

Supplementary Information

Structure and electric field gradients in three fentanyl solid forms from first-principles calculations and solid-state NMR

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1 Sample Characterization

The fentanyl freebase powder used in this study was prepared from fentanyl hydrochloride by aqueous sodium hydroxide basification followed by extraction into dichloromethane, concentration, and drying under vacuum. The synthetic route and representative solution-phase NMR characterization are shown in Figs. S1–S3. These data support the molecular identity of the material as fentanyl freebase. However, solution-phase molecular characterization does not establish the exact solid-state phase, hydration state, or local protonation environment of the powder used for SSNMR.

The ^1H NMR spectrum also contains a signal attributable to residual water, consistent with the aqueous workup and non-anhydrous handling of the freebase material. This observation supports the plausibility of trace water as a local perturbation, including possible water-assisted hydrogen bonding, but does not establish a stoichiometric hydrate or the solid-state protonation state of the measured powder.

This distinction is important for interpreting the piperidine ^{14}N electric field gradient. Attempts to obtain single crystals suitable for single-crystal X-ray diffraction from the measured freebase powder were unsuccessful. Powder X-ray diffraction was not feasible under the approved safety controls available for handling fentanyl powder on the available instrument. Therefore, the literature neutral freebase crystal structure was used as the structural model for the DFT calculations, but the exact solid-state phase, hydration state, and local protonation environment of the measured nominal freebase powder could not be independently verified. For this reason, the H-added and H-added/ H_2O calculations discussed in the main text are treated as local-environment sensitivity tests rather than definitive structural assignments of the bulk freebase powder.

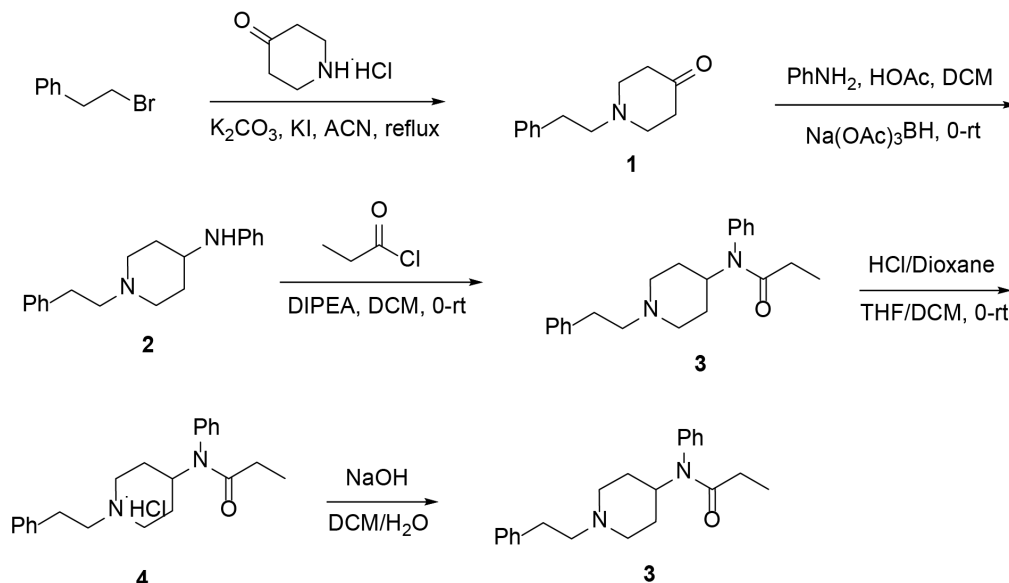


Figure S1: Synthetic route used to prepare fentanyl hydrochloride and fentanyl freebase. The freebase used in this study was generated from fentanyl hydrochloride by aqueous NaOH basification followed by dichloromethane extraction. Adapted from Ref. [1].

Table S1: Summary of the freebase sample assignment and remaining structural limitations relevant to the piperidine ^{14}N EFG.

Question	Status in this study
Molecular identity	Supported by the synthesis route and solution-phase ^1H and ^{13}C NMR characterization of fentanyl freebase.
^{15}N SSNMR characterization	Static $^{15}\text{N}\{^1\text{H}\}$ CP SSNMR spectra were acquired for selectively labeled freebase samples. These spectra support the aniline/piperidine site assignments and provide site-specific chemical-shift tensor parameters, but do not by themselves establish the bulk solid-state phase, hydration state, or local protonation state.
Preparation route	Generated from fentanyl hydrochloride by aqueous NaOH basification and dichloromethane extraction, followed by concentration and drying under vacuum.
Independent phase verification	Not available. Attempts to grow single crystals suitable for SCXRD were unsuccessful, and PXRD was not feasible under the available safety approvals.
Additional unavailable diagnostics	CHN elemental analysis, ^1H MAS SSNMR, and ^1H - ^{14}N correlation measurements were not performed within the approved safety and handling workflows for fentanyl-containing powders. Static $^{15}\text{N}\{^1\text{H}\}$ CP SSNMR spectra were acquired for selectively labeled freebase samples and are reported separately in Table S2.
Hydration or local protonation state	Not independently established. Because the workup involved water and the sample was not handled under rigorously anhydrous conditions, trace water or local hydrogen-bonding/protonating environments cannot be excluded.
Use in DFT comparison	The literature neutral freebase crystal structure was used as the computational reference structure. The H-added and H-added/ H_2O structures discussed in the main text are treated as local-environment sensitivity tests, not definitive structural assignments of the bulk freebase powder.

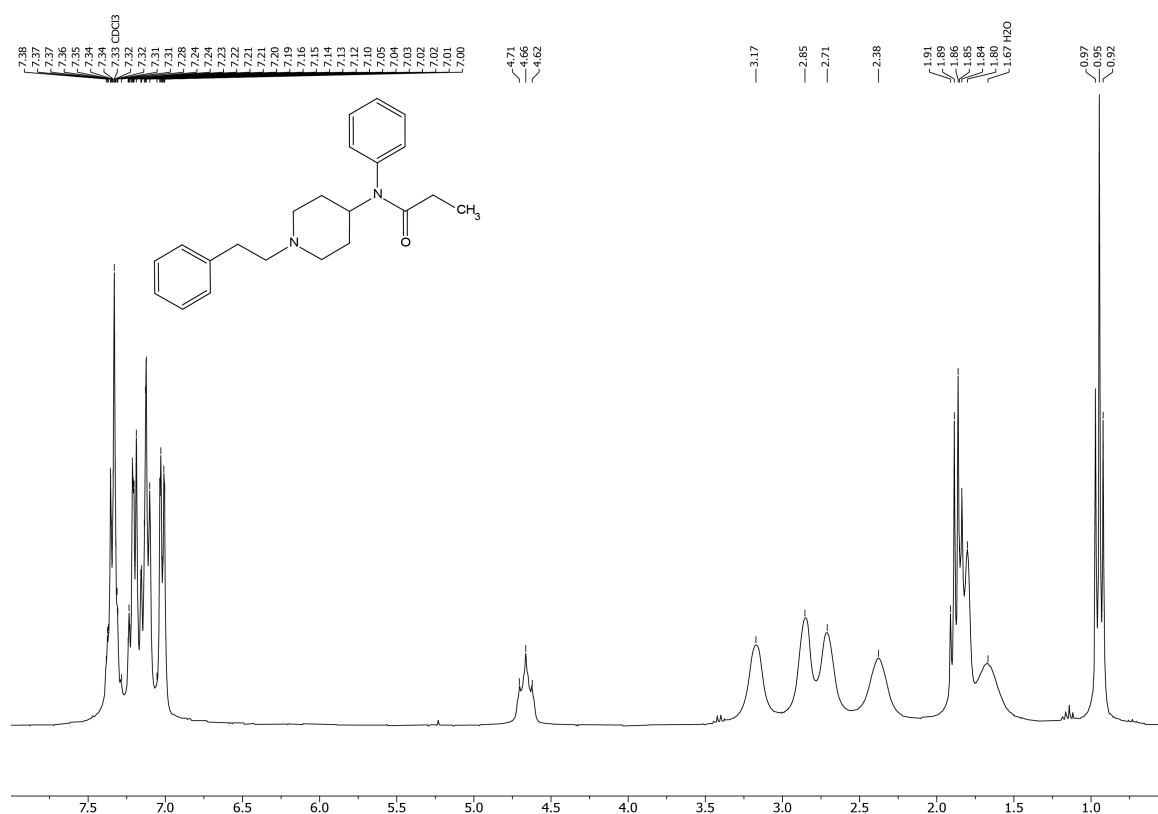


Figure S2: Solution-phase ^1H NMR spectrum of fentanyl freebase. The spectrum supports the molecular identity of the freebase material and contains a signal attributable to residual water, consistent with the aqueous workup and non-anhydrous handling. The spectrum does not determine the solid-state phase, hydration state, or local protonation environment of the powder used for SSNMR. Adapted from Ref. [1].

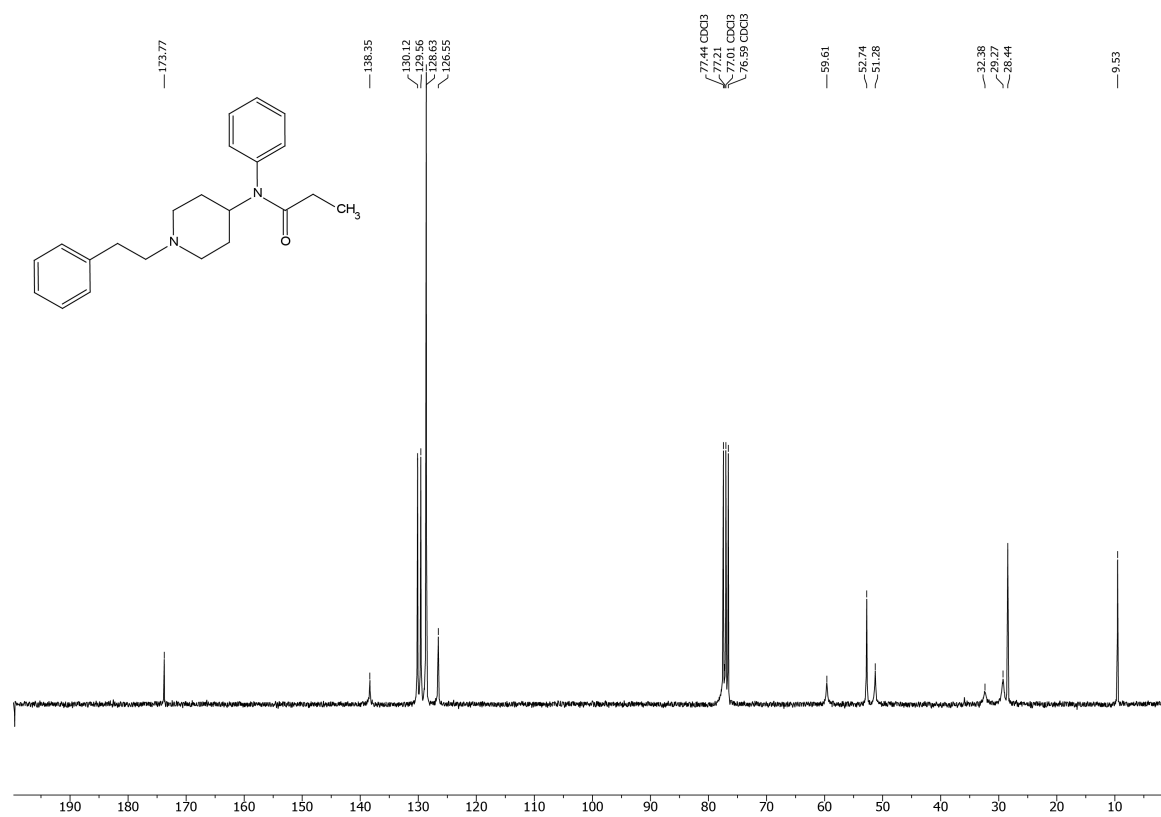


Figure S3: Solution-phase ^{13}C NMR spectrum of fentanyl freebase. The spectrum supports the molecular identity of the freebase material but does not determine the solid-state phase, hydration state, or local protonation environment of the powder used for SSNMR. Adapted from Ref. [1].

2 ^{15}N SSNMR Chemical-Shift Parameters

Static $^{15}\text{N}\{^1\text{H}\}$ cross-polarization SSNMR spectra were acquired for selectively ^{15}N -labeled fentanyl freebase samples. Because ^{15}N is a spin-1/2 nucleus, these measurements provide site-specific chemical-shift information without the first-order quadrupolar broadening present for ^{14}N . Representative spectra and simulations are shown in Fig. S4, and the fitted chemical-shift tensor parameters are summarized in Table S2.

The ^{15}N spectra provide an independent check of the aniline and piperidine site assignments used in the ^{14}N lineshape analysis. The piperidine and aniline sites exhibit clearly distinct chemical-shift tensor parameters. These data provide additional site-specific information about the local nitrogen environments, but they do not by themselves establish the exact solid-state phase, hydration state, or local protonation environment of the nominal freebase powder. They are therefore used as supporting spectroscopic evidence for the local-environment interpretation discussed in the main text, rather than as a definitive bulk structural assignment.

Table S2: ^{15}N SSNMR chemical-shift tensor parameters for selectively ^{15}N -labeled fentanyl freebase samples. The asymmetry parameter η_{CS} refers to the chemical-shift tensor, not the EFG tensor.

Site	δ_{iso} (ppm)	δ_{aniso} (ppm)	η_{CS}
Piperidine	114.6	18.07	0.84
Aniline	146.7	100.4	0.22

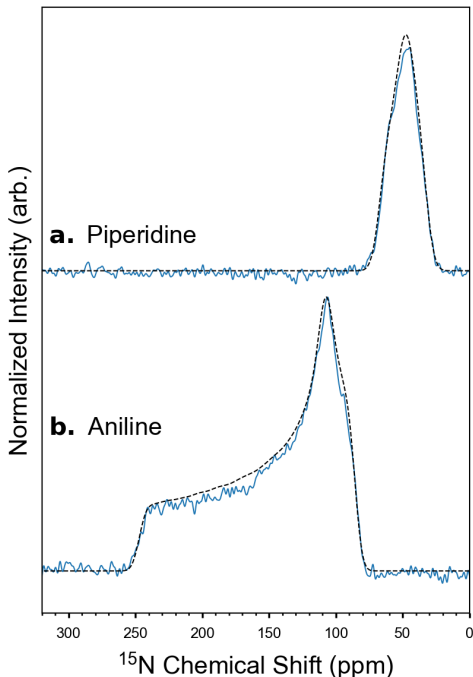


Figure S4: Static $^{15}\text{N}\{^1\text{H}\}$ CP SSNMR spectra of selectively ^{15}N -labeled fentanyl freebase samples. The blue curves show experimental spectra and the dashed black curves show simulations using the fitted chemical-shift tensor parameters in Table S2.

3 Modified-Cell Geometry Diagnostics

This section provides structural diagnostics for the modified-cell calculations discussed in the main text. These calculations include the H-added fentanyl freebase test, the H-added/H₂O fentanyl freebase test, and the Cl-removed/H-retained fentanyl HCl test. As emphasized in the main text, these structures are not treated as definitive bulk structural assignments. Instead, they are used as local-environment sensitivity tests to examine how N–H formation, proximal hydrogen bonding, and removal of counterions affect the piperidine ¹⁴N EFG and the finite-temperature stability of the local motif.

Figures S5–S7 show representative geometry diagnostics for the modified-cell DFT-MD tests. These distance traces are used to identify whether an added or retained H atom remains associated with the piperidine nitrogen or dissociates during the trajectory. Figure S5 corresponds to the H-added freebase test, in which H atoms were added to all four crystallographically distinct piperidine sites. Figure S6 corresponds to the H-added/H₂O freebase test, in which a nearby water molecule was included to probe stabilization of the H-added N₂^p site. Figure S7 corresponds to the Cl-removed/H-retained HCl test, in which the chloride ions were removed while the piperidinium H atoms were retained.

Table S3: Reference crystallographic parameters, unit-cell volumes, and atom counts for the unmodified fentanyl freebase, fentanyl citrate, and fentanyl HCl structures used in the calculations.

Parameter/Type	fentanyl freebase	fentanyl citrate	Fentanyl HCl
a(Å)	5.69263	8.963	10.7319
b(Å)	25.1851	11.2533	27.228
c(Å)	13.8608	14.874	7.0662
$\alpha(^{\circ})$	90	109.411	90
$\beta(^{\circ})$	104.2037	96.728	95.843
$\gamma(^{\circ})$	90	107.486	90
Space group	<i>P</i> 2 ₁ / <i>c</i> (# 14) Monoclinic	<i>P</i> $\bar{1}$ (# 2) Triclinic	<i>C</i> ₂ (# 9) Monoclinic
Volume (Å ³)	1926.4652	1309.7207	2054.0739
N	8	4	8
O	4	16	4
C	88	56	88
H	112	72	116
Cl	0	0	4
Total atoms	212	148	220

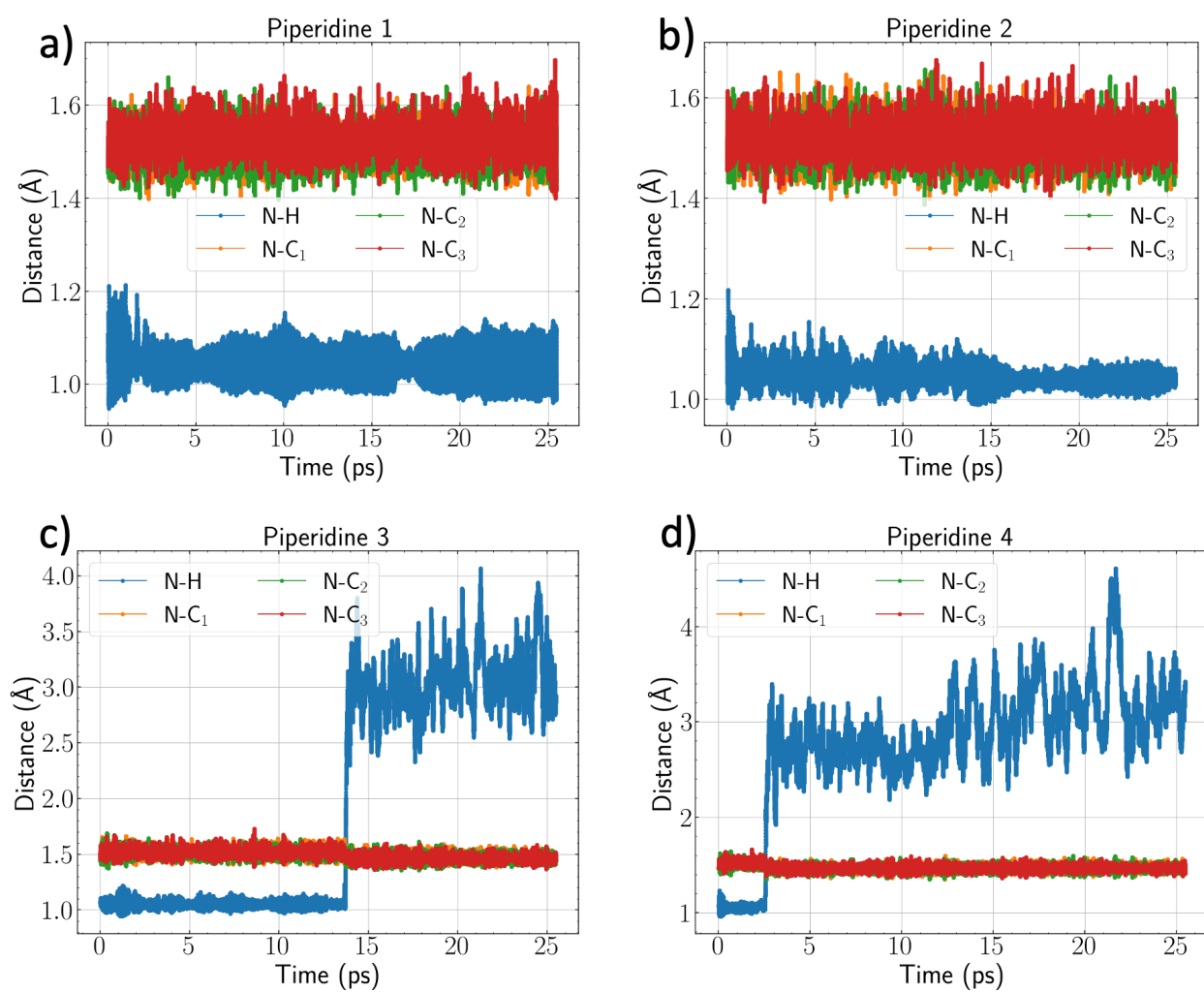


Figure S5: The four subplots represent how the nearest-neighbor distances around each H-added piperidine site in fentanyl freebase change during DFT-MD, including a) piperidine 1, b) piperidine 2, c) piperidine 3, and d) piperidine 4.

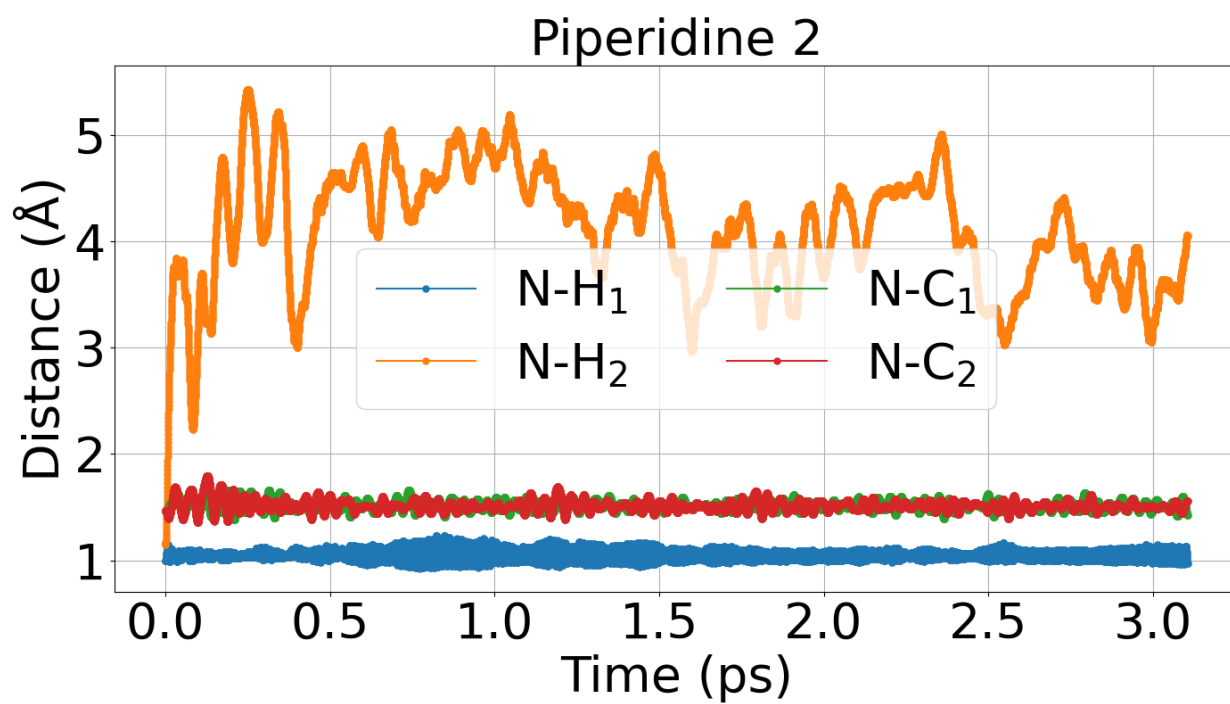


Figure S6: Nearest-neighbor distances around the H-added N_2^p piperidine site in fentanyl freebase with a nearby H_2O molecule included during DFT-MD.

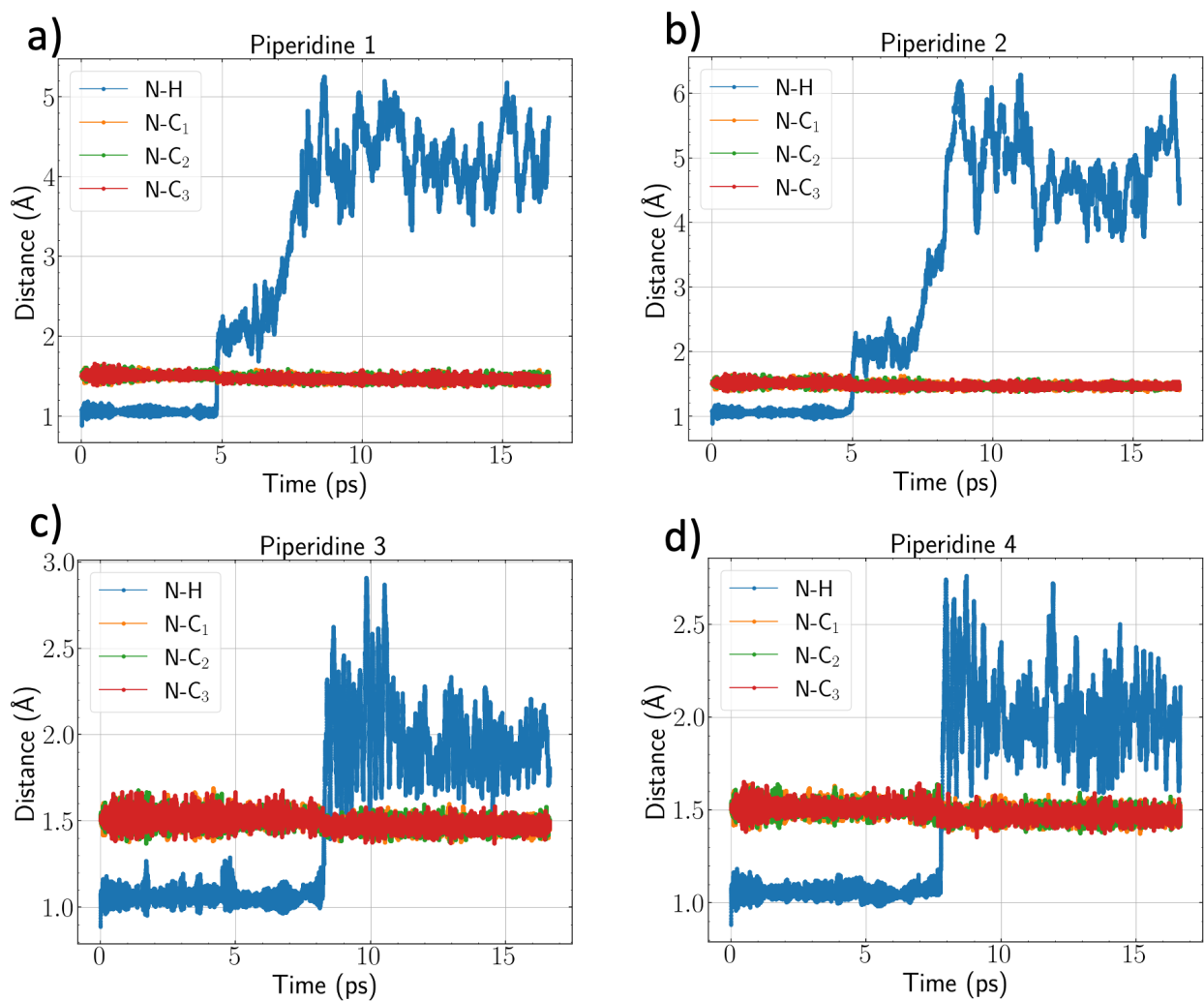


Figure S7: The four subplots represent how the nearest-neighbor distances around each Cl-removed/H-retained piperidine site in fentanyl HCl change during DFT-MD, including a) piperidine 1, b) piperidine 2, c) piperidine 3, and d) piperidine 4.

4 Phonon densities of states

To ensure convergence of vibrational properties from the MD trajectory, we calculate the phonon density of states (PDOS) of individual atoms in each of the three fentanyl structures. The convergence was assured with the help of PDOS obtained from larger cell size ($2 \times 1 \times 1$) from representative fentanyl freebase. All the PDOS spectra shown in Fig. S8 are calculated using the velocity autocorrelation (VAC) of the MD trajectories. For a Representative structure (fentanyl freebase), this was also in close agreement with a static phonon obtained using the finite displacement method as implemented in the Phonopy. [2, 3] The agreement in the PDOS spectrum of common atom types across fentanyl types as shown in Fig. S8 is also reflective of the fact that MD trajectories are sufficiently accurate.

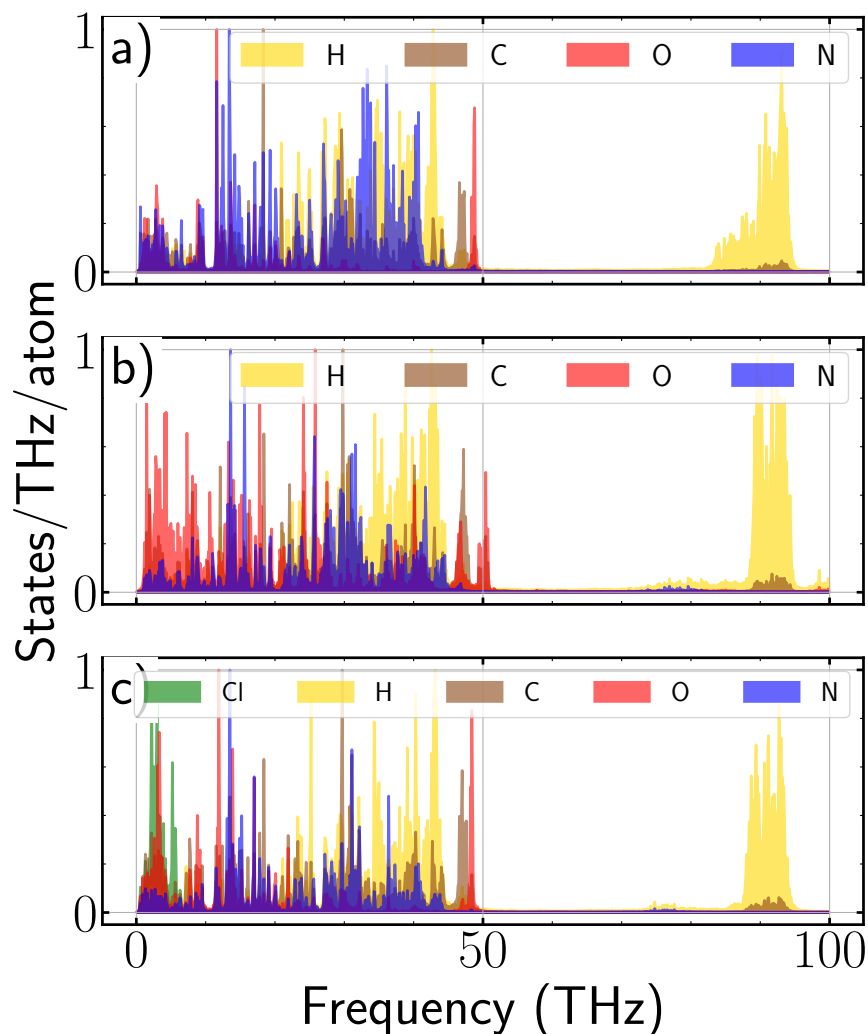


Figure S8: Normalized phonon density of states for each atom in a) fentanyl freebase, b) fentanyl citrate, and c) fentanyl HCl.

5 EFG Tensor Averaging

For each sampled DFT-MD snapshot, the full Cartesian EFG tensor $V_{ij}(t)$ was calculated at each quadrupolar nucleus in the fixed simulation-cell reference frame. The DFT-MD EFG values reported in the main text were obtained using component-wise tensor averaging. The mean EFG tensor is

$$\langle V_{ij} \rangle = \frac{1}{N_t} \sum_{t=1}^{N_t} V_{ij}(t), \quad (\text{S1})$$

where N_t is the number of sampled MD snapshots. The tensor $\langle V_{ij} \rangle$ was then diagonalized and its eigenvalues were ordered according to the standard convention

$$|V_{zz}| \geq |V_{yy}| \geq |V_{xx}|. \quad (\text{S2})$$

The resulting time-averaged V_{zz} and η values were converted to quadrupolar coupling constants using the definitions given in the main text. This procedure differs from averaging the instantaneous principal components, $\langle V_{zz}(t) \rangle$, because the principal-axis system can fluctuate along the trajectory and the eigenvalue ordering is applied independently at each snapshot. Therefore,

$$\text{diag}(\langle V_{ij} \rangle) \neq \langle \text{diag}(V_{ij}) \rangle \quad (\text{S3})$$

in general. The instantaneous $V_{zz}(t)$ values shown in the main-text time-series figures are included only to illustrate the magnitude and stability of thermal fluctuations. The numerical DFT-MD values reported in the tables and used for comparison with experiment are obtained from $\text{diag}(\langle V_{ij} \rangle)$.

References

- [1] Michael W Malone, Harris E Mason, Adam R Altenhof, Michelle A Espy, Marc A Alvarez, Rami J Batrice, Amber J Day, Adam P Dioguardi, Michihiro Hirata, Margaret R Jones, et al. Standoff detection of fentanyl hydrochloride via nuclear quadrupole resonance: A multimodality pursuit. *PS Nexus*, 4(7):pgaf190, 2025.
- [2] Atsushi Togo. First-Principles Phonon Calculations with Phonopy and Phono3py. *J. Phys. Soc. Jpn.*, 92(1):012001, 2023.
- [3] Togo, Atsushi and Chaput, Laurent and Tadano, Terumasa and Tanaka, Isao. Implementation strategies in phonopy and phono3py. *J. Phys.: Condens.Matter*, 35(35):353001, 2023.