
N	-2.36256	0.90784	0.98124
C	-1.04735	0.76986	0.67692
C	1.79323	1.85926	-0.99749
H	0.90551	-0.39302	-1.72900
H	0.59128	-2.29429	0.44054
H	1.90005	-2.23306	-0.76238
H	1.88916	-0.93236	2.02330
H	3.20209	-1.86047	1.24489
H	3.56866	-0.04123	-0.40553
H	3.35248	0.85292	1.13652
H	-0.32071	1.38914	1.20562
H	-4.37703	0.40378	0.72477
H	-3.81244	-1.30134	-1.08174
H	-1.39799	-1.62304	-1.72473
H	0.81484	2.26849	-1.29828
H	2.33342	1.53711	-1.91166
H	2.36765	2.66146	-0.51175
H	-2.61697	1.59036	1.69775

Pyri-NIC-H^+ MP2/aug-cc-pVTZ

C	1.36937	-1.64383	0.01835
C	0.80382	-0.34210	-0.61803
N	1.59854	0.74625	-0.05959
C	2.85240	0.15883	0.42100
C	2.37715	-1.13557	1.05556
C	-0.65623	-0.15107	-0.30508
C	-1.65811	-0.89019	-0.94338
C	-2.99511	-0.72358	-0.59621
C	-3.33347	0.19361	0.38417
N	-2.34733	0.89748	0.97104
C	-1.04232	0.76100	0.66915
C	1.78384	1.84924	-0.99257
H	0.89896	-0.39661	-1.71250
H	0.59019	-2.27429	0.44492
H	1.88043	-2.22062	-0.75098
H	1.88609	-0.92113	2.00467
H	3.17994	-1.84730	1.23441
H	3.54307	-0.04778	-0.41000
H	3.33986	0.84138	1.11555
H	-0.32169	1.37271	1.19392
H	-4.34195	0.39224	0.71374
H	-3.77801	-1.29077	-1.07824
H	-1.38649	-1.59921	-1.71670
H	0.81610	2.25866	-1.28678
H	2.31554	1.53269	-1.89998
H	2.35610	2.64041	-0.51168
H	-2.60216	1.57631	1.68150

S6. Cartesian coordinates or Pyrro-NIC-H^+ at the MP2/aug-cc-pV*n*Z; *n* = D, T levels of theory.

Pyrro-NIC-H^+ MP2/aug-cc-pVDZ

C	-1.44123	-1.07311	-1.18500
C	-0.70140	-0.61762	0.07595
N	-1.48035	0.65110	0.48808
C	-2.86847	0.57083	-0.15678
C	-2.91135	-0.81374	-0.82044
C	0.76512	-0.29679	-0.02164
C	1.69624	-0.87224	0.86497
C	3.04808	-0.51901	0.73571
C	3.41412	0.40735	-0.26047
N	2.53239	0.97298	-1.11631
C	1.23961	0.61075	-0.99368
H	-3.62346	0.73292	0.62314
H	-3.26760	-1.57238	-0.10614
H	-3.58438	-0.81635	-1.68862
H	-1.13241	-0.47004	-2.05450
H	-1.22108	-2.12754	-1.40291
H	-2.92928	1.38267	-0.89477
H	-0.88129	-1.33795	0.89182
H	0.55681	1.07014	-1.72150
H	4.45817	0.71018	-0.38202
H	3.80805	-0.94690	1.39427
H	1.37308	-1.58890	1.62774
C	-1.49474	0.85135	1.97080
H	-0.96811	1.44131	0.07462
H	-0.45727	0.82886	2.33116
H	-2.07661	0.03318	2.41498
H	-1.95913	1.81939	2.19827

Pyrro-NIC-H^+ MP2/aug-cc-pVTZ

C	-1.41627	-1.01823	-1.24682
C	-0.72724	-0.61022	0.04656
N	-1.51512	0.63749	0.41516
C	-2.95745	0.32992	0.08371
C	-2.90720	-0.80955	-0.94998
C	0.73628	-0.31245	0.00275
C	1.62475	-0.91896	0.89175
C	2.97313	-0.59105	0.81326
C	3.38151	0.34485	-0.13695
N	2.54070	0.94162	-0.99412
C	1.25083	0.60223	-0.92168
H	-3.43655	0.03378	1.01372
H	-3.33832	-1.71086	-0.52034
H	-3.47276	-0.56334	-1.84431
H	-1.07883	-0.37502	-2.06119
H	-1.17362	-2.04406	-1.51348
H	-3.42258	1.24426	-0.27622
H	-0.95061	-1.32849	0.84059
H	0.60572	1.08682	-1.65197
H	4.42287	0.62943	-0.21888
H	3.69683	-1.04509	1.47578
H	1.27021	-1.63870	1.62077
C	-1.29024	1.11326	1.80478
H	-1.18601	1.36842	-0.22170
H	-0.23105	1.32112	1.93293
H	-1.60834	0.32643	2.48373
H	-1.87761	2.01265	1.96901

Pyrro-NIC-H^+ N syn MP2/aug-cc-pVDZ

N	-0.65760	-2.93452	-0.87255
C	-0.57353	-1.60403	-1.07427
H	-1.12907	-1.21236	-1.93560
C	0.18021	-0.73013	-0.26364
C	0.89471	-1.27636	0.82353
H	1.51659	-0.65538	1.47812
C	0.81217	-2.65872	1.04652
H	1.35114	-3.12885	1.87293
C	0.02659	-3.44189	0.17657
H	-0.05549	-4.52260	0.32492
C	0.16432	0.74331	-0.55536
H	-0.37652	0.94069	-1.49802
C	1.48632	1.51474	-0.52118
H	2.06990	1.32825	-1.43265
H	2.09056	1.17871	0.33662
C	1.06533	2.99784	-0.36030
H	1.02242	3.50066	-1.33589
H	1.76983	3.55275	0.27273
C	-0.35210	2.95964	0.26612
H	-1.12842	3.31266	-0.42675
H	-0.45237	3.49663	1.21878
N	-0.64228	1.49125	0.51096
C	-2.09576	1.14323	0.54192
H	-2.51970	1.38390	-0.44176
H	-2.19559	0.07037	0.75074
H	-2.58485	1.73744	1.32470
H	-0.23125	1.22173	1.41652

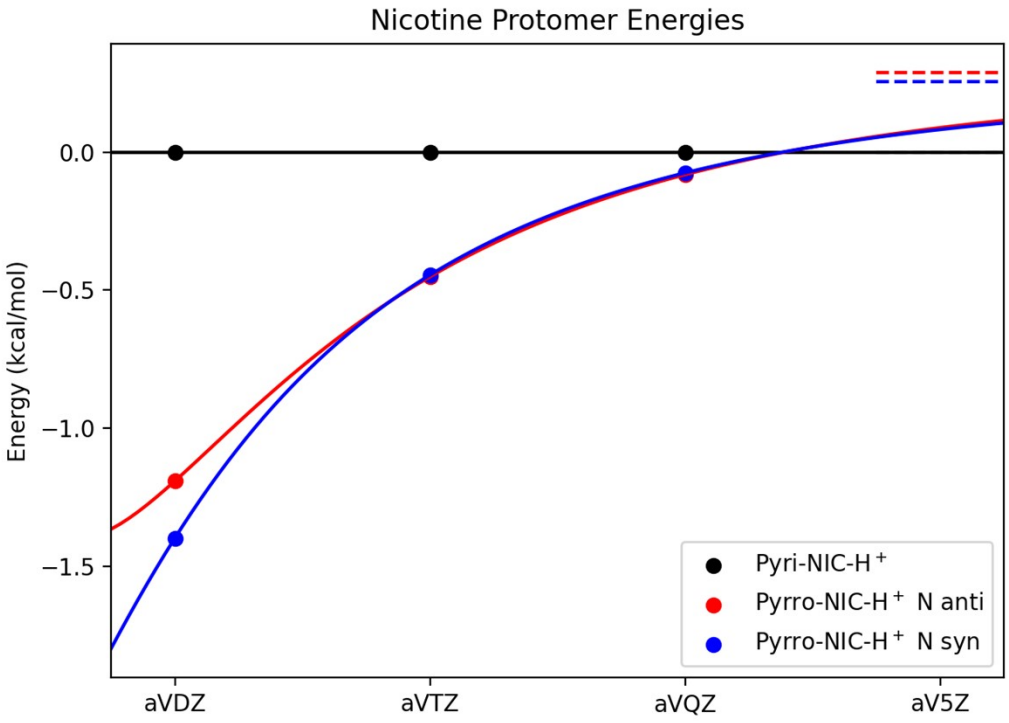
Pyrro-NIC-H^+ N syn MP2/aug-cc-pVTZ

N	-0.61056	-2.92499	-0.87030
C	-0.54419	-1.60579	-1.06978
H	-1.08634	-1.22514	-1.93103
C	0.17870	-0.73075	-0.25567
C	0.87483	-1.26512	0.83242
H	1.47114	-0.64130	1.48978
C	0.80930	-2.63488	1.05295
H	1.33694	-3.09147	1.87872
C	0.05798	-3.42134	0.17835
H	-0.01132	-4.49205	0.32316
C	0.15997	0.73295	-0.54553
H	-0.36291	0.92726	-1.48633
C	1.46969	1.50188	-0.50156
H	2.08017	1.28819	-1.37546
H	2.04016	1.21289	0.38286
C	1.02395	2.96614	-0.42175
H	0.85592	3.36221	-1.42070
H	1.75970	3.59754	0.06833
C	-0.30427	2.93813	0.35372
H	-1.12297	3.40017	-0.19193
H	-0.25146	3.37731	1.34668
N	-0.64938	1.47354	0.51027
C	-2.10537	1.17856	0.48006
H	-2.49058	1.49492	-0.48551
H	-2.24665	0.10902	0.61215
H	-2.59294	1.72981	1.27939
H	-0.28447	1.15093	1.41025

S7. Total MP2 energies of Pyri-NIC-H$^+$ and Pyrro-NIC-H$^+$ with the aug-cc-pVDZ (E_{aVDZ}), aug-cc-pVTZ (E_{aVTZ}), and aug-cc-pVQZ (E_{aVQZ}) basis sets and extrapolated MP2/CBS energies (E_{CBS}) in a.u. The MP2/aug-cc-pVQZ energies are calculated at the MP2/aug-cc-pVTZ geometries. Relative energies (kcal/mol) are listed in parentheses.

Conformer	E_{aVDZ}	E_{aVTZ}	E_{aVQZ}	E_{CBS}
Pyri-NIC-H$^+$	-497.90102 (0.00)	-498.34046 (0.00)	-498.47863 (0.00)	-498.58667 (0.00)
Pyrro-NIC-H$^+$ (N anti)	-497.90292 (-1.19)	-498.34118 (-0.45)	-498.47876 (-0.08)	-498.58621 (0.29)
Pyrro-NIC-H$^+$ (N syn)	-497.90325 (-1.40)	-498.34117 (-0.45)	-498.47875 (-0.08)	-498.58626 (0.26)

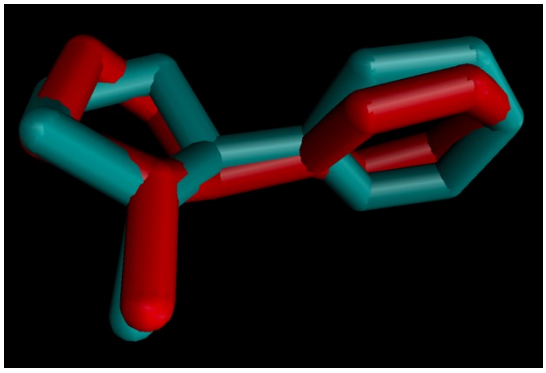
S8. Extrapolation of the energy difference between the various NIC protomers to the MP2/CBS limit using the (4-5) polynomial: $E_{aVnZ}(n) = E_{CBS} + \frac{A}{(n+1)^4} + \frac{B}{(n+1)^5}$.



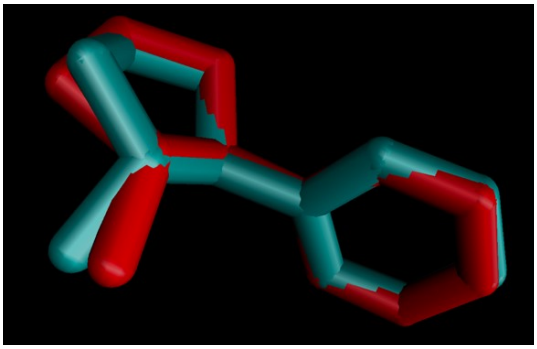
S9. Total MP2/CBS energies (E_e), zero-point corrected energies (E_o), standard state (T = 298.15 K) enthalpies ($H°$), and standard state free energies ($G°$) in au of Pyri-NIC-H^+ and Pyrro-NIC-H^+. Thermal corrections are computed at the ωB97XD/aug-cc-pVDZ level of theory. Relative energies (kcal/mol) are listed in parentheses.

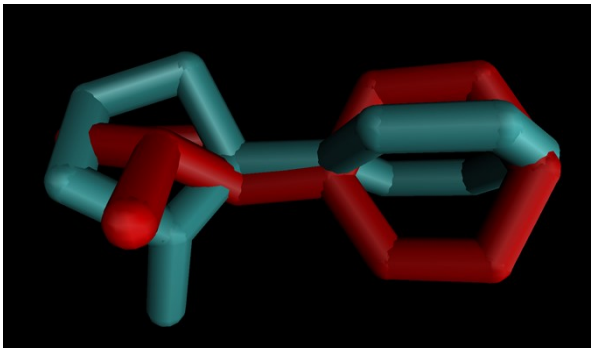
Conformer	E_e	E_o	$H°$	$G°$
Pyri-NIC-H^+	-498.58667 (0.00)	-498.34472 (0.00)	-498.33316 (0.00)	-498.38202 (0.00)
Pyrro-NIC-H^+ (N anti)	-498.58621 (0.29)	-498.34274 (1.25)	-498.33125 (1.20)	-498.38014 (1.18)
Pyrro-NIC-H^+ (N syn)	-498.58626 (0.26)	-498.34286 (1.17)	-498.33120 (1.23)	-498.38138 (0.40)

S10. Structural differences between Pyri-NIC-H^+(S, *trans*, *anti*) / Pyrro-NIC-H^+(N, *trans*, *syn* and N, *trans*, *anti*) at the MP2/aug-cc-pVTZ level of theory and the crystal structure reported by Morales-Perez et.al.[1] Geometries and RMSD values taken from heavy atoms only.



Structure of Pyri-NIC-H^+ (Red) compared to Crystal Ligand Geometry (Blue).[1] RMSD = 0.503





Structures of Pyrro-NIC-H^+ (N, *trans*, *anti*) (left, red) RMSD = 0.271 and (N, *trans*, *syn*) (right, red) RMSD = 1.620 compared to the Crystal Ligand Geometry (Blue).[1]

References

1. Morales-Perez, C. L.; Noviello, C. M.; Hibbs, R. E. X-ray structure of the human α4β2 nicotinic receptor. *Nature.* **2016**, *538*, 411-415. DOI: 10.1038/nature19785