A curious case of dynamic disorder in pyrrolidine rings

elucidated by NMR crystallography

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Section 1 - Experimental.

¹³*C solid-state NMR.* **1a** was packed in a 4 mm zirconium oxide MAS rotor, and experiments were performed on a Bruker Avance III HD spectrometer operating at a ¹H Larmor frequency of 400 MHz using a 4 mm Bruker HFX probe. A magic angle spinning rate of 10 kHz was used throughout all experiments. The 1D ¹³C CPMAS spectra were acquired using a ramped contact pulse,¹ a contact time of 2000 μ s, a ¹H π /2 pulse duration of 2.4 μ s, a recycle delay of 10 seconds, and co-adding 2048 transients. SPINAL64 proton decoupling² was used with a ¹H nutation frequency of 104 kHz. The ¹³C spectrum was calibrated using glycine and referenced to 176.0 ppm relative to TMS at 0 ppm.^{3, 4} The *T*₁(¹³C) measurements were performed using the same cross-polarization parameters, but co-adding 224 transients, followed by an inversion recovery sequence with a ¹³C π /2 pulse duration of 3.3 μ s. A total of 8 delays were used for the inversion recovery experiments (0.1 s, 0.25 s, 0.5 s, 1.2 s, 2.0 s, 5.0 s, 10.0 s, 20.0 s), with the resulting curves reported in the Supporting Information (see Figures S1 and S2). Temperatures were calibrated externally using the ²⁰⁷Pb resonance of lead nitrate.^{5, 6}

NMR calculations. All DFT⁷⁻⁹ calculations were performed using the gauge-including projector augmented-wave (GIPAW)¹⁰ method as implemented in CASTEP¹¹ as part of Materials Studio version 17.¹² The structural model used in the calculations were based on previous data obtained from X-ray crystallography. The GGA PBE functional¹³ was employed for all calculations, beginning with a geometry optimization routine with constrained unit cell parameters prior to calculating the NMR chemical shifts. The geometry optimization was performed with TS DFT-D correction,¹⁴ 600 eV cutoff energy, on the fly ultrasoft pseudopotentials, Koelling-Harmon relativistic treatment and a k-point separation of 0.05 Å⁻¹. NMR calculations were subsequently performed using the same parameters, but with a cutoff energy of 700 eV. The calculated σ_{iso} values were extracted using MagresView version 1.6.2¹⁵ and converted into δ_{iso} using a $\sigma_{ref}(^{13}C)$ of 172.9 ppm. $\sigma_{ref}(^{13}C)$ was chosen to coincide with experimental shifts.¹⁶

Transition state calculations. The transition state search calculations were performed using CASTEP, with a RMS convergence of 0.05 eV Å⁻¹, using a 570 eV energy cutoff, medium SCF tolerance, 1x1x1 k-point set, OFG ultrasoft pseudopotentials, and the linear synchronous transit method.^{17, 18} The N-C-C-C* torsion angle varied from 29.8° to -20.1° for C^{dis}, and 22.9° to -19.1° for C^{ord}. The C* denote the disordered carbon atom of interest (C^{ord} or C^{dis}). Each model was optimized with constrained unit cell parameters prior to the calculations, and the transition state calculations were performed individually for both C^{ord} and C^{dis}. In the case of C^{ord}, while only a single position was observed experimentally, a tentative structure for the second conformation was generated through modelling and DFT optimizations. Additional models were generated by retaining the original geometry but removing the counterion or isolating either molecule of **1** and adding 9 Å of spacing along the *a*, *b*, and *c* axes of the unit cell.¹⁹

Crystal Interactions Analysis. Crystal Interaction (CrysIn), a tool developed in-house, was used to evaluate the static interactions between molecules present in a crystal based on DFT.²⁰ The intermolecular interaction energies in the first coordination cell of each molecule in the asymmetric unit of the crystal were calculated using B3LYP-D3/6-31G(d,p) as reported in GAUSSIAN16.²¹ This is a comparable method to that employed in, for instance, the energy framework calculations in Crystal Explorer²² or PIXEL.²³ This approach enables the quantification of the intermolecular interactions present in a crystal.^{24, 25}

Differential scanning calorimetry. Sample **1a** was placed in a crimped aluminium pan and heated at a rate of 10°C/minute. The measurement was performed on a TA Instruments Q2000 differential scanning calorimeter.

Section 2 - $T_1(^{13}C)$ Fitting Equations & Constants.

$$\frac{1}{T^{1}} = a \cdot D_{C-H^{2}} \cdot \left[\frac{\tau_{c}}{1 + (\omega_{H} - \omega_{C})^{2} \tau_{c}^{2}} + \frac{3\tau_{c}}{1 + (\omega_{C})^{2} \tau_{c}^{2}} + \frac{6\tau_{c}}{1 + (\omega_{H} + \omega_{C})^{2} \tau_{c}^{2}} \right]$$
 Eq. S1

$$D_{C-H} = -\frac{\mu_0}{4\pi} \cdot \frac{\hbar \gamma_H \gamma_C}{r_{C-H}^3}$$
 Eq. S2

$$\tau_c = \tau_0 \exp{\frac{E_a}{RT}}$$
 Eq. S3

In Eq S1, τ_c corresponds to the correlation time (s), *a* is a fitting parameter accounting for motional amplitude, D_{C-H} is the dipolar coupling factor (rad s⁻¹, given by Eq. S2), ω_H and ω_C are the Larmor frequencies of ¹H and ¹³C (rad s⁻¹). In Eq. S2, ^h is the reduced Plank constant (1.054x10⁻³⁴ kg m² s⁻¹), μ_0 is the vacuum permeability of space ($4\pi \times 10^{-7}$ kg m s⁻² A⁻²), γ_H and γ_C are the gyromagnetic ratios of ¹H (2.68x10⁸ rad s⁻¹ T⁻¹) and ¹³C (6.73x10⁷ rad s⁻¹ T⁻¹), respectively, and r_{C-H} is the C-H bond length (1.09x10⁻¹⁰ m). In Eq. S3, τ_0 is the correlation time at T = 0 K (s), E_a is the activation energy (J mol⁻¹), and *R* is the gas constant (8.3145 J mol⁻¹ K⁻¹). As we have employed a fixed dipolar coupling constant using a C-H bond length of 1.09 Å and assume no motional averaging of the dipolar coupling, the value of τ_0 is an estimate and was not further considered in our analysis.

Section 3 - Experimental & Calculated Results.

Temperature / °C	$T_1(^{13}\mathrm{C})$ of $\mathrm{C}^{\mathrm{ord}}$ / s	$T_1(^{13}\mathrm{C})$ of $\mathrm{C}^{\mathrm{dis}}$ / s
0	6.5	0.9
10	7.1	1.1
20	9.7	1.4
30	10.2	1.9
40	12.5	2.0
50	12.8	2.5
60	14.2	3.1

Table S1. Experimental $T_1({}^{13}\text{C})$ relaxation time^a of C^{ord} (26.7 ppm) and C^{dis} (24.5 ppm) of **1a** (see Figures S1 and S2) at several temperatures.

^a Experimental errors on the temperatures are within 1°C and the errors on the $T_1(^{13}C)$ measurements were estimated to be 10%.

Table S2. DFT calculated (using CrysIn) total intermolecular interaction energies involving $1 \cdots 1$ and $1 \cdots a$ for C^{dis} and C^{ord} when they are puckered up, in their transition state, and puckered down.

site / conformation	1 ···· a (kJ mol ⁻¹)	$1 \cdots 1 (kJ mol^{-1})$ beneath ^b	$1 \cdots 1 (kJ mol^{-1})$ side ^b	$1 \cdots 1 (kJ mol^{-1})$ above ^b
C ^{dis} / up	-166.3	50.5	103.1	104.0
C ^{dis} / transition state	-158.9	51.6	103.9	100.7
C ^{dis} / down	-167.2	51.8	101.5	103.8
C^{ord} / up	n/a ^a	51.8	104.8	101.5
C ^{ord} / transition state	n/a ^a	64.4	105.0	103.5
C ^{ord} / down	n/a ^a	62.3	105.1	104.6

^a No **1**…**a** interactions involving C^{ord} were observed.

^b Interactions from beneath, the side, or above the pyrrolidine ring relative to Figure 1a.

Additional discussion of Table S2.

The $1 \cdots a$ interactions have highly stabilizing energies due to their opposing charges. Interestingly, the energies of the $1 \cdots a$ interactions involving C^{dis} are very similar for both conformations, with values of -166.3 kJ mol⁻¹ and -167.2 kJ mol⁻¹ when puckered up and down, respectively. This difference may have been reflected in the CASTEP calculations as a slightly higher stability of the puckered down conformation of C^{dis} (see Fig. 2b of the main text). Meanwhile, there is a much larger disparity in the energies of the interactions involving both conformations for Cord. For example, the contributions from 1...1 interactions from beneath the ring (relative to Fig. 1a) is 51.8 kJ mol⁻¹ when C^{ord} is puckered up (experimentally observed conformation), and 62.3 kJ mol⁻¹ when puckered down (not experimentally observed). The differences in these interaction energies may partially explain the origin of the energy gap of 22.3 kJ mol⁻¹ between both conformations of C^{ord} in the CASTEP calculations performed on the full structure of 1a (see Fig. 2a), and why a single librating conformation is observed in the structural model. In order to decompose the intermolecular contributions to the energy barriers for the dynamics of C^{dis} and C^{ord}, the approach discussed above was applied to the transition states obtained from the DFT calculations (see Table S2). In this case, the energies involving specific intermolecular interactions were computed for the transition states and compared to the puckered up / down conformation, for both C^{dis} and C^{ord}.



Figure S1. $T_1({}^{13}C)$ inversion recovery curves of C^{ord} (left) and C^{dis} (right) of compound 1a. The dashed lines denote the lines of best fit, and the experimental temperatures are shown on the left. See Figure S2 for additional plots.



Figure S2. (continued from Figure S1) $T_1(^{13}C)$ inversion recovery curves of C^{ord} (left) and C^{dis} (right) of compound **1a**. The dashed lines denote the lines of best fit, and the experimental temperatures are shown on the left.

Section 4 - Cambridge Structural Database (CSD) Search.

Table S3. List of organic structures on the CSD^{26} featuring disorder in a pyrrolidine ring.^a The structures with a $Z^{2} = 2$ and distinctly disordered pyrrolidine groups, such as in the case **1a** investigated herein, are underlined.

ACEZUF	EABMOJ	HOLSAC	<u>LEXQEL</u>	PEYSER	SIFDAN	WOFVUJ
AKASUA	ECUDEO	HOSLIN	LIRXUH	PEYSIV	SIFPOP	WUCQOB
ASEKEO	ECUDOY	HOXQOC	LOTGOS	PEYSOB	<u>SUYJUT</u>	XAGGUJ
AXUTAQ	EJOYIL	HURNIT	LUTFUD	PEYSUH	SUYKAA	XASXIZ
BEPSAT	EKOLUL	IFIMUF	MERTAF	PEYTES	TADPAR	XENNAG
BEYYEL	ELEYUP	IVOXOG	<u>MEXQOY</u>	PEYTIW	TAJYOT	<u>XIBBOB</u>
<u>BIKHEL</u>	EPUWAP	JAWLIC	MINNIJ	PEZHIO	TAMDIX	<u>XOKFUY</u>
BOTTUC	EQUQIQ	JAZHIC	MITJAC	PIZGAG	<u>TAVKEI</u>	XOTPEE
BOVKUU	ESIJOH	JIPLAY	<u>MOTHIN</u>	PUCPEK	TIMFEA	XULZIP
BOXYOF	ETUYOH	JISYAM	MOXHOY	QAYBOJ	TIYNIA	XUSQIL
BUDLUI	ETUYUN	JOBDUA	MUYXAG	<u>QEDLUI</u>	TONXOK	<u>YEBHUK</u>
BUFYEJ	EZAJUL	KEKREZ	NAMXAA	QEZXEZ	TOSKIX	YICVIS
BUTBUP	FAVZAG	KEKSAW	NARLIE	QILHIC	TOSKOD	YIHDIE
CATVUP	FENPOF	KEKSEA	NAXGOL	QIPKIL	TUWGUP	YIHDOK
CEVFIU	FENQEW	KETSEJ	<u>NAXQUB</u>	QIPKOR	UDAWAA	YIHDUQ
CEWBOY	FILFAK	KIBFOT	NOCXOU	QUTDUG	UQIQES	YOXSOW
CIYNEE	FIQXIP	KISQOV	NOJFUN	RAMBAI	URIHAF	YUDVEA
COPVOV	<u>FUBYAE</u>	KOHLUO	NOJQUY	RIJJOM	VEWGOV	YUSXUG
CORKUS	GAQDUZ	KUFTUC	NUKROB	RIWLAK	VEWGUB	YUWXUJ
CUGPEB	GARJOA	<u>KUSYIH</u>	ODEYUU	<u>ROCNON</u>	VIWVAB	ZECFIW
DAHQAH	GEKBOO	LAGLIO	OKUBUT	ROFQUZ	VUBXIC	ZEVFEN
DAXDUC	<u>GIBROY</u>	LALWIF01	OQADOB	ROLNIR	WACDOV	ZOJXAX
DEBHIE	GOFTOL	LEBDEB	PEDDAD	ROPLIU	WATYOG	ZUYPOA
DEBHOK	GOSVUI	LEFWAW	PEDDEH	ROQMOZ	WEFGOF	
DIGDIJ	GOYGOT	<u>LEPBIT</u>	PEMXIR	SAKVOP	WILROZ	
EABMID	HOFNAS	LEPSOP	PETYIY	<u>SECVIH</u>	WITYAB	

^a The search was performed using Conquest on the CSD database version 5.41 (March 2020), specifying the pyrrolidine ring with any substitutions apart from hydrogen on the nitrogen atom or on the carbon adjacent to that nitrogen, as shown on Fig 1a. The search selected for single crystal X-ray structures of organic compounds, which featured disorder in the structure. Polymeric structures were excluded. The 592 resulting hits from this search was then manually analysed to identify structures where the disorder occurred in the pyrrolidine ring.

Section 5 - Anisotropic displacement ellipsoid plots & surrounding environment.



Figure S3. Anisotropic displacement ellipsoid plots of 1a showing (a) the ordered pyrrolidine group containing C^{ord} , and (b) the disordered pyrrolidine group containing C^{dis} . This figure was generated with ORTEP3.²⁷



Figure S4. Diagrams showing all contacts within a 3 Å radius of the hydrogen or carbon atoms for either pyrrolidine groups in the unoptimized structural model of **1a**. The arrows highlight the carbon atoms of interest.

Section 6 – Differential Scanning Calorimetry.



Figure S5. Differential scanning calorimetry of compound 1a.

Section 7 - References.

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