

Electronic Supplementary Information (ESI)

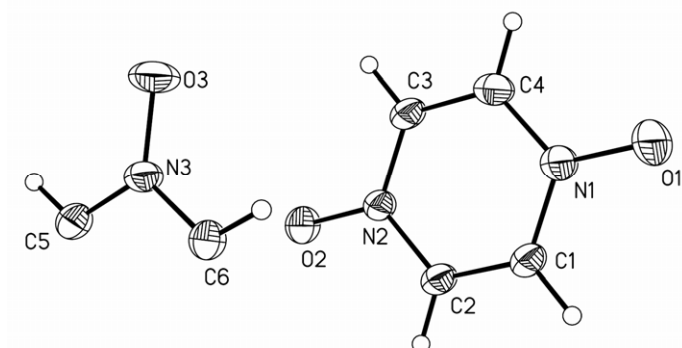


Figure S1 ORTEP of pyrazine-*N,N'*-dioxide (form 1, space group *Pnma*) drawn at 35% probability level for non-hydrogen atoms. There are two half molecule in the asymmetric unit cell. One half molecule resides on the inversion center and another molecule on the mirror plane with 50% atom occupancy.

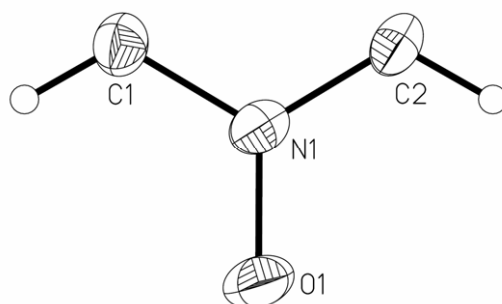
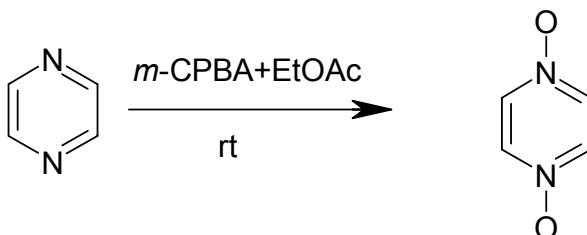


Figure S2 ORTEP of pyrazine- *N,N'*-dioxide (form 2, *P2*₁/*c*) drawn at 35% probability level for non-H atoms. The 0.5 molecule resides on the inversion center.

Pyrazine-N,N'-dioxide



0.5 g (6.25 mmol) of pyrazine was dissolved in 10 mL EtOAc. To the stirred solution, 2.76 g (12.5 mmol) of 70-75% purity *m*-CPBA dissolved in 15 mL EtOAc was added, and the mixture was allowed to react for 24 h. The white to pale brown colored precipitate was filtered and washed with EtOAc, dried and weighed.

Yield: 0.37 g, m.p: 285 °C (dec.).

IR (KBr, cm^{-1}): 3107, 3024, 2096, 1915, 1714, 1483, 1446, 1261, 1032, 873, 804, 542, 410.

$^1\text{H-NMR}$ (D_2O): δ 9.0 (s, 4H).

Crystallization

Pyrazinamide (48 mg, 0.392 mmol), pyrazine-N,N'-dioxide (20 mg, 0.196 mmol) were dissolved in 5 mL water in a 25 mL beaker and the solvent was allowed to evaporate slowly over 3-4 d. X-ray data collection on single crystals showed it to be pure pyrazine-N,N'-dioxide in the orthorhombic space group *Pnma*. This is the first data set collected on PYZNO in our lab. The expected cocrystal was not formed in this crystallization.

Subsequently, form 1 was obtained by crystallization from water, DMF or MeOH + water by slow evaporation at room temperature. This form was most commonly produced in crystallizations.

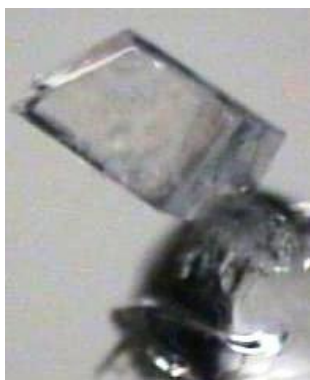


Figure S3 Block-shaped single crystal of pyrazine-N,N'-dioxide (form 1) in space group *Pnma*.

Form 2 was obtained in co-crystallization experiment. Carbamazepine (CBZ, 80 mg, 0.339 mmol) and pyrazine-N,N'-oxide (19 mg, 0.169 mmol) in 1 : 0.5 molar ratio were ground in mortar–pestle via liquid-assisted grinding (few drops of acetonitrile solvent).

IR confirmed the formation of a new binary phase, and the material was dissolved in 5 mL DMF and allowed to evaporate slowly in a 25 mL beaker. Two types of crystals appeared after 1 d – plate and needle morphology corresponding to new form 2 and form 1 respectively. Both forms were obtained concomitantly. If crystals were not separated from the flask after 1 d, they re-dissolve into the solution in 4-5 d and after slow evaporation for a few more days the 1 : 0.5 cocrystal of CBZ and PYZNO crystallizes from solution.

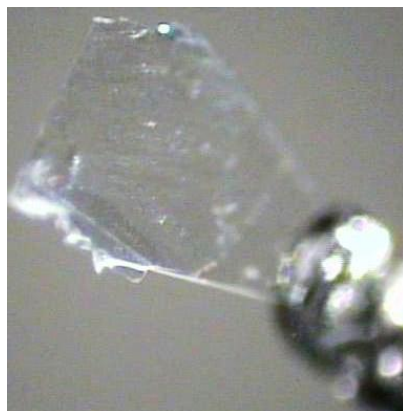


Figure S4 Plate-like single crystal of pyrazine-N,N'-dioxide (form 2) in space group $P2_1/c$.

The as-prepared PYZNO crystallized from EtOAc is a concomitant mixture of form 1 (~75%) and form 2 (~25%) based on powder XRD match. The 2nd crystallization batch yielded pure form 2. Subsequent preparations in several batches of PYZNO (3rd, 4th and 5th) gave pure form 2. Single crystal quality material was obtained only by co-crystallization with CBZ as described above.

Crystal data

Form 1: $C_4H_4N_2O_2$ $M = 112.09 \text{ g mol}^{-1}$, size $0.41 \times 0.21 \times 0.06 \text{ mm}^3$, orthorhombic, space group $Pnma$, $a = 11.8672(18)$, $b = 12.2217(19)$, $c = 6.4287(10) \text{ \AA}$, $V = 932.4(2) \text{ \AA}^3$, $Z = 8$, $\rho_{\text{cal}} = 1.597 \text{ g cm}^{-3}$, $T = 293(2) \text{ K}$, $\mu = 0.131 \text{ mm}^{-1}$, $F(000) = 464$, $2\theta_{\text{max}} = 52^\circ$, 4790 reflections collected, 956 unique ($R_{\text{int}} = 0.031$), 643 observed reflections with $I > 2\sigma(I)$, 85 parameters, $R_1 = 0.0605$, $wR_2 = 0.1584$ (all data).

Form 2: $C_4H_4N_2O_2$, $M = 112.09 \text{ g mol}^{-1}$, size $0.48 \times 0.20 \times 0.02 \text{ mm}^3$, monoclinic, space group $P2_1/c$, $a = 3.7239(13)$, $b = 11.010(4)$, $c = 5.683(2) \text{ \AA}$, $\beta = 96.237(5)$, $V = 231.62(14) \text{ \AA}^3$, $Z = 2$, $\rho_{\text{cal}} = 1.607 \text{ g cm}^{-3}$, $T = 293(2) \text{ K}$, $\mu = 0.132 \text{ mm}^{-1}$, $F(000) = 116$, $2\theta_{\text{max}} = 52^\circ$, 2286 reflections collected, 455 unique ($R_{\text{int}} = 0.029$), 401 observed reflections with $I > 2\sigma(I)$, 37 parameters, $R_1 = 0.0564$, $wR_2 = 0.1220$ (all data).

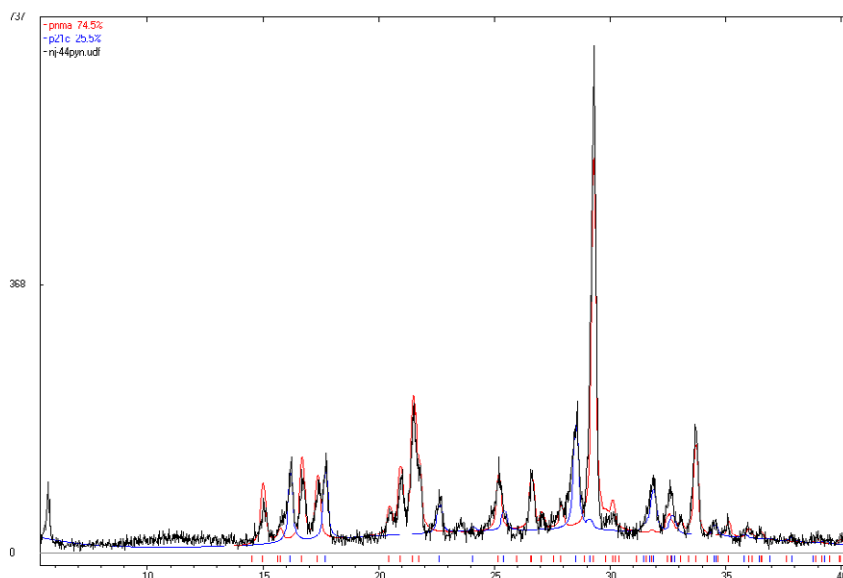
X-ray data on single crystals were collected on Bruker-Nonius Smart Apex CCD diffractometer using Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$). SMART was used for collecting

frames, indexing reflections, and determining lattice parameters. SAINT was used for integration of reflections intensity and scaling. Absorption correction was done in SADABS and SHELX-TL was used for space group determination, structure solution, and least-squares refinements on F^2 . Structures were solved by direct methods and non-hydrogen atoms were refined anisotropically. Hydrogen atoms (C–H) were generated geometrically and allowed to ride on the bound heavy atom. Figures were prepared in X-Seed.

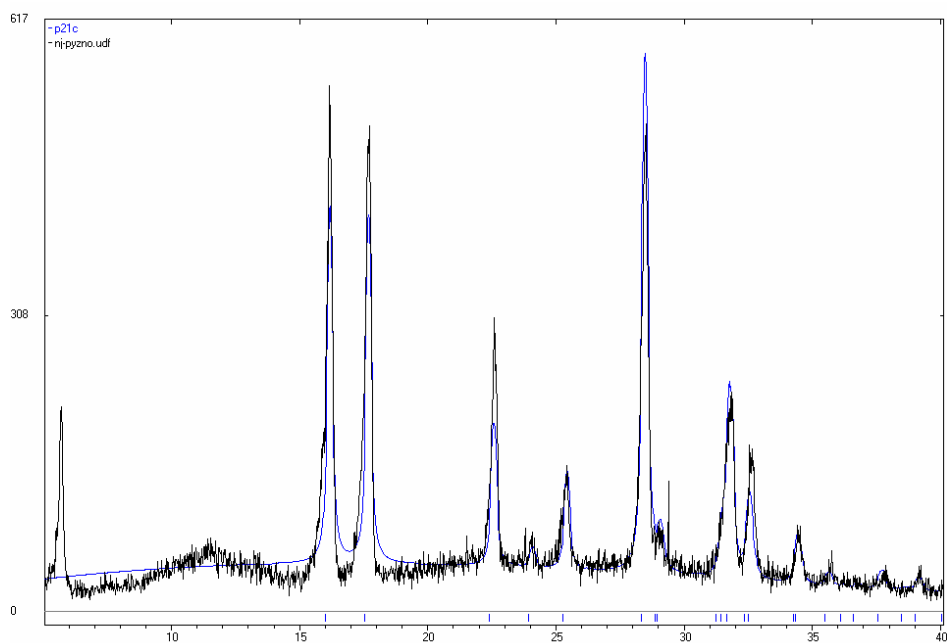
- 1 G. M. Sheldrick, *SHELXS-97* and *SHELXL-97*, Programs for the Solution and Refinement of Crystal Structures, University of Göttingen, Germany, 1997.
- 2 G. M. Sheldrick, *SADABS*, Program for Empirical Absorption Correction of Area Detector Data, University of Göttingen, Germany, 1997.
- 3 L. J. Barbour, *X-Seed*, Graphical Interface to *SHELX-97* and *POV-Ray*, University of Missouri-Columbia, USA, 1999.
- 4 N. Kraus, G. Nolze, *POWDER_CELL*, version 2.3, Federal Institute for Materials Research and Testing, Berlin, Germany, 2000.

Phase transitions

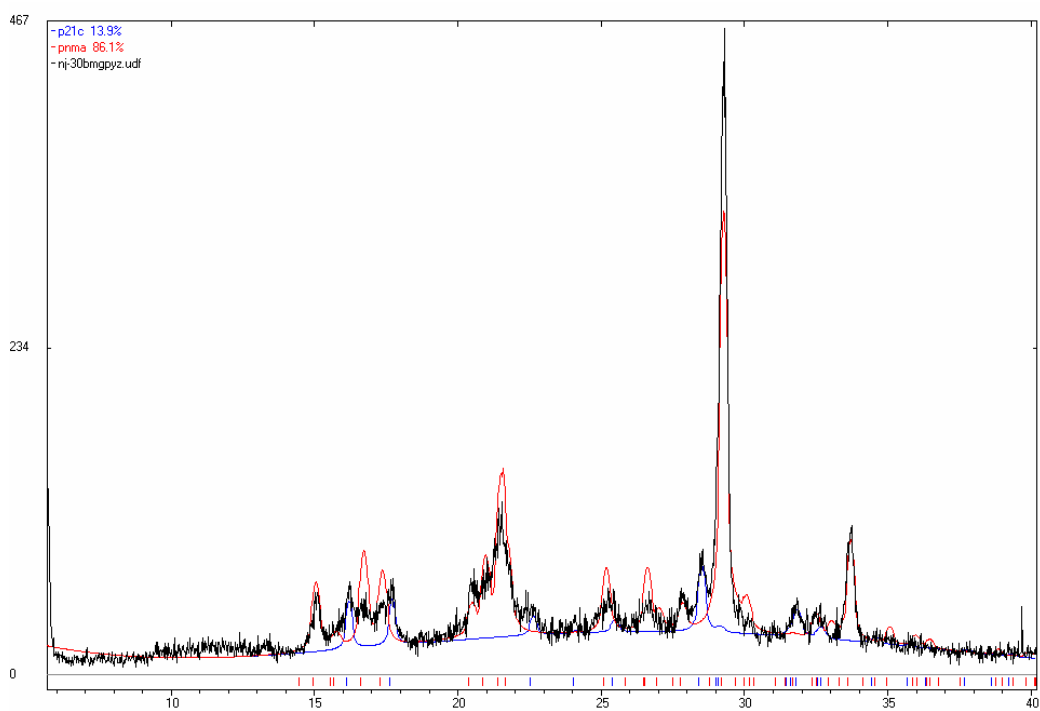
Bulk material of both the polymorphs was readily obtained in preparative quantities. 100% pure $P2_1/c$ form 2 was obtained from EtOAc. 100 % pure $Pnma$ form 1 was obtained either by solid-state grinding for 1 h of form 2 or slow crystallization from DMF. Powder X-ray diffraction patterns were recorded on a PANalytical 1830 (Philips Analytical) diffractometer using Cu-K α X-radiation ($\lambda = 1.54056 \text{ \AA}$) at 35 kV and 25 mA, over 2θ range of 5-50° at scan rate of 1° min^{-1} . Powder_Cell program was used for least squares refinement and to generate calculated diffraction lines from the X-ray crystal structure.



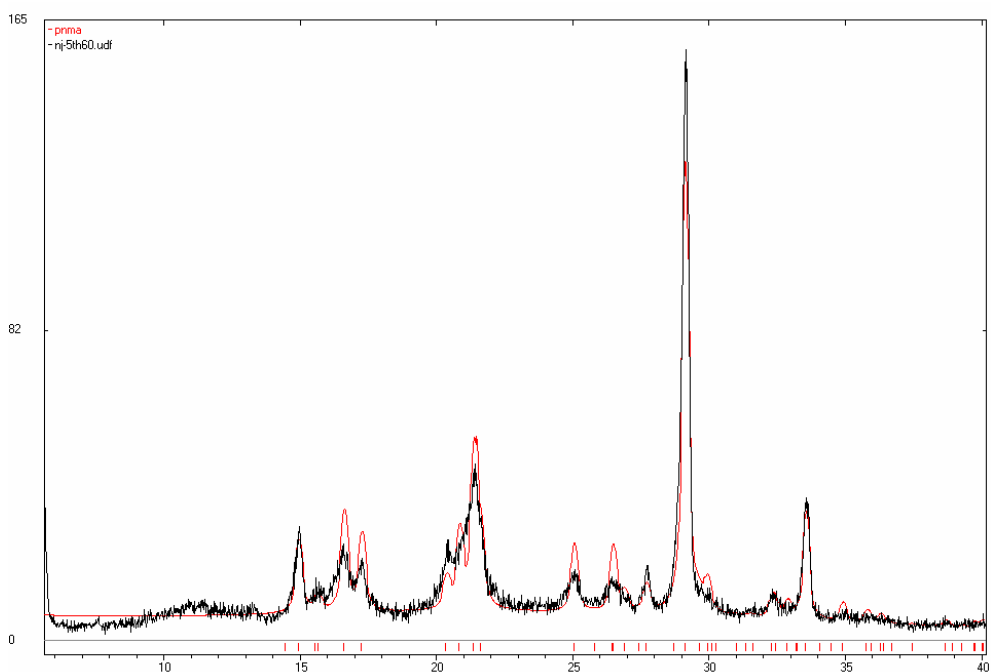
(a)



(b)



(c)



(d)

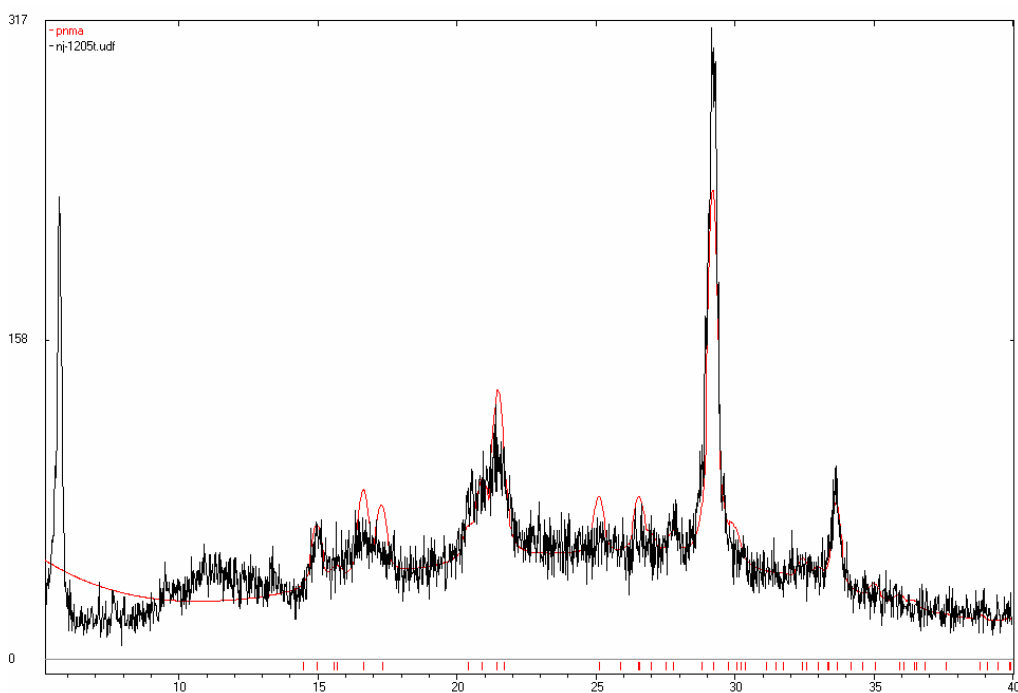


Figure S5 (a) Freshly prepared PYZNO by *m*-CPBA oxidation is a mixture of form 1 (75%) and form 2 (25%) by least-squared refinement in Powder_Cell. (b) Second batch of PYZNO prepared using *m*-CPBA is 100% form 2. (c) 100 mg of pure form 2 was ground in mechanical ball-mill for 30 min. PXRD shows 85% conversion to form 1 and 15% unreacted form 2. (d) After 60 min of further grinding the material in (c) is

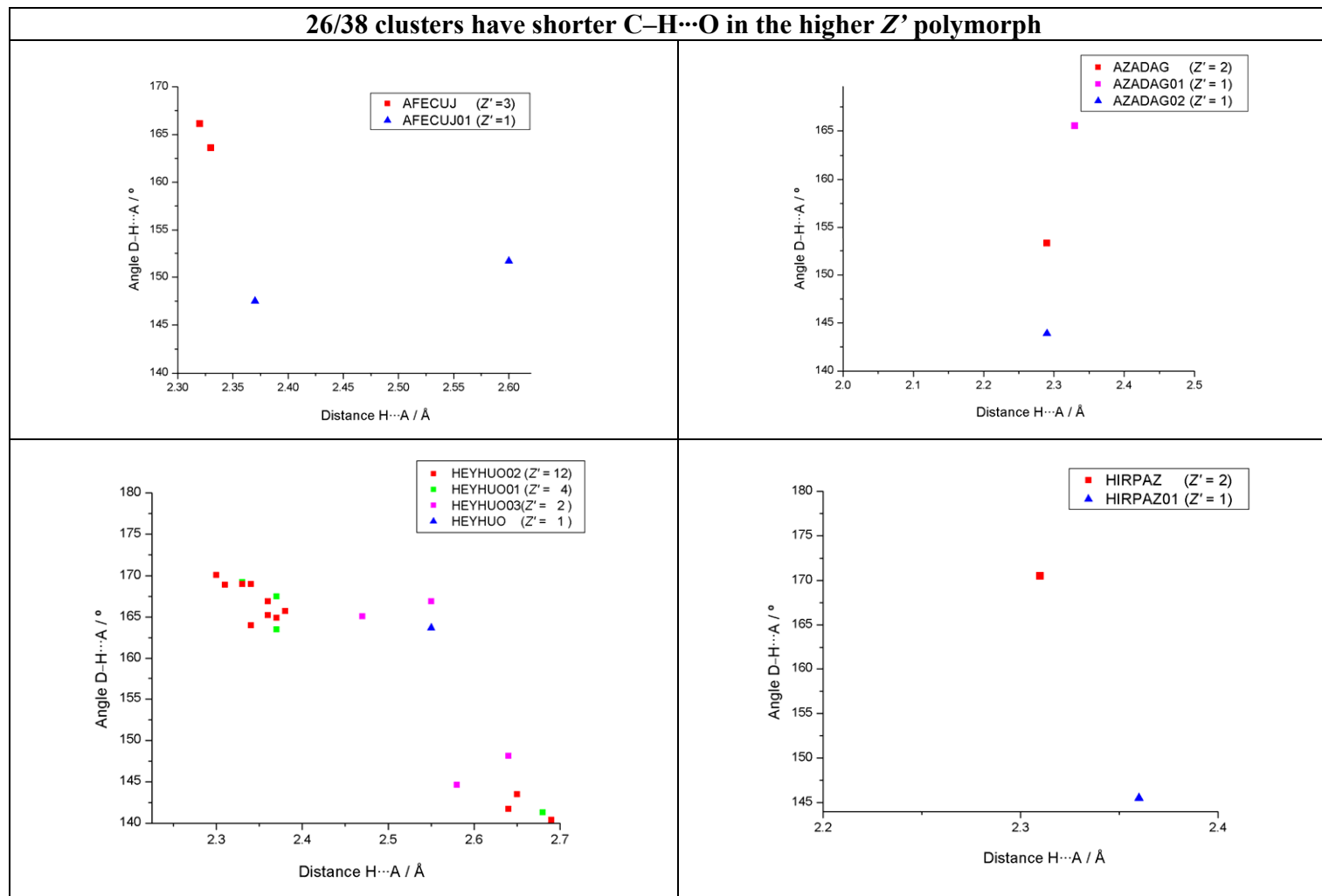
completely converted to form 1. (e) Continuing the grinding for another 1 h gave form 1 (no change) but the amorphous content increases because of prolonged grinding. These phase transition experiments suggest that form 1 is the thermodynamic phase and form 2 is the kinetic polymorph. Black trace is the experimental powder pattern and red and blue lines are for form 1 and form 2, respectively. The intense peak at ca. 5° is due to instrument artifact.

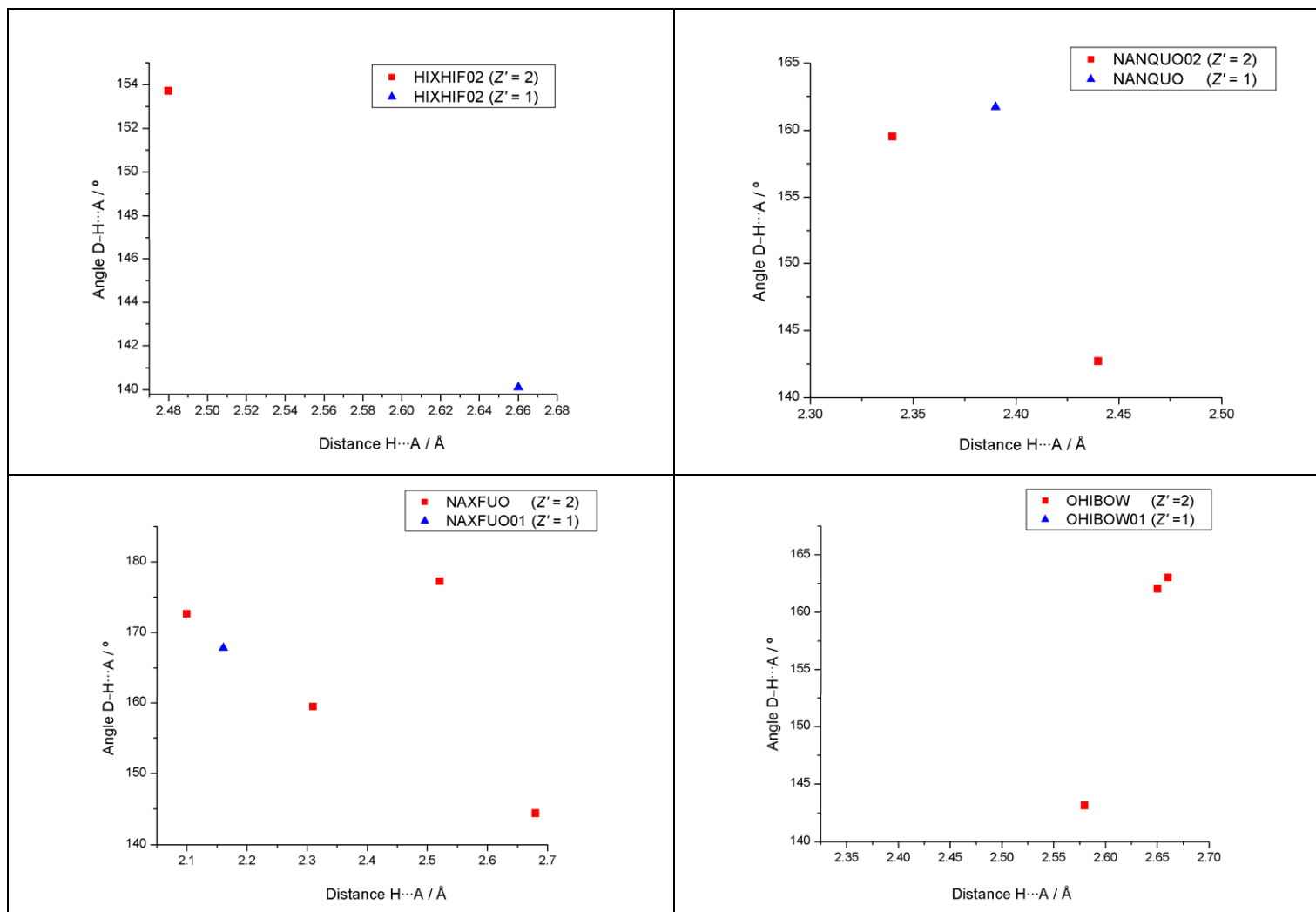
Cambridge Structural Database (CSD) search for C–H···O polymorph clusters

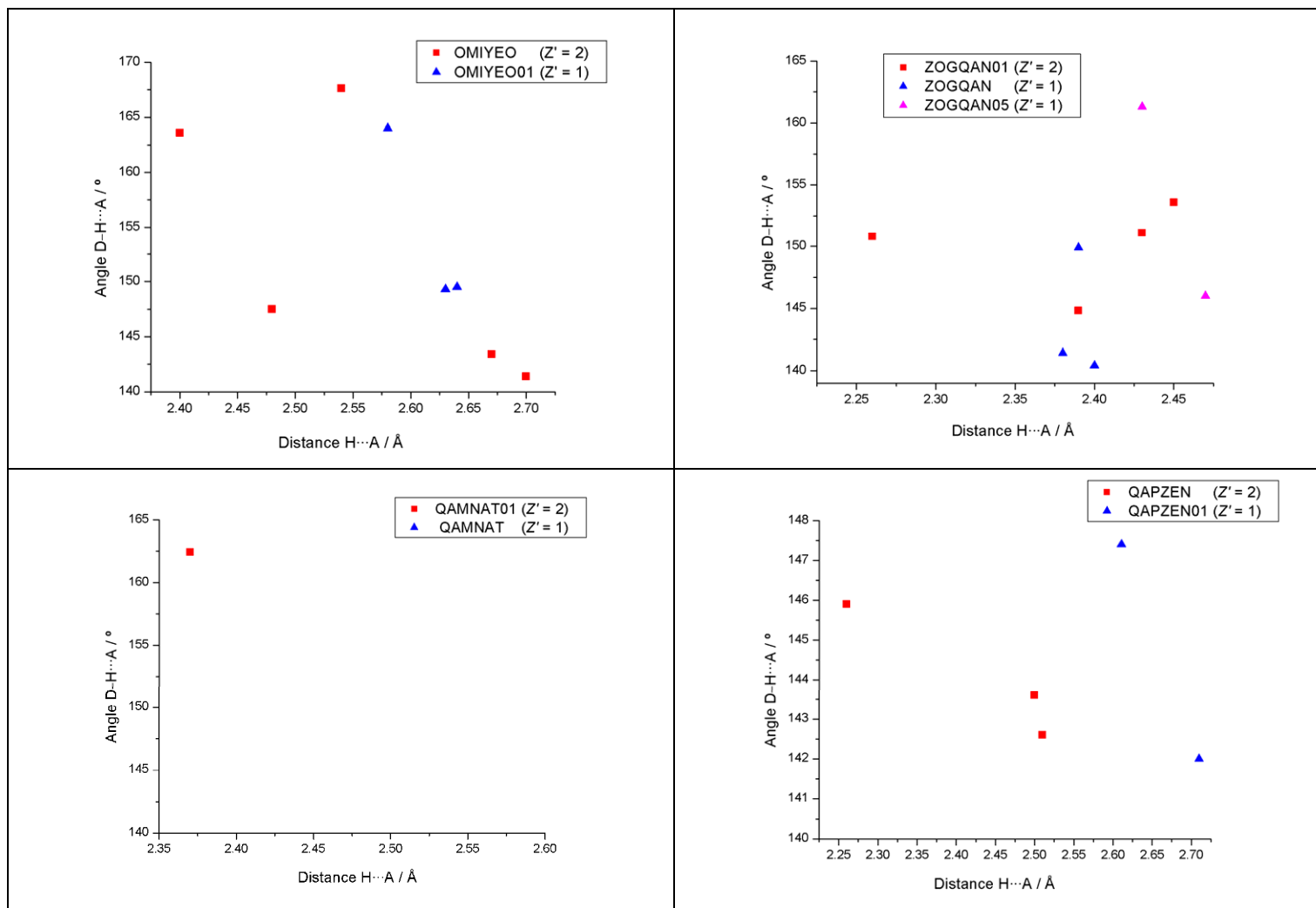
CSD version 5.27, ConQuest 1.9, November 2006 release, May 2007 update was searched to assess the correlation of C–H···O interaction strength with high Z' in polymorphic systems. Crystal structures with $Z' > 1$, polymorph, no O–H, no N–H, 3D coordinates determined, R -factor < 0.1 , no disorder, no errors, not polymeric, no powder structures and only organic compounds were searched. Structures published between 1995-present were considered (after 1994) because it is possible to determine multiple Z' crystal structures accurately in the post-CCD X-ray diffractometer era. Out of 184 CSD hits, 38 polymorphic pairs are selected manually where different polymorphs contain different Z' in the asymmetric unit. All crystal structures were visualized in Mercury 1.5. C–H···O interactions were neutron-normalized and values were tabulated. Distance–angle scatter plot of C–H···O interactions was plotted in Origin 7.0. We found that 26/36 (68%) structures show that the higher Z' structures has shorter C–H···O bond compared to the lower Z' polymorph of longer interaction. The reverse of this trend is true in 12/36 (32%) crystal structures – the lower Z' form has shorter C–H···O interaction. Scatter plots are displayed in Figure S6.

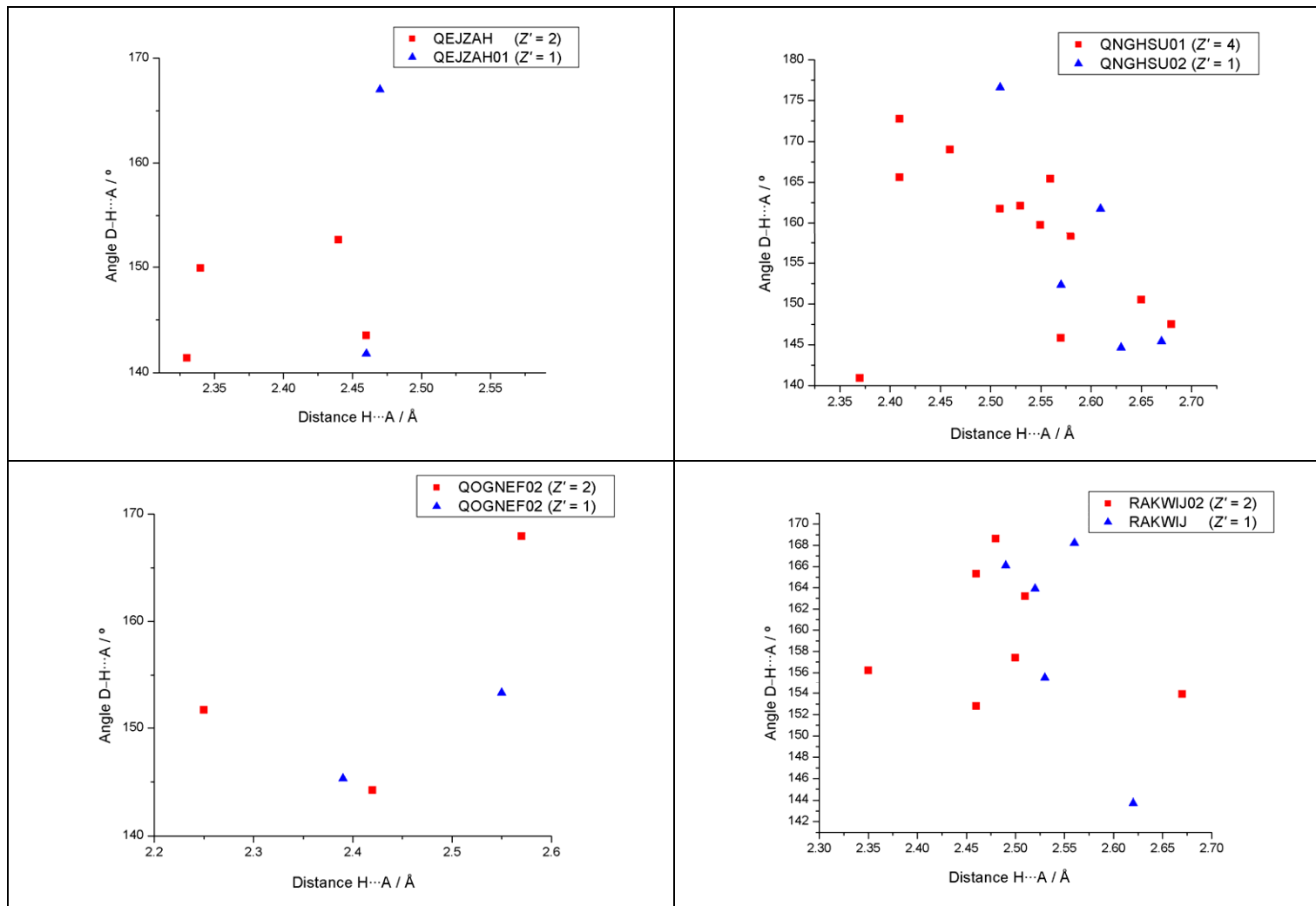
Cambridge Structural Database (CSD) search for O–H···O polymorph clusters

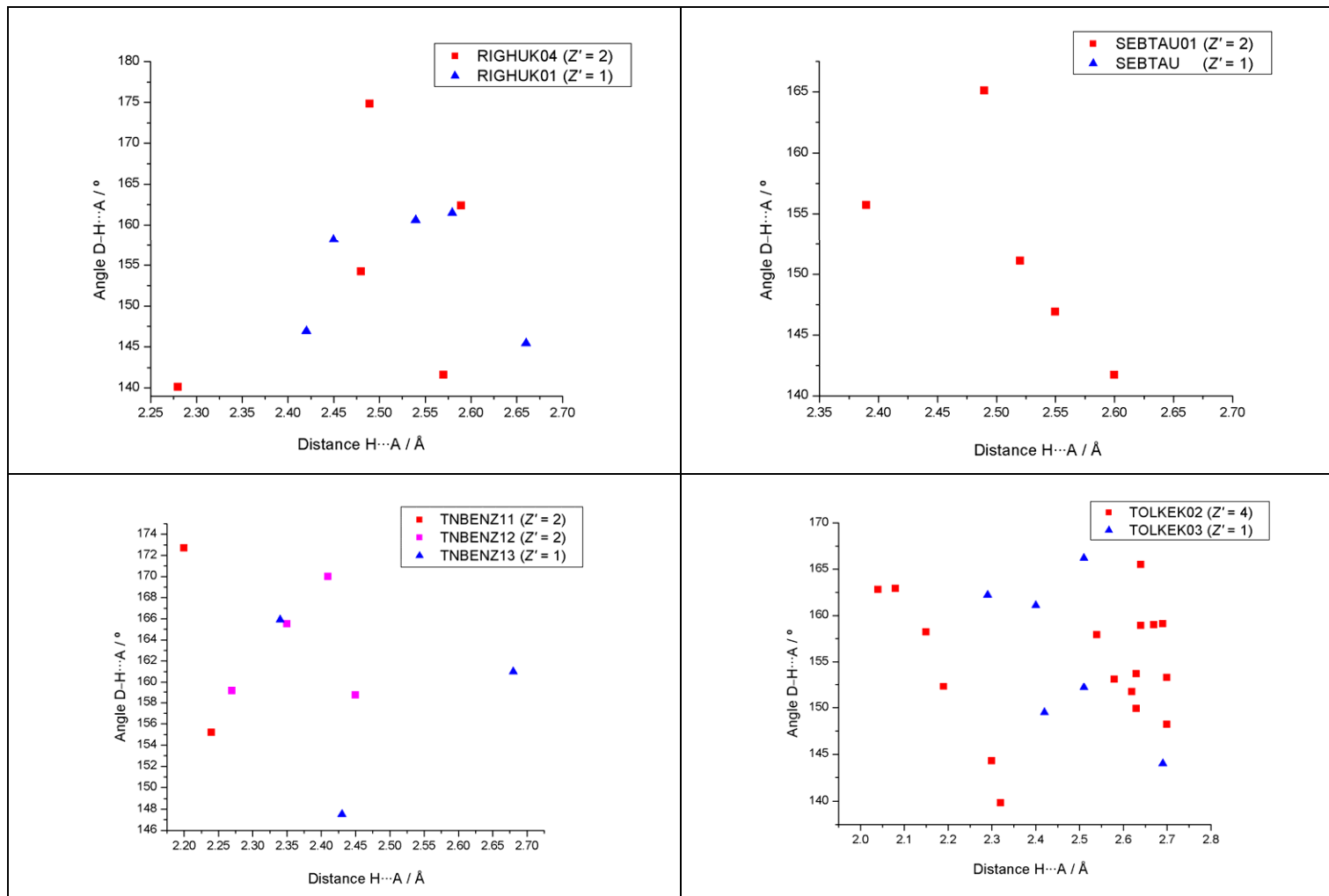
Polymorph, after 1994, must have O–H, must not have COOH, no N–H, 3D coordinates reported, R -factor < 0.1 , not disordered, no errors, not polymeric, no powder structures and only organics were the search criteria. Cambridge Structural Database, CSD version 5.27, ConQuest 1.9, November 2006 release with May 2007 update gave 327 hits. 39 polymorphic pairs are selected manually where different polymorphs contain different Z' in the asymmetric unit. 8 clusters of polymorphs with REFCODE (ASIXEF, CACBAK, FEFQUD, INOCET, REPFOH, VOSQUP, WEFKEY and YAXDUW) have either O–H not participating in O–H···O interactions or involved in intramolecular O–H···O interactions. We were now left with 31 sets. One example from the recent literature that is not yet included in the CSD (M. Gdaniec, *CrystEngComm*, 2007, **9**, 286.) was added to the list. Total number of polymorph clusters analyzed is 32. Neutron normalized O–H···O interactions in each of these polymorphic systems were plotted in Origin 7.0. In 22/32 structures (69%) higher Z' structures have shorter O–H···O H bonds than their corresponding lower Z' structure. In 7/32 cases (21%) lower Z' structure has shorter O–H···O H bonds. There is no definite conclusion in 3 sets (10%) when the temperature correction is taken into consideration because the distance difference is too small for comparison. Scatter plots are displayed in Figure S7.

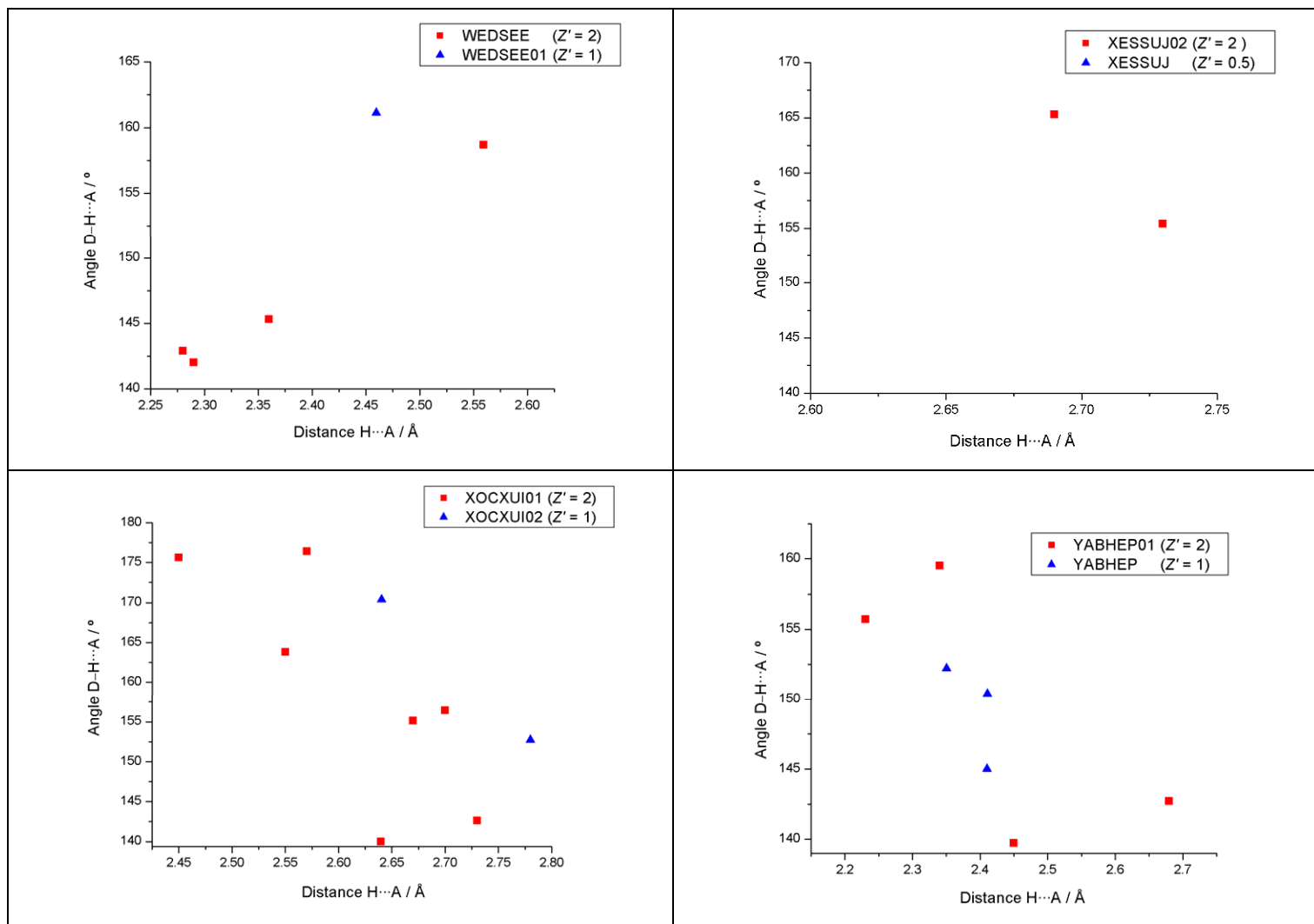


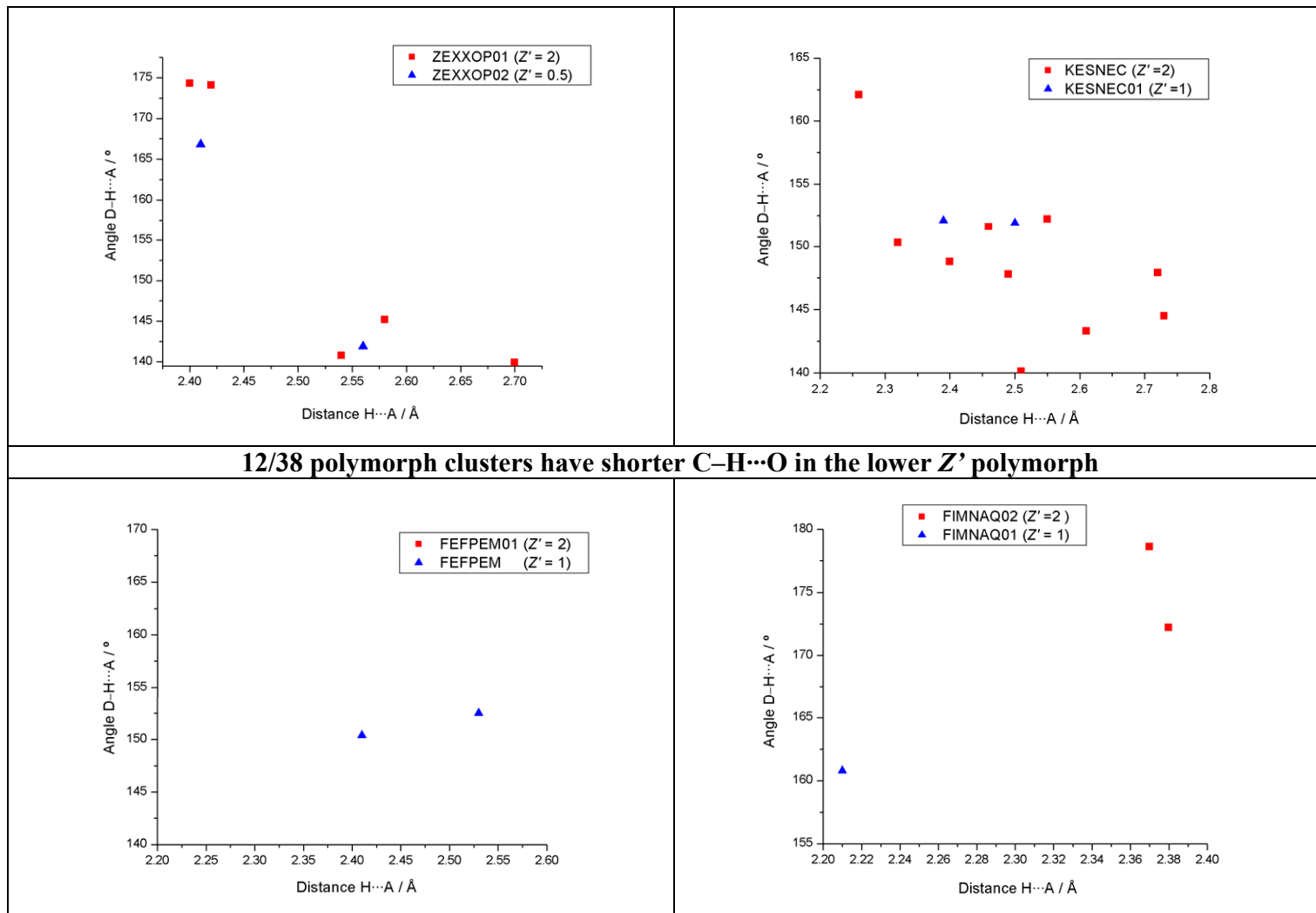


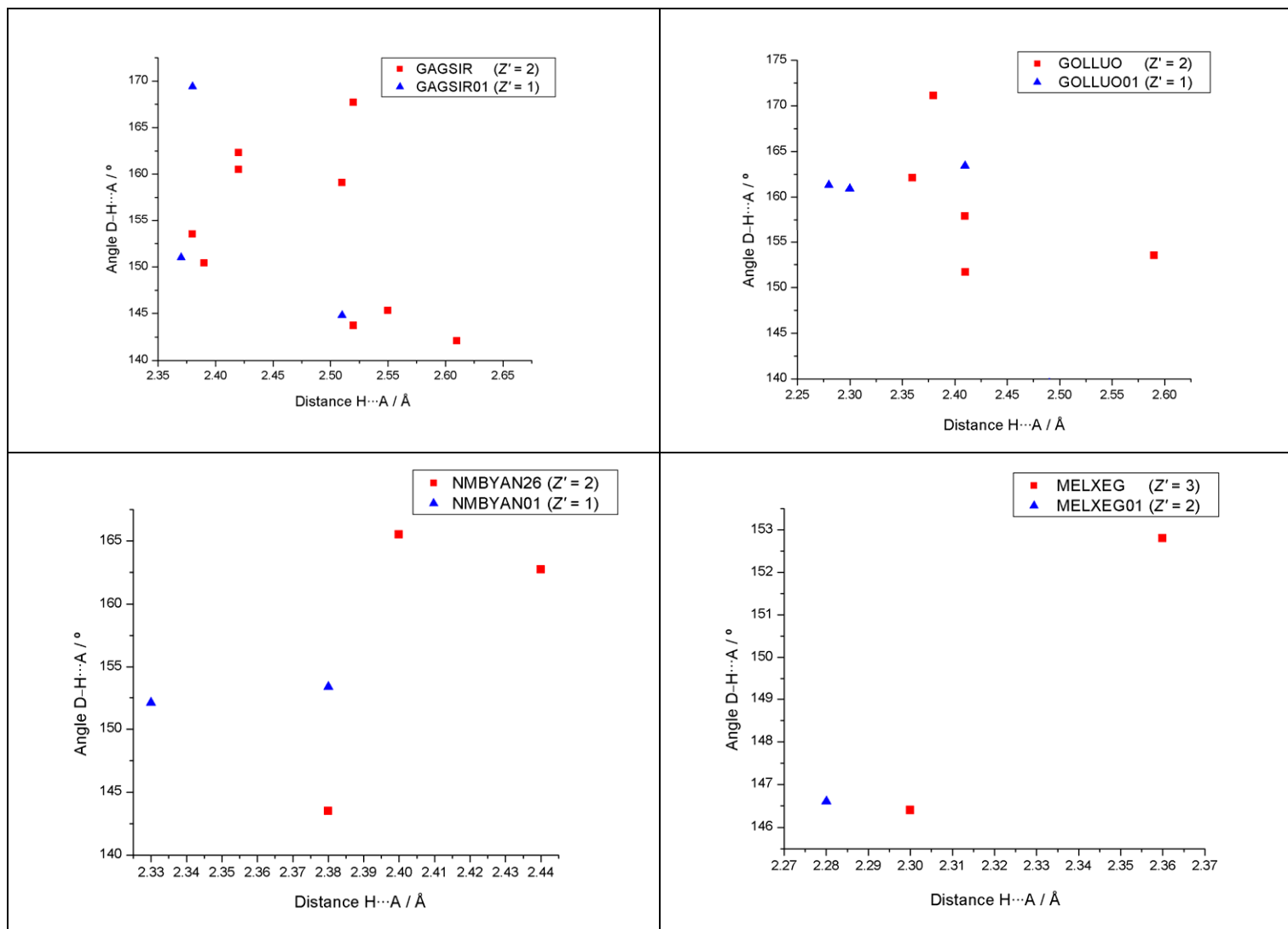


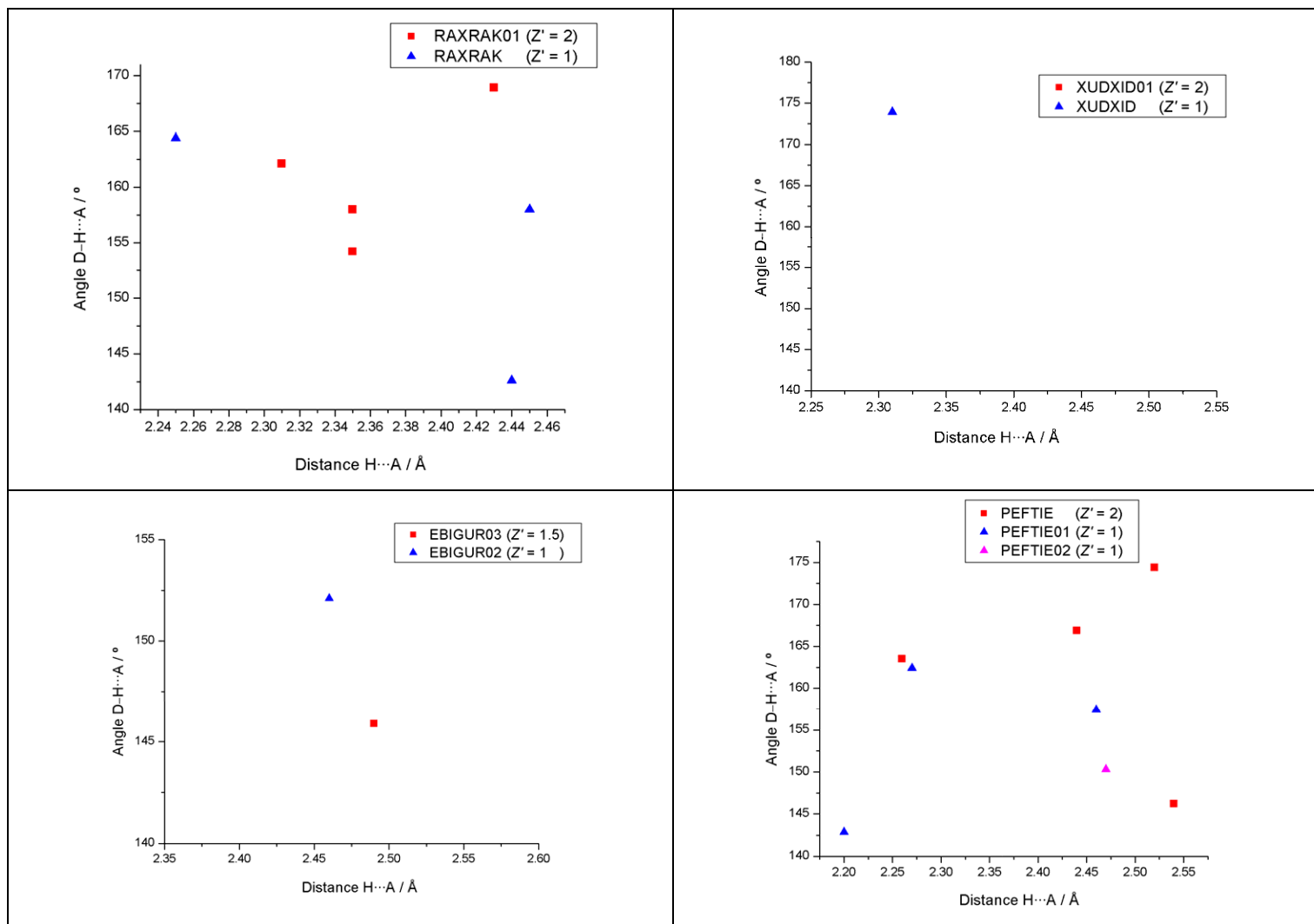












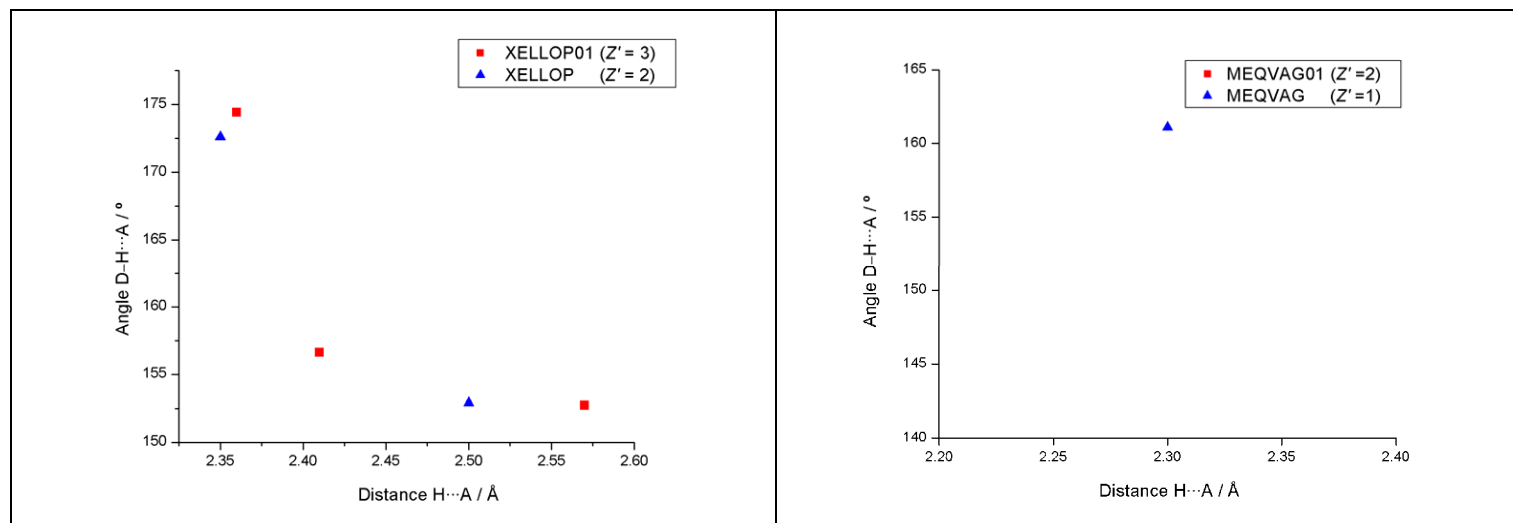
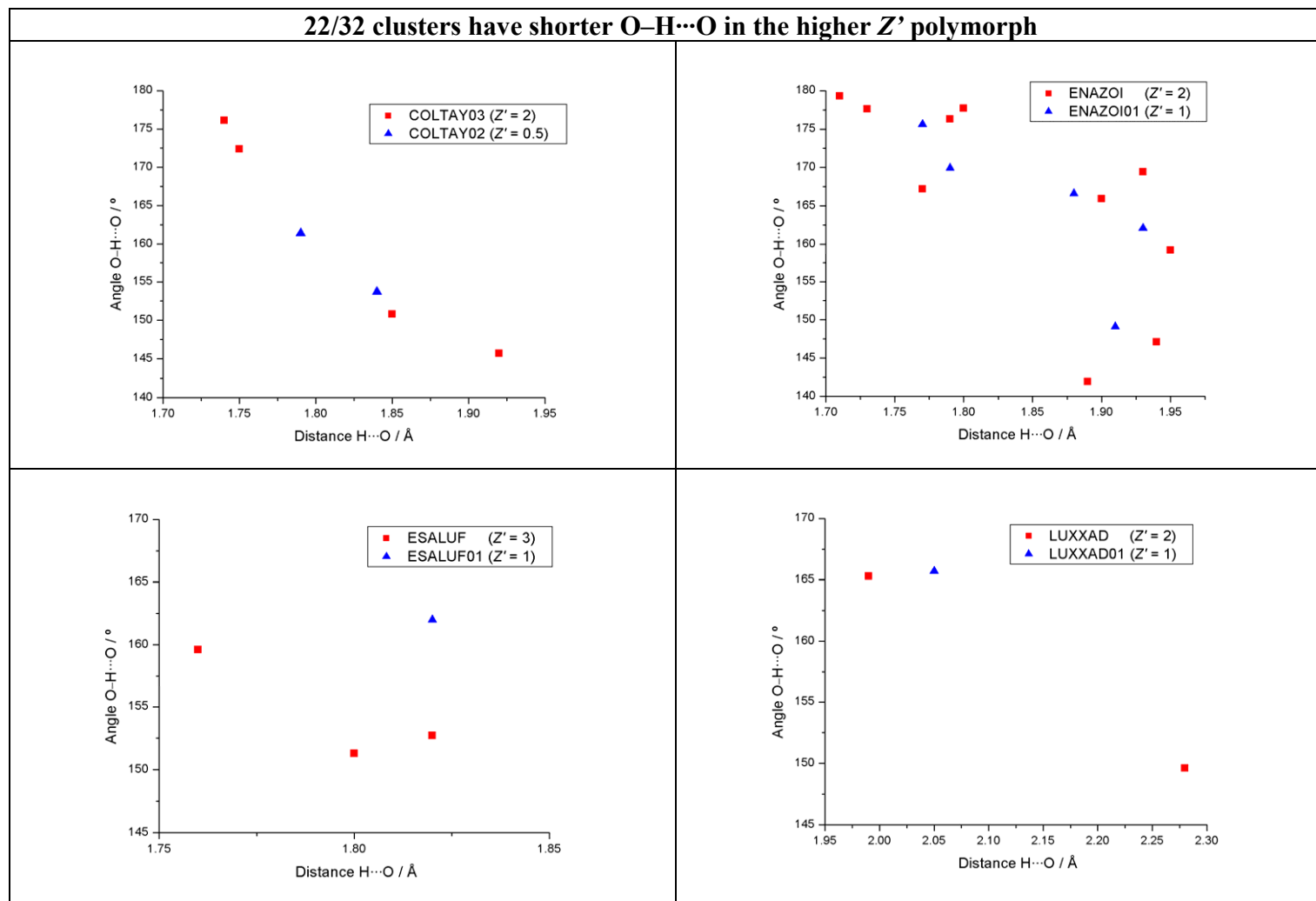
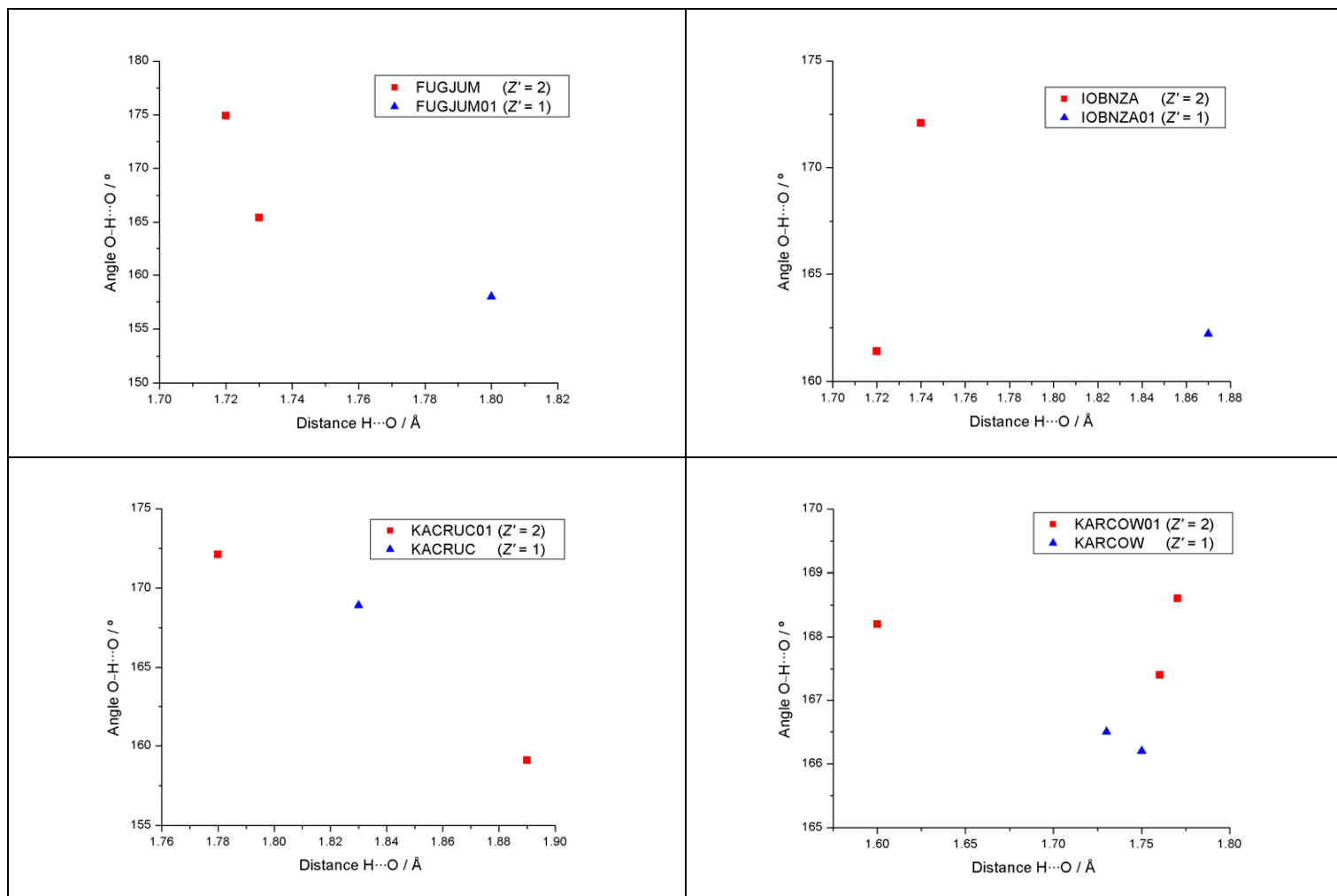
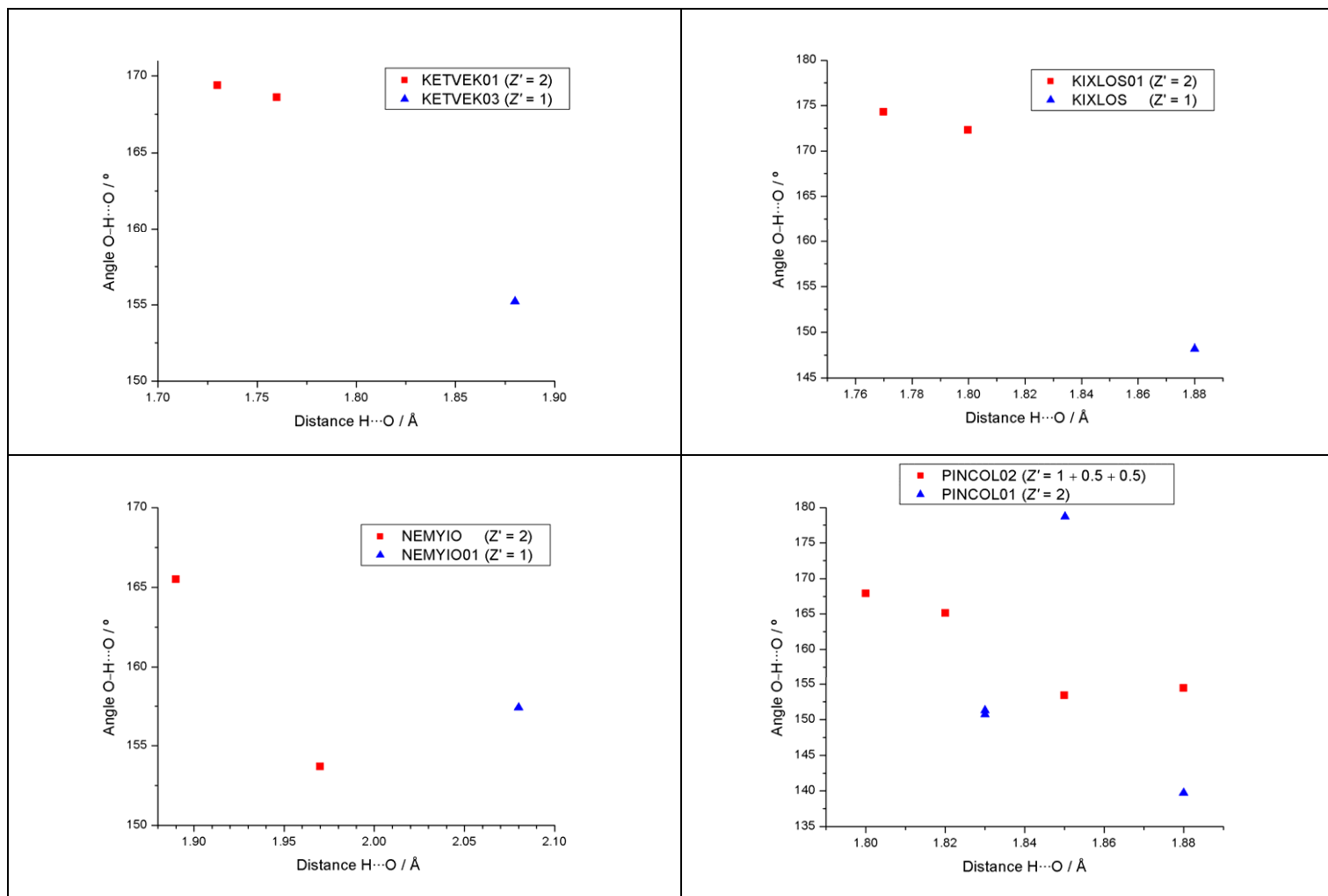
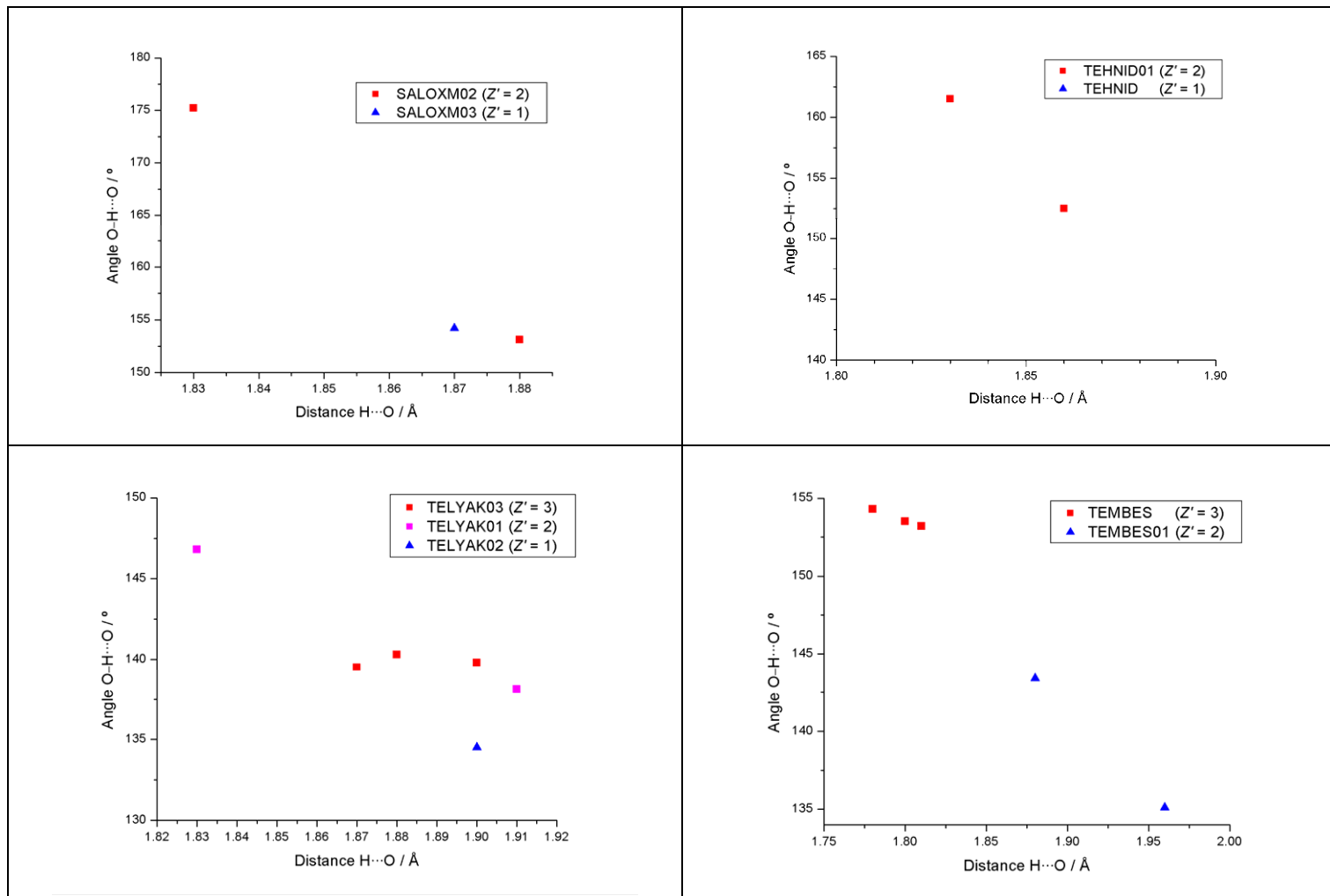


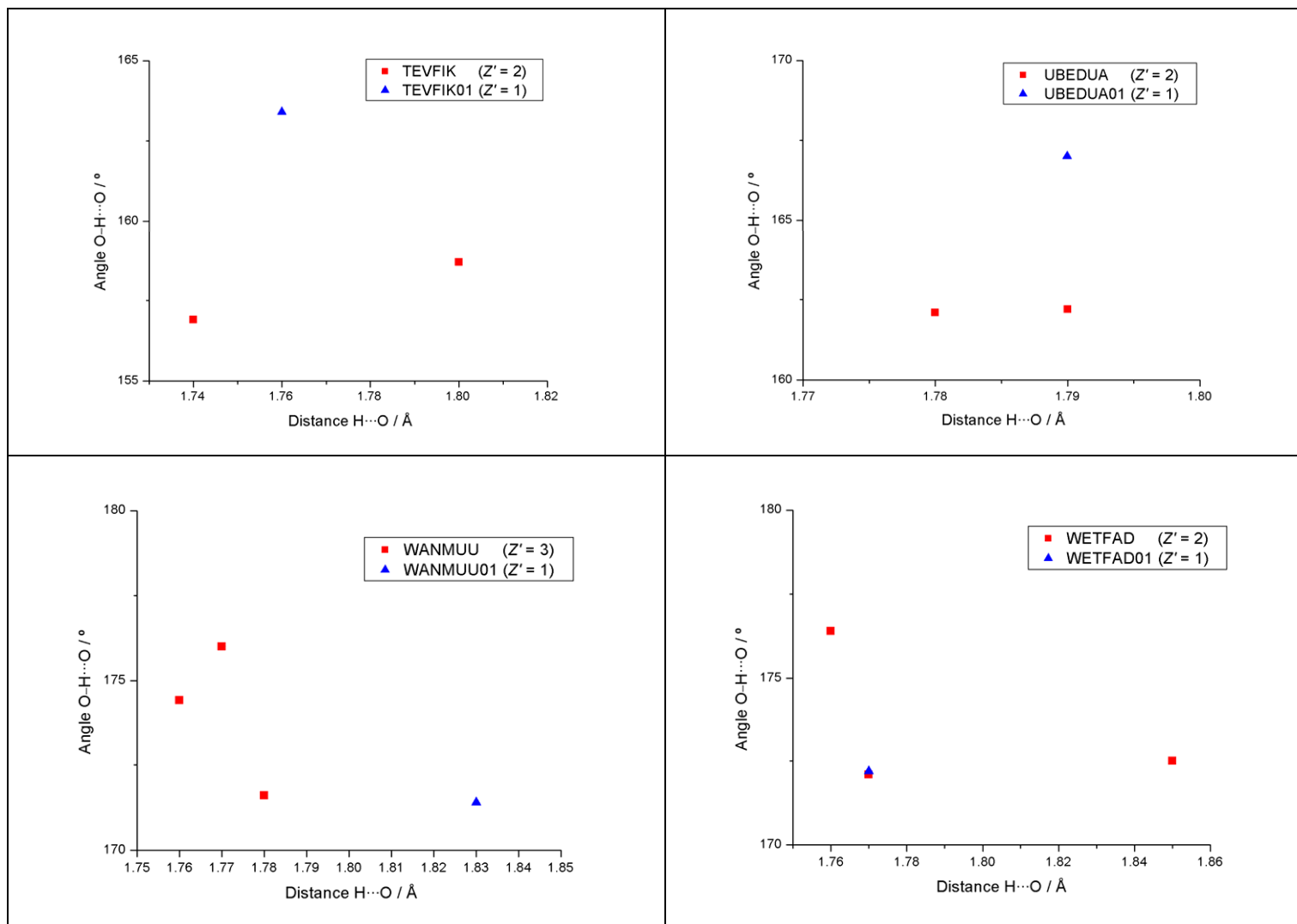
Figure S6 Distance–angle C–H...O scatter plot of polymorph clusters having different Z' in different crystal structures published during 1995-2007. CSD reftcodes are indicated in each case.

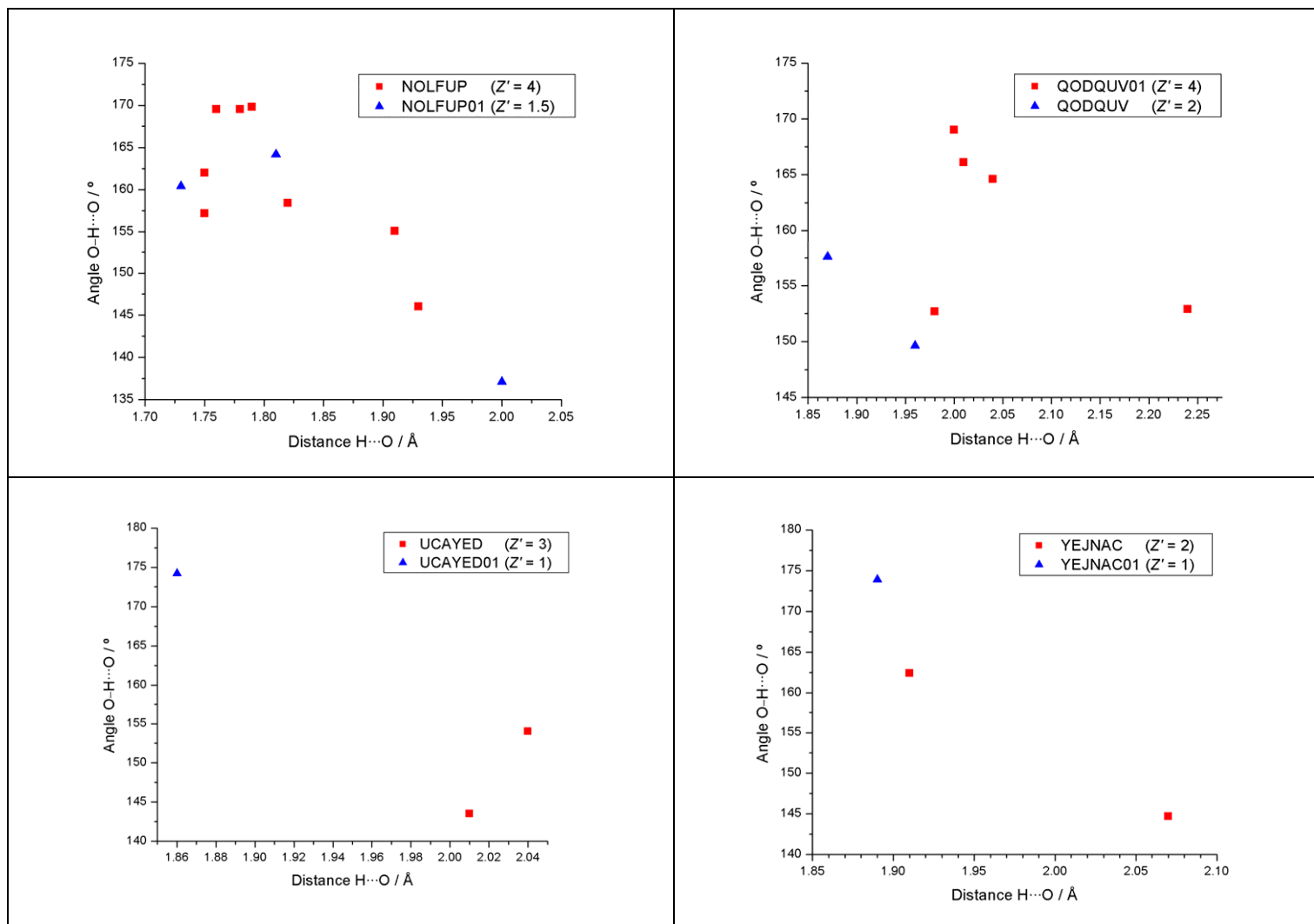


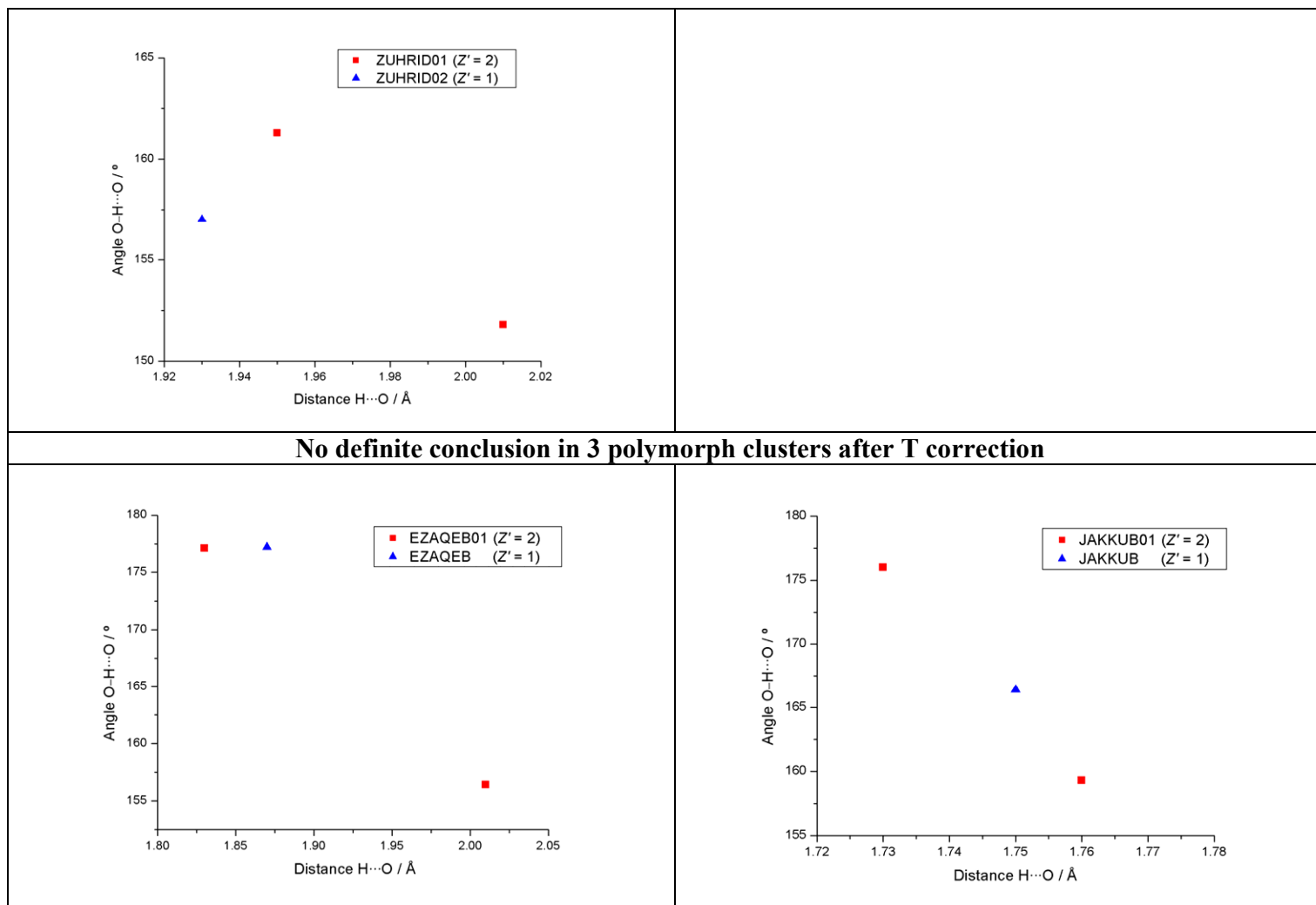












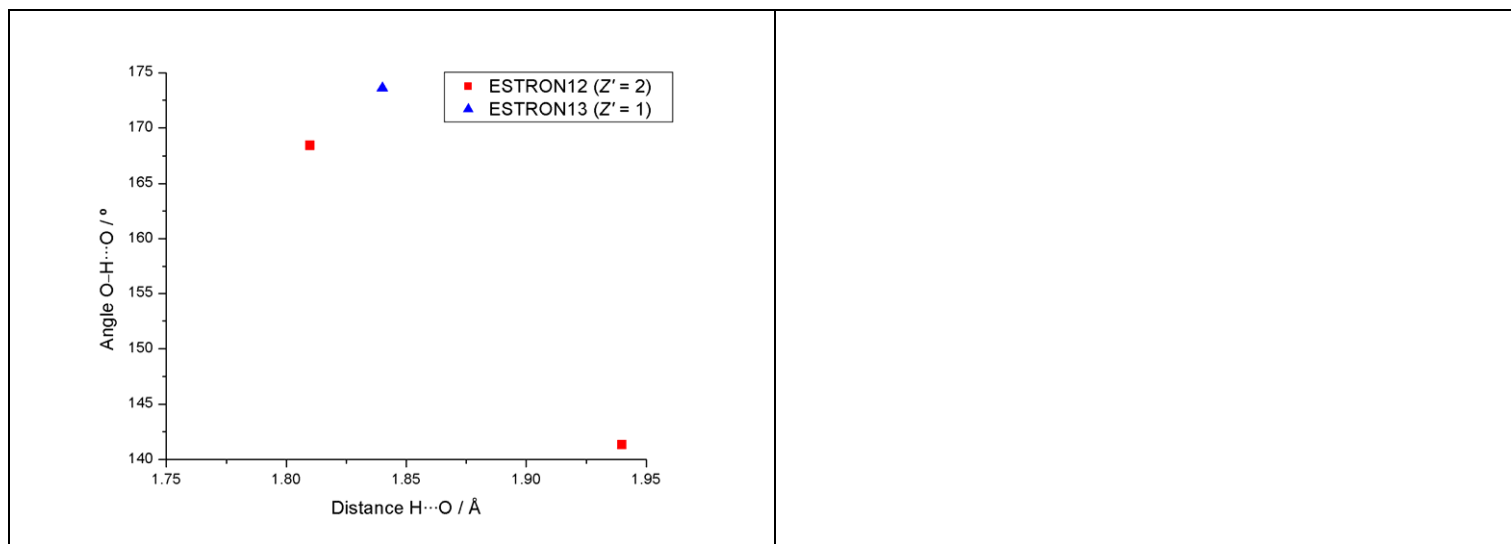


Figure S7 Distance–angle O–H...O scatter plot of polymorph clusters having different Z' in different crystal structures published during 1995-2007. CSD refcodes are indicated in each case.