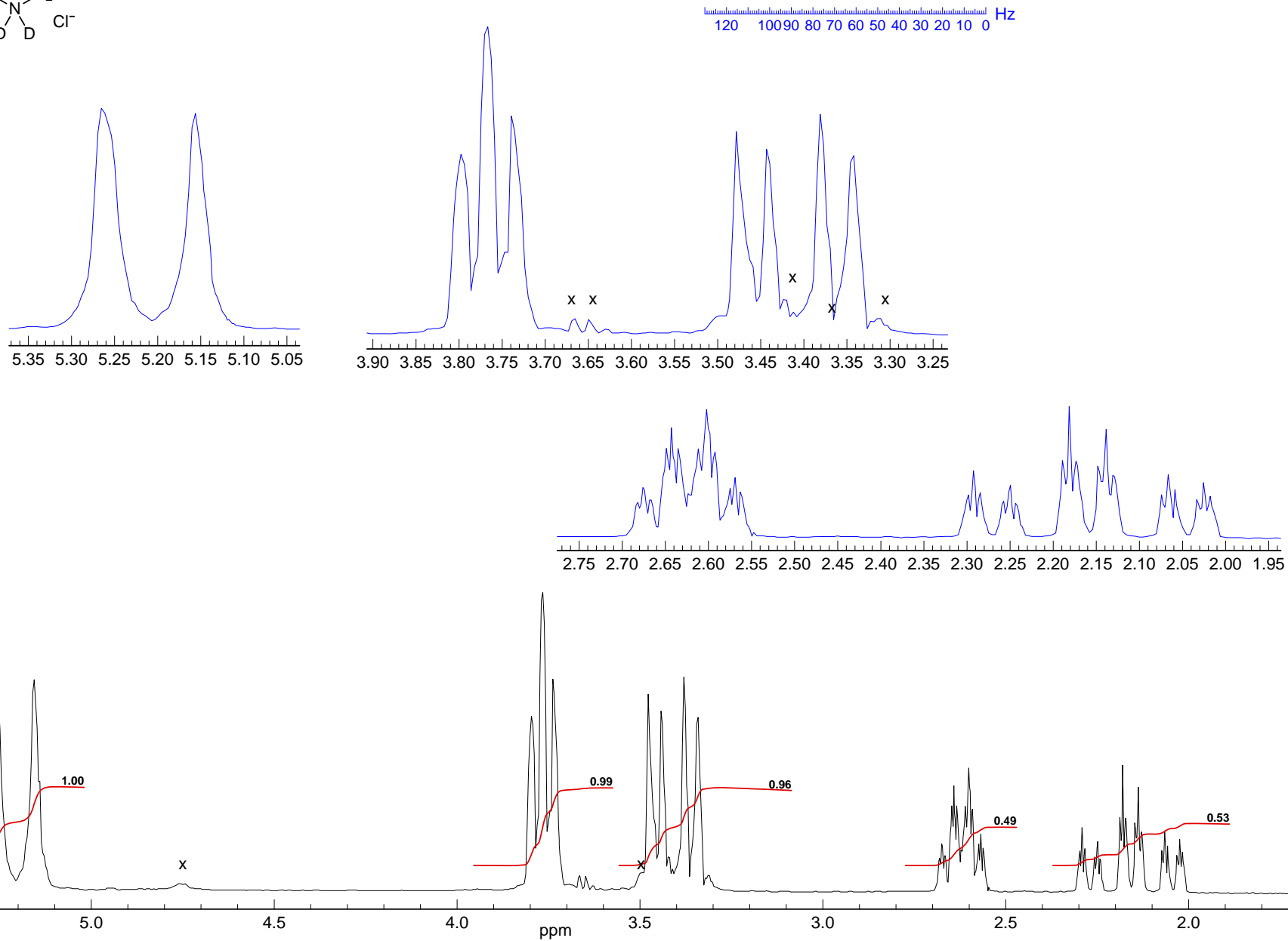
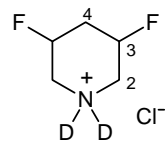


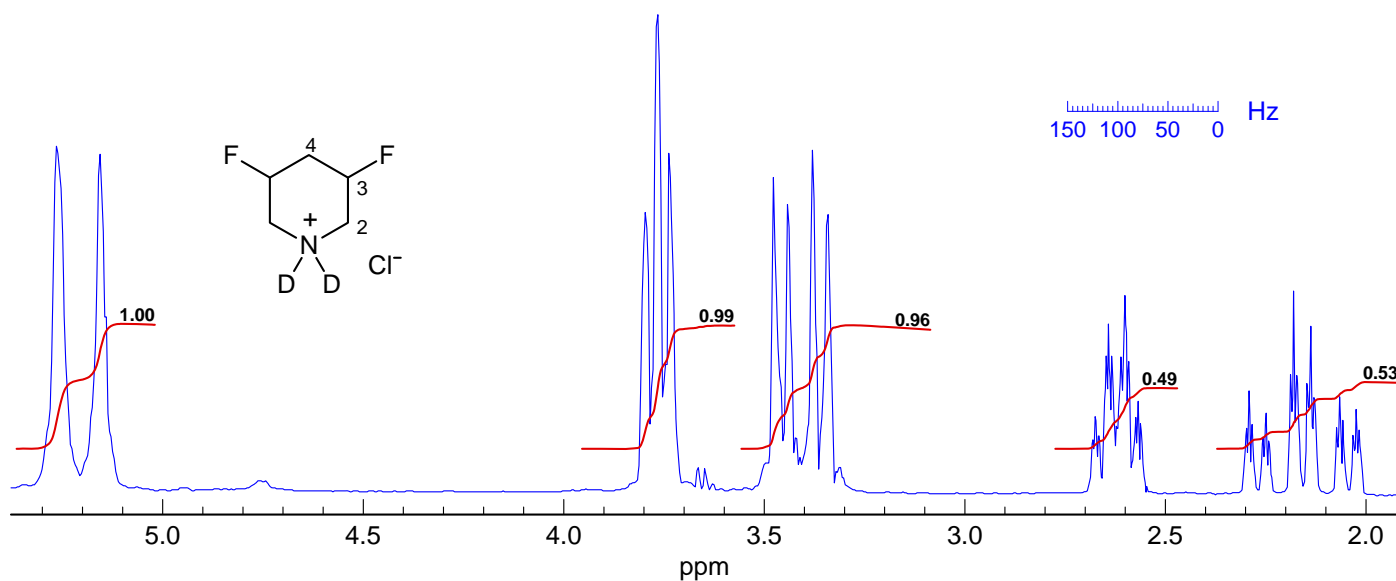
Problem R-10M (C₅H₉F₂N·HCl).

400 MHz ¹H NMR spectrum in D₂O

Source: *J. Am. Chem. Soc.* **2000**, 122, 544 (Reich digitized hard copy) g

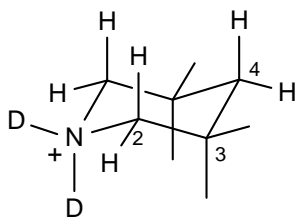


Problem R-10M. Interpret the room temperature 400 MHz ^1H NMR spectrum of a difluoropiperidine ammonium salt (D_2O solvent, expansions on next page, some minor impurities are marked x) and determine stereochemistry and conformation (J. P. Snyder, N. S. Chandrakumar, H. Sato, D. C. Lankin *J. Am. Chem. Soc.* **2000**, 122, 544).



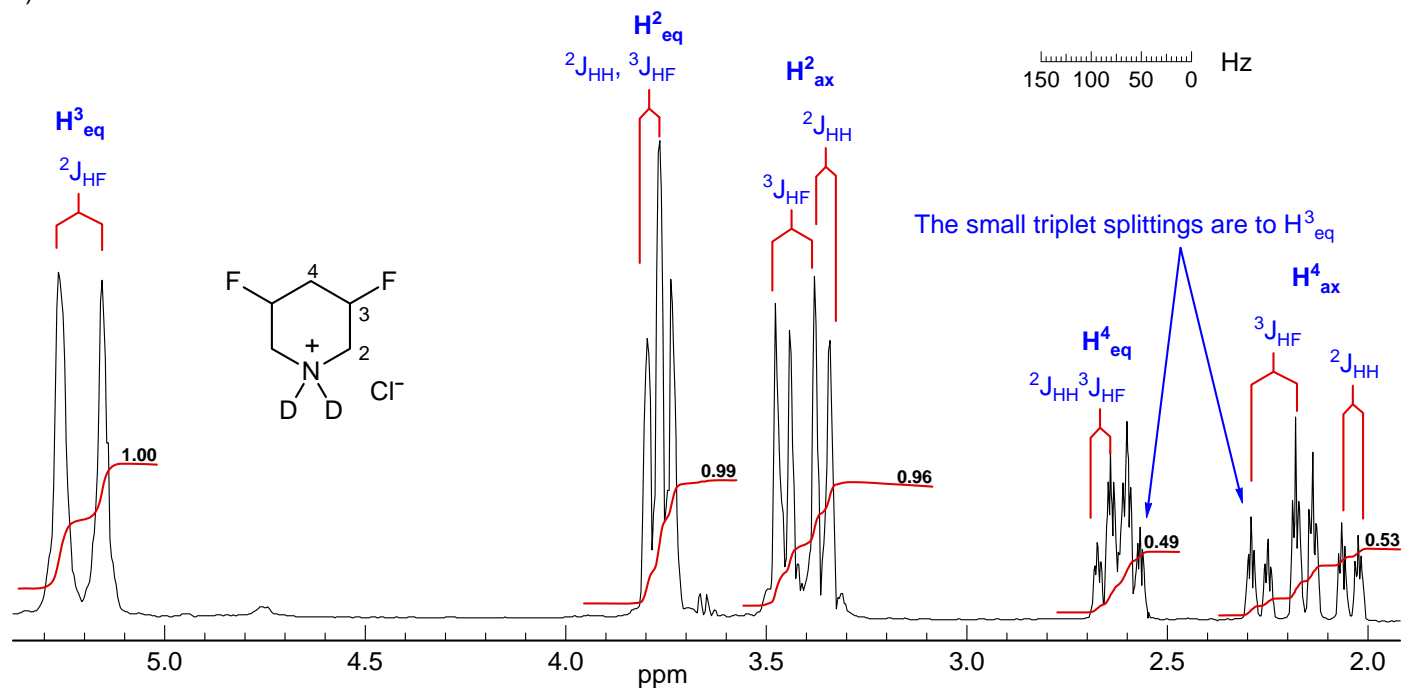
(a) Are the two fluorines cis or trans to each other? Explain briefly.

(b) Add the fluorines to the cyclohexane conformation below, and explain how you arrived at this conformation. Write the chemical shifts next to the protons on carbons 2, 3, and 4 on the structure, and, in parenthesis, the approximate $J_{\text{H-F}}$ coupling for each proton (δ 0.00, $^nJ_{\text{H-F}} = 0.00$ Hz).

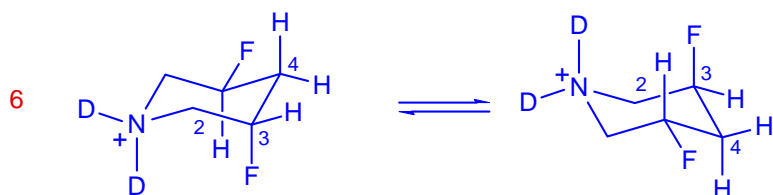


(c) Why are the signals at δ 3.3-5.4 broadened compared to the signals at δ 2-2.7?

Problem R-10M. Interpret the room temperature 400 MHz ^1H NMR spectrum of a difluoropiperidine ammonium salt (D_2O solvent, expansions on next page) and determine stereochemistry and conformation (*J. Am. Chem. Soc.* **2000**, 122, 544).



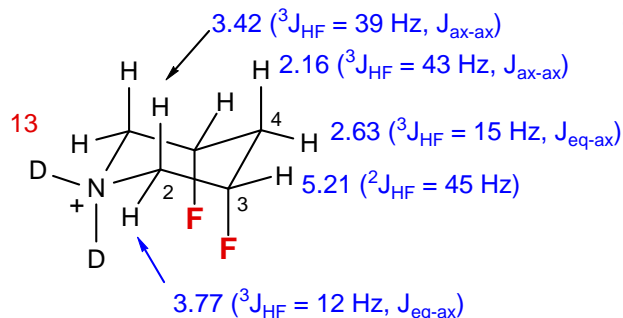
(a) Are the two fluorines cis or trans to each other? Explain briefly.



There are two signals for the protons on H^4 (2.15, 2.60). If the two fluorines were trans, rapid inversion of the ring would give only one chemical shift for the H^4 protons.

Similarly, the protons at H^2 (3.4, 3.8) would have only one shift, two are observed

(b) Add the fluorines to the cyclohexane conformation below, and explain how you arrived at this conformation. Write the chemical shifts next to the protons on carbons 2,3, and 4 on the structure, and, in parenthesis, the approximate $J_{\text{H-F}}$ coupling for each proton (δ 0.00, $^nJ_{\text{H-F}} = 0.00$ Hz).



The two fluorines have to be cis, and both are axial:

- There are large $J_{\text{Hax-Fax}}$ couplings to both H^2 and H^4 (ca 40 Hz)
- H^4_{ax} shows only one additional large coupling ($^2J_{\text{H-H}}$)
- H^2_{ax} shows only one additional large coupling ($^2J_{\text{H-H}}$) and no $^3J_{\text{Hax-Hax}}$.
- If H^3 was axial, there should be a ca 10 Hz J to both H^2_{ax} and H^4_{ax}

(c) Why are the signals at δ 3.3-5.4 broadened compared to the signals at δ 2-2.7?

H^2 : The signals at δ 3.4-3.8 are probably broadened by small unresolved coupling to the N-14 and the D. There are also unresolved $^3J_{\text{HH}}$ couplings to the equatorial H^3 protons

5 H^3 : There are several unresolved H-H couplings ($J_{\text{eq-eq}}$ and $J_{\text{eq-ax}}$) to H^2 and H^4 ; also a possible unresolved coupling to ^{14}N - there is an anti relationship between H^3 and N, and the N could be undergoing relatively slow quadrupolar relaxation (high symmetry).

Problem R-10M (C₅H₉F₂N·HCl).

400 MHz ¹H NMR spectrum in D₂O

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