Supplementary Information

Controlled Isolation of a Novel Polymorphic Form of Chlorothiazide by Spray Drying

Alice Parkes[1], Enrico Spoletti[2], John O'Reilly[2], Matteo Lusi[2], Ahmad Ziaee[3], Emmet O'Reilly`[1]

[1]Department of Chemical Sciences, SSPC the Science Foundation Ireland Research Centre for Pharmaceuticals*, Bernal Institute, University of Limerick, Limerick, Ireland.*

[2]Department of Chemical Sciences, Bernal Institute, University of Limerick, Limerick, Ireland.

[3]Cook Medical, Castletroy, Limerick, Ireland.

Methods

Single Crystal Experiments

To attempt to isolate single crystals of CTZ form IV, the following experiments were carried out:

1. Slow evaporation of a saturated solution of CTZ form I in Acetone.
2. Slow evaporation of a saturated solution of CTZ form IV in Acetone.
3. Cooling crystallisation of a saturated solution of CTZ form I in Acetone. 3ml of Acetone were heated to 40 °C, CTZ form I was added until the solution was supersaturated. The solution was then filtered and covered with parafilm. It was set aside and checked every half hour for crystals.
4. Cooling crystallisation of a saturated solution of CTZ form I in Water. The procedure outlined in 3 was followed.
5. Saturated solution of CTZ form I in water seeded with a small amount of CTZ form IV.

Results

Crystal Structure Determination

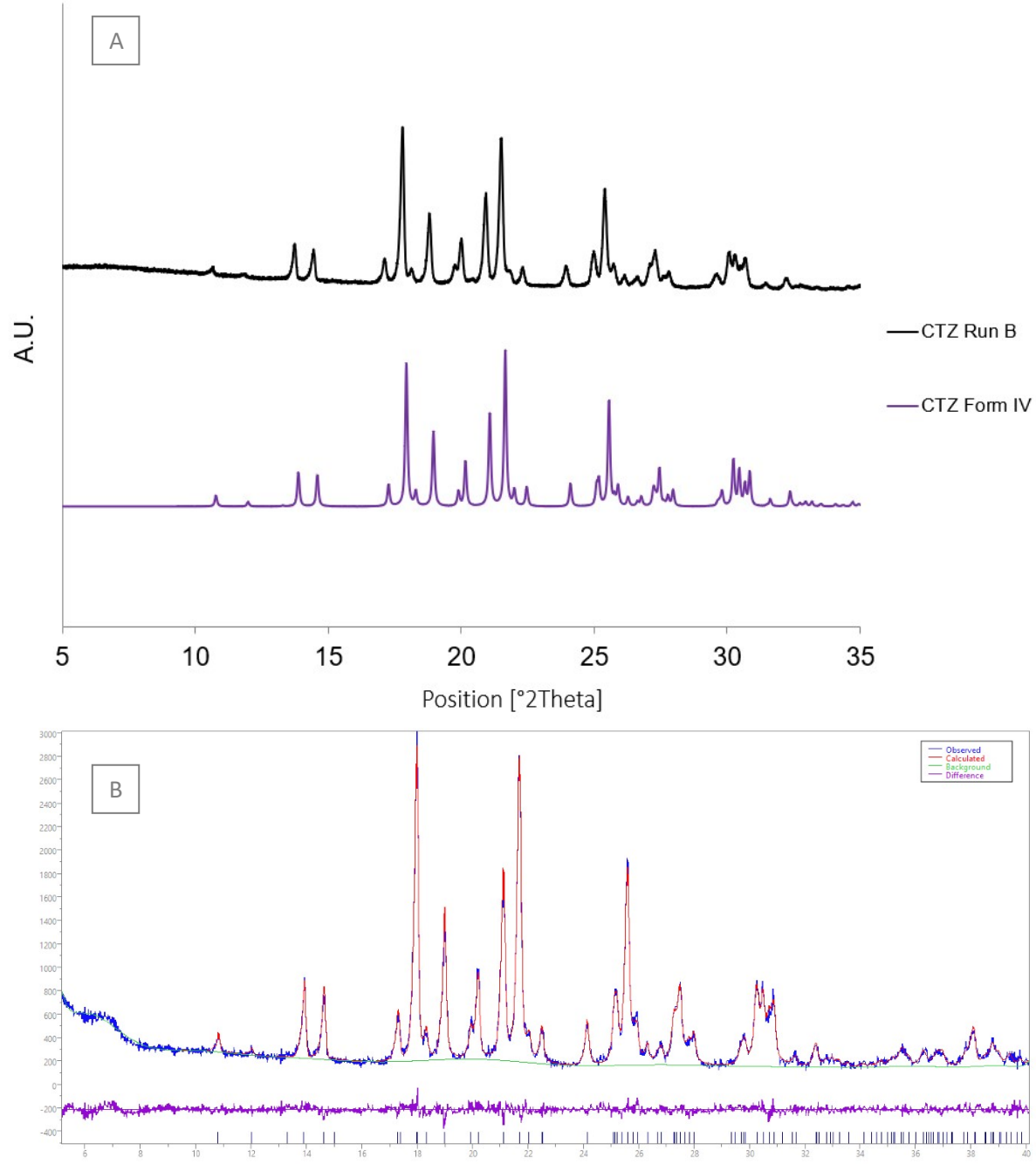


Figure S1 [A] PXRD Diffractogram of the experimental CTZ Run B and calculated CTZ form IV [B] Difference profile between observed and calculated powder pattern for CTZ form IV.

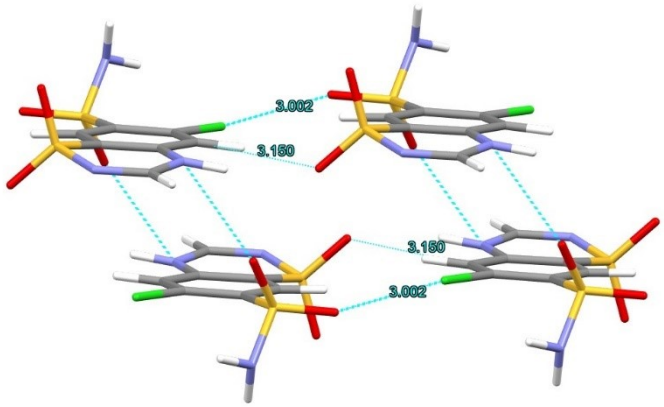


Figure S2 Representation of the Cl···O and O···H-C interactions between parallel dimers.

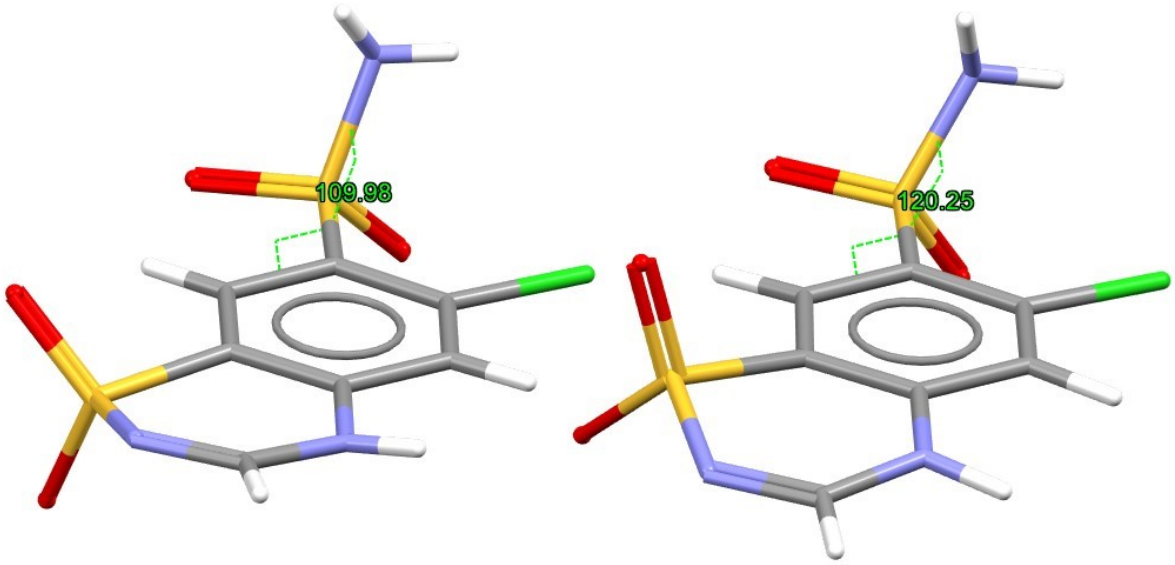


Figure S3 Representation of the molecular conformation for CTZ form I (left) and form IV (right), and the torsional angle of the sulfonamide group in green dashed line.

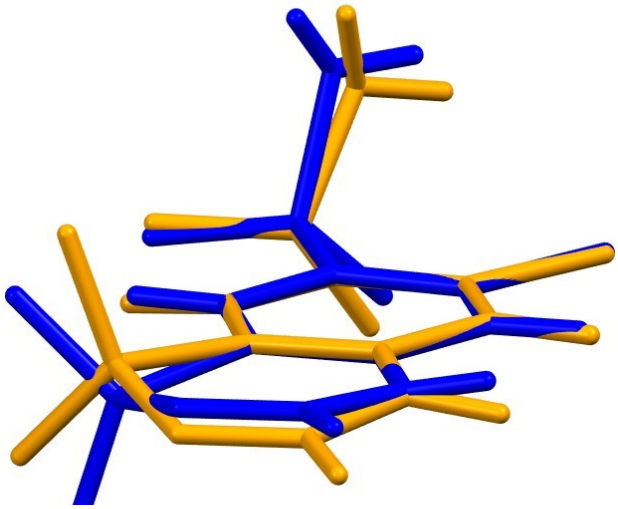


Figure S4 Superimposition of the CTZ molecule for form I (blue) and form IV (orange).

Differential Scanning Calorimetry

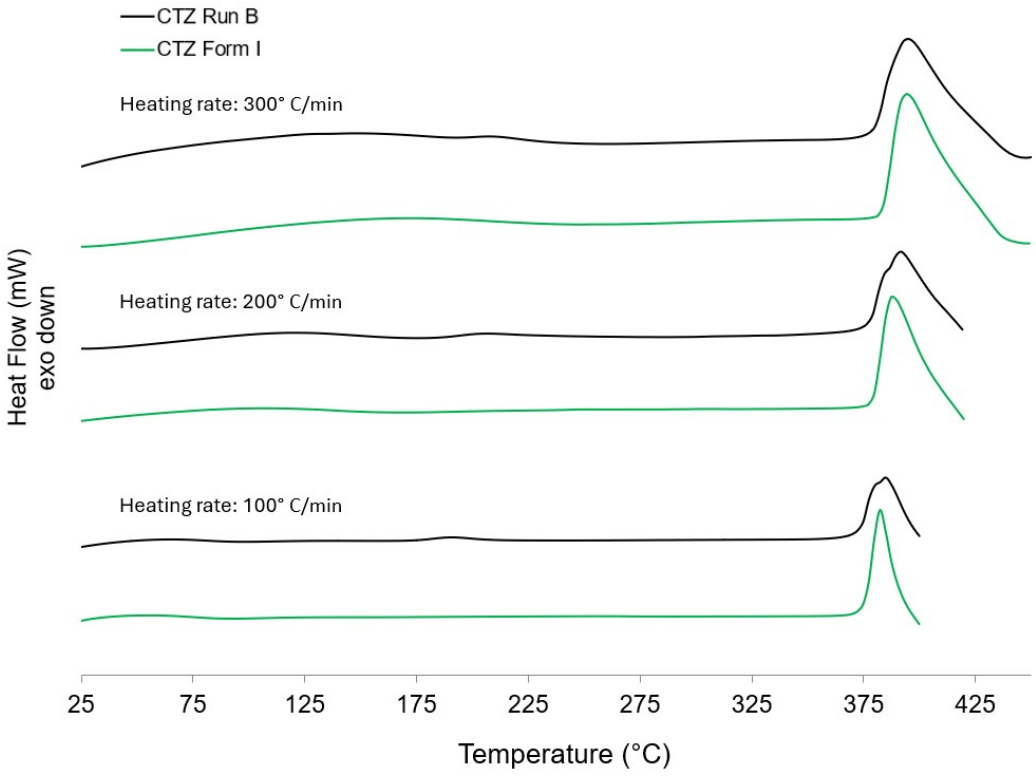


Figure S5 DSC thermogram of CTZ Run B at accelerated heating rates of 100 °C/min, 200 °C/min and 300 °C/min.

Fourier-transform Infrared

FTIR analysis showed differences between CTZ Run B (CTZ form IV) and CTZ form I. Fig. S6 shows the full spectra of CTZ Run B and CTZ form I and it can be seen that the main differences between the spectra are in the fingerprint region, 400-1400 cm^{-1}.

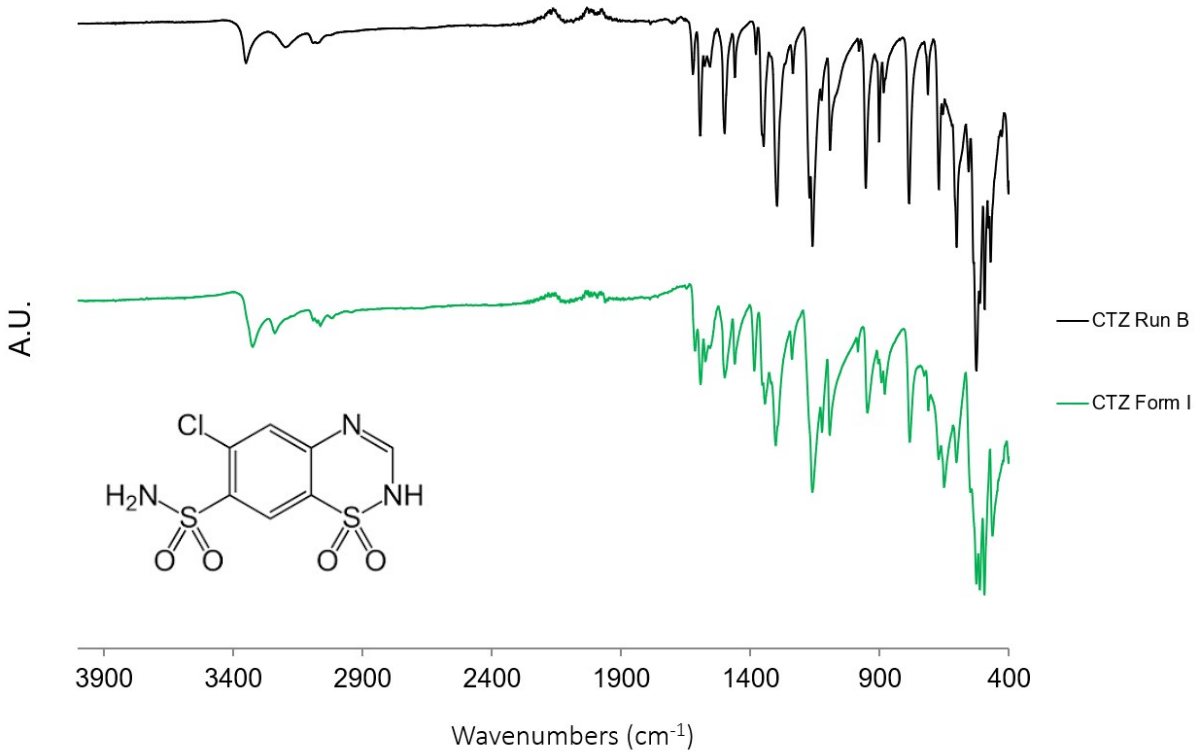


Figure S6 FTIR Spectra of CTZ Run B and CTZ form I

Nuclear Magnetic Resonance

D_20 was added to CTZ Run B sample in order to check if there were any exchangeable protons present. It was found that both NH and NH_2 are exchangeable with D_20, and the peaks diminish by the Nuclear Overhauser effect (nOe). NOe is the transfer of nuclear spin polarization from one population of spin-active nuclei to another nuclei through space, not through bonds.

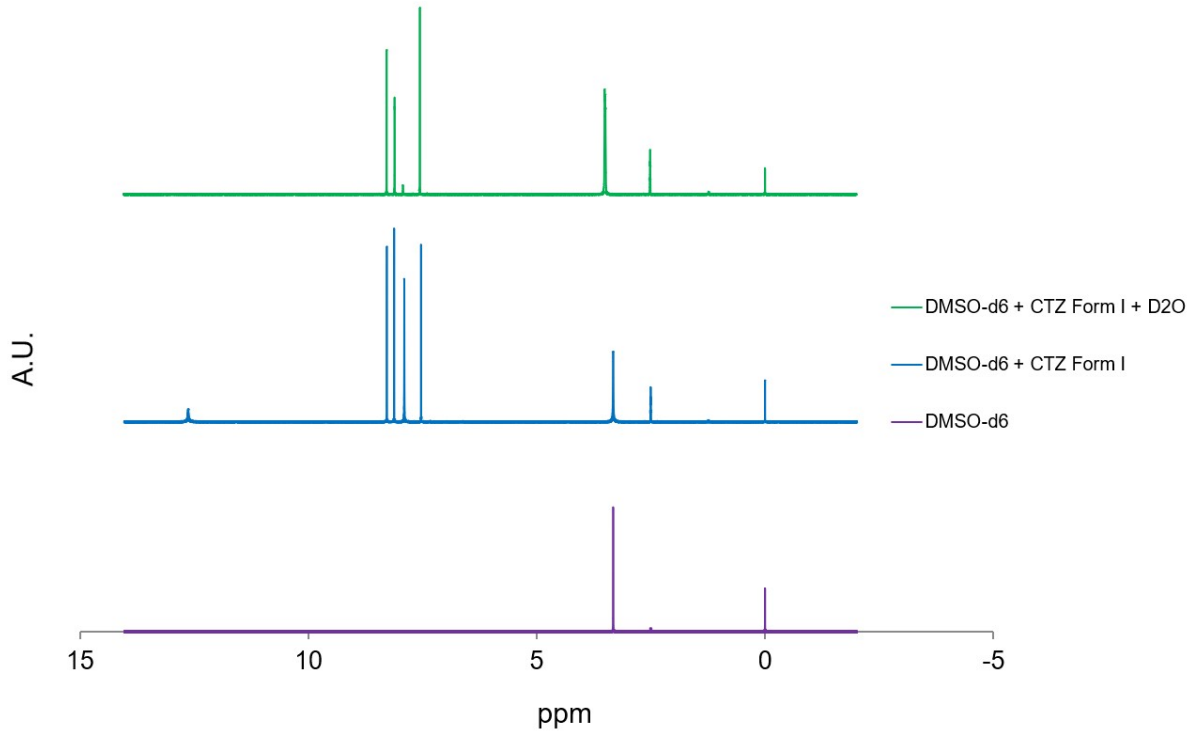
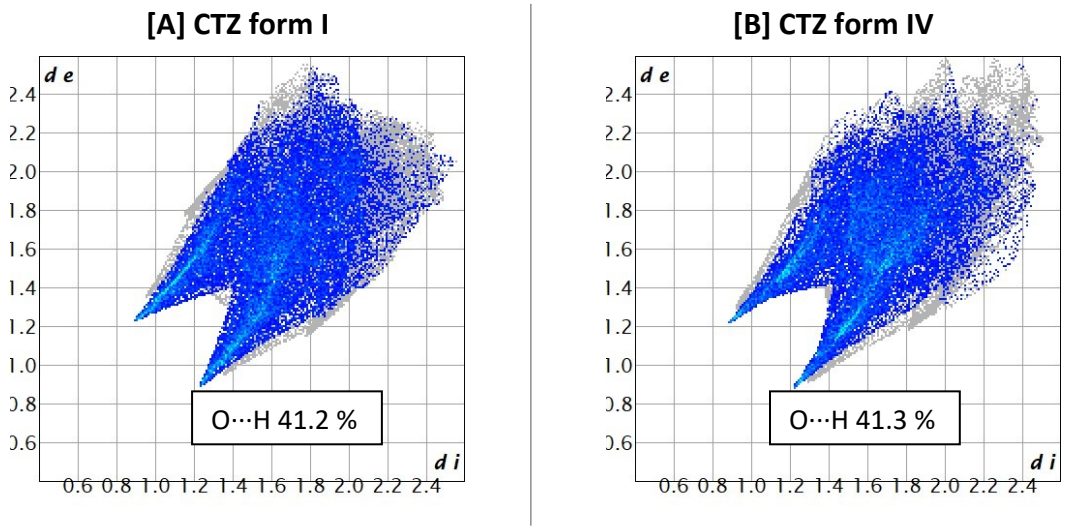


Figure S7 NMR of DMSO-d6 + CTZ form I + D_2O compared with DMSO-d6 + CTZ form I and DMSO-d6 to show the presence of exchangeable protons

Hirshfield Analysis



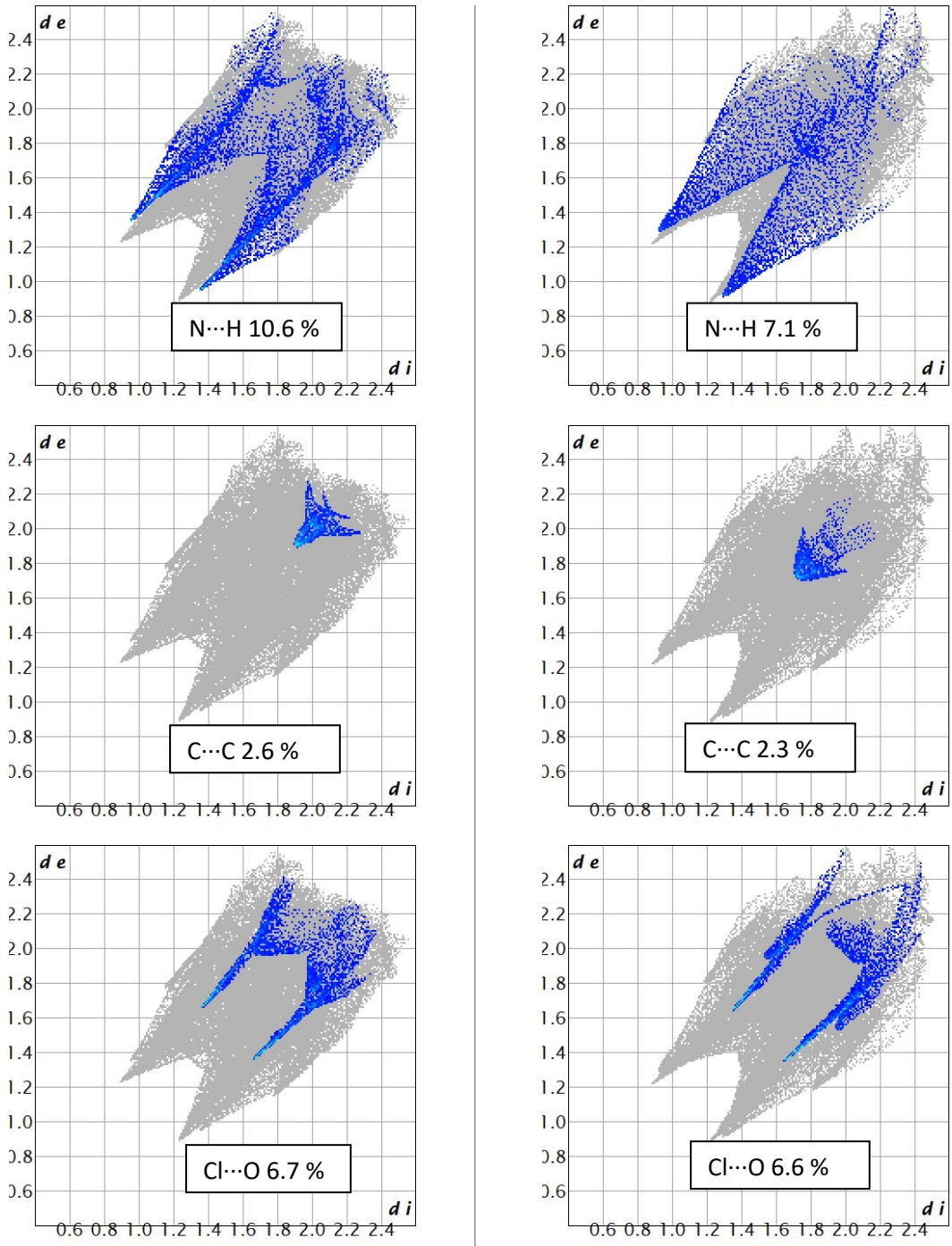


Figure S8 Contd. Hirshfeld 2-D fingerprint plots for [A] CTZ form I and [B] CTZ form IV.