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Supporting Information for
Accurate Crystal Structures and Chemical Properties from NoSpherA2

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Table S1: Crystallographic, measurement and refinement details of the compounds measured for this study

	New Measurements			*Re-Refinements*	
Structure	$OsH_6(PC_{12}H_{19})_2$	CaF_2	$B_6H_6(NH_4)_2$	$C_{10}H_{10}N_4F_2$	$(C_6H_6O_2)(CO_2)_{0.854}$
Space group	P 2_1/n	Fm-3m	Fm-3m	P 2_1/n	R-3
a /Å	10.8918(1)	5.45095(5)	9.10295(12)	6.9196(1)	16.1737(2)
b /Å	13.7619(1)	5.45095(5)	9.10295(12)	14.5749(2)	16.1737(2)
c /Å	17.0714(2)	5.45095(5)	9.10295(12)	9.7248(1)	5.7050(1)
β /°	98.563(1)	90	90	90.637(1)	90
V /Å^3	2530.34(4)	161.963(3)	754.304(17)	980.71(2)	1292.42(3)
T /K	120	100	100	120	100
Resolution /Å	0.58	0.40	0.40	0.70	0.45
Wavelength /Å	0.71073	0.56087	0.71073	0.71073	0.71073
R_{int}	0.0582	0.0673	0.0243	0.0519	--
Avg. redundancy	19.05	55.20	11.91	4.77	1
Completeness	1.00	1.00	1.00	1.00	0.997
Average I/σ	40.3	85.1	85.5	35.1	39.4
# of refln. measured	196209	5299	4336	13911	3389
# of unique refln.	13109	96	364	2975	3388
Criterium for observed refln.	$F_o^2 > 2\sigma(F_o^2)$				
# of observed refln.	11278	96	364	2456	2937
Weighting scheme	0.0005/0.2531	0.0175/ 0.0607	0.0110/0.0085	0.0177/0.0	0.0295/0.0367
Level of theory	DKH2-PBE/x2c-TZVPP	PBE/def2-TZVPP			
QM-software	ORCA				
Partitioning code/ accuracy	NoSpherA2 / High				
Wfn options	SlowConv/NormalSCF	NormalConv/NormalSCF			
Other options:	Relativistics, No AFIX, DISP	DISP	No AFIX, H Aniso, DISP	DISP	No AFIX, H Aniso, DISP
Final R_1	0.0119	0.0114	0.0095	0.0214	0.0253
Final wR_2	0.0185	0.0279	0.0234	0.0483	0.0655
Max residual density /eÅ^{-3}	1.2148	0.6860	0.1093	0.1588	0.5303
Min residual density /eÅ^{-3}	-0.8989	-0.4146	-0.0662	-0.2130	-0.2211
CCDC deposition number	2034388	2034386	2034385	2034387	2034389

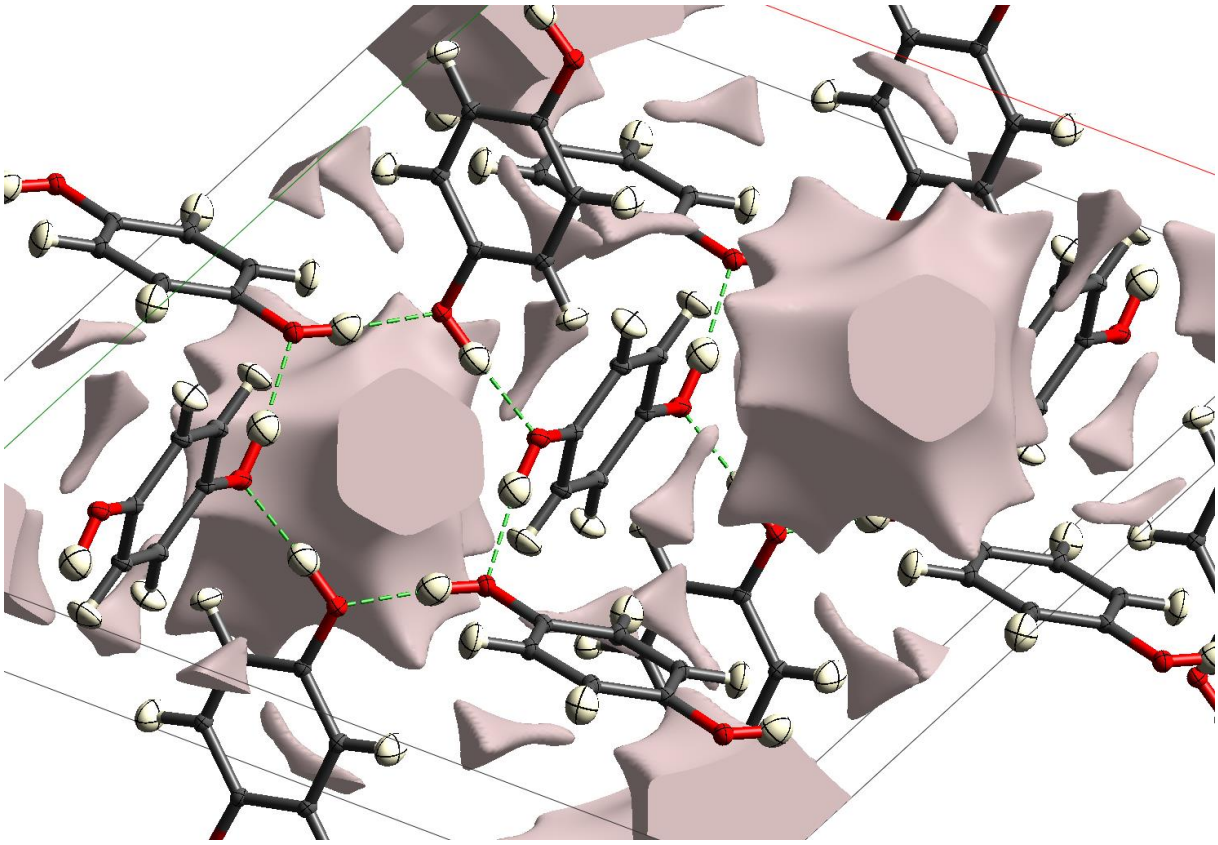

Figure S1: Visualization of voids based on 0.002 a.u. ED isosurfaces of the unit cell of HQ-CO2 if the CO_2 molecules are artificially removed from the structure.

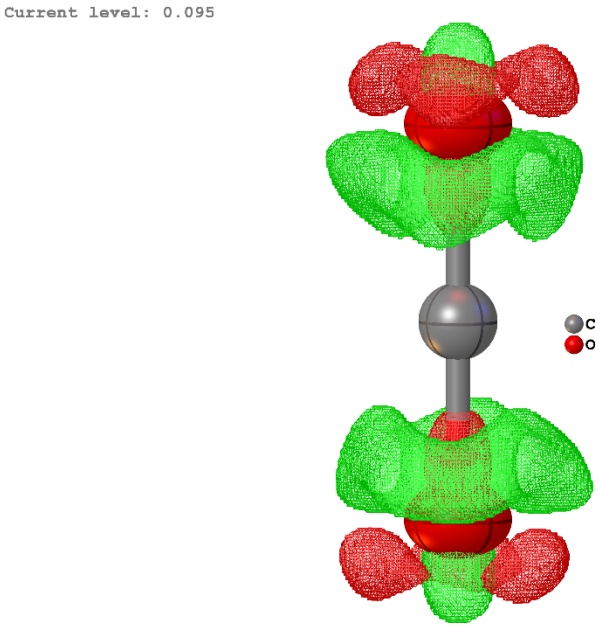

Figure S2: Residual density around the CO_2 molecule inside HQ signaling anharmonic motions. Iso-value = 0.10 $eÅ^{-3}$ (green = positive, red = negative).

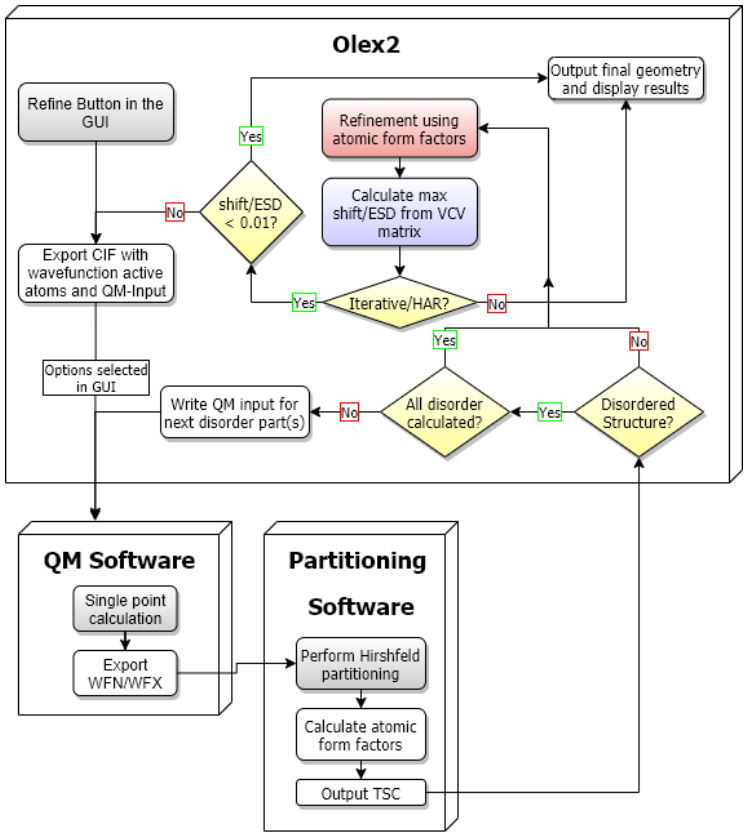

Figure S3: Detailed flowchart of the process behind HAR controlled by *NoSpherA2*.

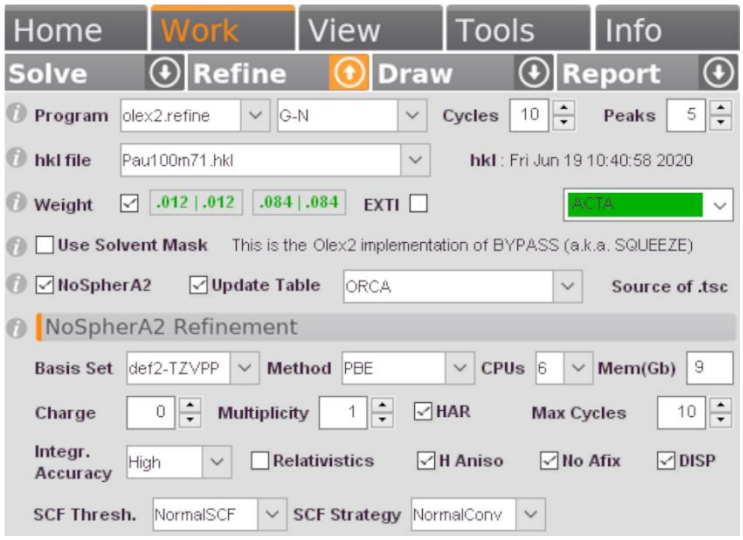

Figure S4: Graphical user interface of *NoSpherA2* inside *Olex2*.

Theoretical framework for non-spherical structure refinement:

This section is an adaptation of reference 65.

Introduction

We have implemented a procedure that allows the use of non-spherical atomic form factors in crystallographic refinement. It is agnostic to the method employed to compute those form factors, as the refinement engine *olex2.refine*[S1] will use tabulated atomic form factors if the file specified below is present. The refinement will proceed as expected from an accomplished crystallographic refinement program, including the ability to make use of constraints, restraints, disorder and other specific tools like twin refinement and solvent masking. This procedure is available from all versions of *Olex2-1.3* and coupled to *NoSpherA2* as described in the main text.[S2]

Crystallographic refinement typically treats atoms as isolated, stand-alone entities with a spherically symmetrical electron charge distribution. A non-spherical treatment arises naturally from the fact that the electron density distribution of an atom is influenced by its environment. Historically, Stewart derived non-spherical form factors for bonded hydrogen atoms and commented: “By necessity, if not by choice, crystallographers have treated bonded atoms as point nuclei with a spherically symmetrical distribution of electron charge”.[S3]

The non-spherical form factors of the individual atoms - and their tabulation in the required format - can be obtained by various means. A possible starting point could be a molecular quantum mechanical wave-function calculation, followed by its transformation into electron densities and then the partitioning into atomic contributions. Alternatively, the electron densities themselves can be approximated using data-based contributing fragments.

Refinements based on non-spherical form factors are now possible in *olex2.refine*, and we wish to provide a rigorous mathematical justification for refinements using non-spherical form factors in this way. We would like to clarify that those form factors are not refined by *olex2.refine*. Only the usual parameters (positions, ADPs, occupancies, etc) are refined. These form factors can (and must) be externally recomputed after each refinement cycles, so that the form factor of each atom keeps matching the chemical environment as it changes during refinement.

Tabulated Atomic Form factors

Olex2 and *NoSpherA2* expect a file called *[name].tsc* (matching the *.hkl* file name) containing the following information in order to use the external atomic form factors:

The header of the *[name].tsc* file is free-format, as long as it contains the space-separated list of atom names in the `SCATTERERS:' line and finishes with `DATA:'. Any identifier must be followed by a colon. The identifiers may start with a space.

TITLE: *optional title of the structure*
SYMM: `expanded' *or list of symmetries*[1]
AD: TRUE or FALSE (anomalous dispersion)
SCATTERERS: *space-separated list of all atoms*
[ANYTHING]: *colon must be present*
DATA: (denotes the end of the header)

h	k	l	A_1	A_2	…	A_n
h_1	k_2	l_1	$f_1(h_1,k_1,l_1)$	$f_2(h_1,k_1,l_1)$	…	$f_n(h_1,k_1,l_1)$
h_2	k_2	l_2	$f_1(h_2,k_2,l_2)$	$f_2(h_2,k_2,l_2)$	…	$f_n(h_2,k_2,l_2)$
⋮	⋮	⋮	⋮	⋮	⋮	⋮
h_n	k_n	l_n	$f_1(h_n,k_n,l_n)$	$f_2(h_n,k_n,l_n)$	…	$f_n(h_n,k_n,l_n)$

As will be shown in the theory section, $f_j(h_i,k_i,l_i)$ is the form factor (Fourier transform of the electron density) of the atom A_j calculated in a coordinate system obtained by translating the origin of the crystallographic axes to the centre of atom A_j, at h_i, k_i, l_i. Index $j \in (1,\cdots,N)$ should run over all unique atoms of the asymmetric unit, and $i \in (1,\cdots,m)$ should run over at least all reflections defined in the *.hkl* file and any equivalents under symmetry.
The complex values $f_j(h_i,k_i,l_i)$ must be written as "Re,Im" - their real component followed by a comma followed by the imaginary component, with no spaces.
The format and information specified in the *.tsc* files was motivated by the mathematical derivations presented in the next section.

Theory

We will explain the mathematics behind the use of non-spherical form factors and how *olex2.refine* has adapted to enable their use. We keep the notation close to the one used in Reference [S1]. We will first discuss the standard case and then briefly discuss the modifications needed for twinning.

Monocrystals

Our mathematical arguments focus on the necessary modifications concerning the treatment of the calculated structure factor, which we denote by $F(\mathbf{h},\mathbf{y}(\mathbf{x}))$. Here $\mathbf{h}$ (a row vector) is a triplet of Miller indices, $\mathbf{y}$ comprises the crystallographic parameters (atomic positions and atomic displacement parameters (ADPs) and chemical occupancies) and the refinement is carried out with respect to potentially reduced parameters denoted by $\mathbf{x}$. The dependency of $\mathbf{y}$ on $\mathbf{x}$ is known analytically, and we emphasise this dependency by writing $\mathbf{y}$ as $\mathbf{y}(\mathbf{x})$, which does therefore embody all constraints.
The structure factor is the sum of the individual contributions of all atoms, partitioned into symmetry equivalent atoms to representatives A_j, $j = 1,2,\ldots,N$, in the asymmetric unit

$$F\big(\mathbf{h},\mathbf{y}(\mathbf{x})\big) = \sum_{j=1}^{N} \underbrace{\left(\sum_{(R|\mathbf{t})\in \boldsymbol{s}} s_j f_j^{(R|\mathbf{t})}\big(\mathbf{h},\mathbf{y}(\mathbf{x})\big) \right)}_{\text{atoms equivalent by symmetry to } A_j} \tag{1}$$

[1] In either case, all symmetry equivalent Miller indices must be present in the DATA section. If a list of symmetry operators, expressed as rotation matrices (e.g.: 1 0 0 0 1 0 0 0 1;-1 0 0 0 1 0 0 0 -1) is provided, then the Miller indices must be ordered into corresponding blocks - and each block must have symmetry equivalent indices in the same position in each block and generated by the corresponding matrices. This allows for more efficient calculations during the refinement. Otherwise, if SYMM has the value 'expanded', the indices can be present in any order.

with R the rotational part and $\mathbf{t}$ the translational part of the symmetry operation $(R|\mathbf{t}) \in \boldsymbol{S}$, and $\boldsymbol{s_j}$ the chemical occupancy of the representative $\boldsymbol{A_j}$.
The representative atoms $\boldsymbol{A_j}$ lie at fractional locations $\mathbf{z}_j$ (a column vector) with atomic vibration tensor U_j (a 3×3 symmetric matrix).[2] This information is contained within the vector $\mathbf{y}(\mathbf{x})$. For the chosen representative atom A_j in the asymmetric unit, its individual contribution $f_j^{(\mathbb{1}|\mathbf{0})}$ is given by

$$\begin{aligned} f_j^{(\mathbf{1}|\mathbf{0})}\big(\mathbf{h}, \mathbf{y}(\mathbf{x})\big) &= f_j\big(\mathbf{h}, \mathbf{y}(\mathbf{x})\big) e^{-\mathbf{h}U_j\mathbf{h}^T} e^{i2\pi\mathbf{h}\mathbf{z}_j} \\ &= f_j\big(\mathbf{h}, \mathbf{y}(\mathbf{x})\big)\, G_j\left(\mathbf{h}, \mathbf{y}_j(\mathbf{x})\right). \end{aligned} \tag{2}$$

Here $\mathbf{y}_j(\mathbf{x})$ is the subset of parameters of the structure pertaining to the j-th atom (namely U_j and $\mathbf{z}_j$), whilst the terms $f_j\big(\mathbf{h}, \mathbf{y}(\mathbf{x})\big)$ are derived from the complex values $f_j(h_i, k_i, l_i)$ given in the .tsc-file by various corrections like, for example, anomalous dispersion, extinction etc.
The form factor of the atom A_j is calculated in a coordinate system obtained by translating the origin of the crystallographic axes to the centre of atom A_j, with no change in orientation. The form factor $f_j\big(\mathbf{h}, \mathbf{y}(\mathbf{x})\big)$ is then the Fourier transform of the electron density ρ_j of A_j. In contrast to the case of spherical form factors, this electron density can now depend on the whole structure whose information is given in $\mathbf{y}(\mathbf{x})$, as non-spherical form factors take the dependence of the electron density of the surrounding atomic environment into account.
The relation between $f_j^{(R|\mathbf{t})}$ for a general $(R|\mathbf{t}) \in \boldsymbol{S}$ and f_j is then

$$\begin{aligned} f_j^{(R|\mathbf{t})}\big(\mathbf{h}, \mathbf{y}(\mathbf{x})\big) &= f_j\big(\mathbf{h}R, \mathbf{y}(\mathbf{x})\big) e^{-\mathbf{h}RU_jR^T\mathbf{h}^T} e^{i2\pi\mathbf{h}R\mathbf{z}_j} e^{i2\pi\mathbf{h}\mathbf{t}} \\ &= f_j\big(\mathbf{h}R, \mathbf{y}(\mathbf{x})\big) G_j\left(\mathbf{h}R, \mathbf{y}_j(\mathbf{x})\right) \mathrm{e}^{\mathrm{i}2\pi\mathbf{h}\mathbf{t}} \\ &= f_j\big(\mathbf{h}R, \mathbf{y}(\mathbf{x})\big)\, G_j^{(R|\mathbf{t})}\left(\mathbf{h}, \mathbf{y}_j(\mathbf{x})\right). \end{aligned} \tag{3}$$

Note that in the case of spherical form factors, the functions f_j do not depend on the structure information $\mathbf{y}(\mathbf{x})$ and, additionally, we have $f_j(\mathbf{h}R) = f_j(\mathbf{h})$ since $f_j(\mathbf{h})$ does then not depend on the direction of $\mathbf{h}$ but only on $\mathbf{h}M^*\mathbf{h}^T$, where M^* is the reciprocal metric matrix.
The least square minimization in the refinement procedure requires derivatives of the structure factor with respect to the components of $\mathbf{x} = (x_1, \ldots, x_n)$. Since the structure factor is the above sum (1), we only need to consider the derivatives of the individual terms $f_j^{(R|\mathbf{t})}\big(\mathbf{h}, \mathbf{y}(\mathbf{x})\big)$.
Using the product rule, we have for the derivative (by dropping the arguments $\mathbf{y}(\mathbf{x})$ for ease of reading)

$$\frac{\partial f_j^{(R|\mathbf{t})}}{\partial x_k}(\mathbf{h}) = \frac{\partial f_j}{\partial x_k}(\mathbf{h}R) G_j^{(R|\mathbf{t})}(\mathbf{h}) + f_j(\mathbf{h}R)\, \frac{\partial G_j^{(R|\mathbf{t})}}{\partial x_k}(\mathbf{h}). \tag{4}$$

The partial differentiation with respect to x components will make partial derivatives of $\boldsymbol{y}(\boldsymbol{x})$ appear through Leibniz rule, as the time-honed implementation of constraints commands. It is important to note that the differential $\frac{\partial G_j^{(R|\boldsymbol{t})}}{\partial x_k}$ in the second term involves only exponentials which can be treated identically to the spherical case.

[2] The U_j here agree with $2\pi^2 U_j^*$ as introduced in reference S2.

The differential $\frac{\partial f_j}{\partial x_k}(\mathbf{h}R)$ in the first term on the right hand side of (4) is more difficult to treat due to the complexity of the involved derivations. We assume that the effect of this term for the least square minimisation procedure is relatively minor and thus take it as zero. The errors introduced via this and other assumptions will escalate if the structure changes without frequent updating of the non-spherical form factors. The validity of this assumption is expected to assert itself through the experimental exploration of this refinement technique in the field.

Given these considerations, the contributions of all symmetry equivalent atoms in both the structure factor and its derivatives require only the table $f_j(\mathbf{h})$ of the current structure information $\mathbf{y}(\mathbf{x})$ for each single representative A_j for each step of the refinement procedure. The experimental input to the refinement is a list of $\mathbf{h}$, $F_o^2(\mathbf{h})$ and $\sigma_o(\mathbf{h})$, where the last two items are respectively the measured intensities (scaled and with absorption corrections) and its estimated standard uncertainty (the *.hkl* file). Refinement is then a non-linear least squares (NLS) fit of $\left|F\left(\mathbf{h},\mathbf{y}(\mathbf{x})\right)\right|^2$ to $F_o^2(\mathbf{h}_j)$, for all $\mathbf{h}$. Precisely, the objective function to minimise is

$$\boldsymbol{x} \mapsto \sum_{r=1}^{m} w(\mathbf{h}_r)\left(\left|F\left(\mathbf{h}_r,\mathbf{y}(\mathbf{x})\right)\right|^2 - F_o^2(\mathbf{h}_r)\right)^2, \tag{5}$$

for m measured reflections, where $w(\mathbf{h}_r)$ are suitable weights. For more detail, see Section 2 of Reference [S1].

The set of Miller indices $\mathbf{h}$ required for the tabulated non-spherical form factors (the *.tsc* file) should correspond to the set of measured Bragg reflections and their symmetry equivalents.

Twinning

In the case of twinning, one needs to ensure that the set of Miller indices to be considered contains the measured Bragg peaks for all twin components and their symmetry equivalents. The modification required to the Least Squares (5) is to replace each term $\left|F\left(\boldsymbol{h}_r,\boldsymbol{y}(\boldsymbol{x})\right)\right|^2, r = 1,\dots,m$, by a combination over the contributing twin components indexed by l, namely

$$\sum_{l=1}^{d_r} \alpha_l \left|F\left(\boldsymbol{h}_{r,l},\boldsymbol{y}(\boldsymbol{x})\right)\right|^2 \tag{6}$$

where $d_r \leq d$ is the number of contributing components, α_l the fraction of the crystal volume occupied by the l-th contributing twin domain to the reflection h_r, and $h_{r,l}$ is the corresponding Miller index of this twin component contributing to this reflection. Note by equations (1) and (3), the calculation of $F\left(\mathbf{h}_{r,l},\mathbf{y}(\mathbf{x})\right)$ requires information of the non-spherical form factors for $\mathbf{h}_{r,l}$ and all its symmetry equivalents.

For more information on the general twinning procedure, see Section 5 of Reference [S1].

Therefore, all types of twinning can be handled by providing as input, for each reflection $\mathbf{h}_r$, the corresponding Miller indices $\mathbf{h}_{r,l}$ of the contributing components $l \in \{1,\dots,d\}$, and the matching $F_o^2(\mathbf{h}_r)$ and $\sigma_o(\mathbf{h}_r)$.

For the computation of structure factors using non-spherical form factors, only those Miller indices $\boldsymbol{h}_{r,l}$ and their symmetry equivalents are necessary. It is of course well known that in the case of (pseudo-)merohedral twinning, the Miller indices for a given r and varying l are related to each other by a twin law, but this is only a special case of the general scheme we have just described: the calculation of form factors does not need to be aware of this detail.

Summary

Let us finally cover the relevant differences to be considered when working with non-spherical form factors:

i. Form factors associated to atoms (with the origin at their center) are no longer real, but are usually complex-valued (as the electron densities are non-spherical).
ii. It is no longer the case that $f_j(\mathbf{h}R) = f_j(\mathbf{h})$ for rotations R associated to symmetry equivalent atoms in the unit cell.
iii. Due to the change in the shape of form factors under shifts, there appears an additional term in the derivative of $f_j^{(R|\mathbf{t})}$, the first term on the right hand side of (4). We assume that this is negligible for sufficiently small shifts.
iv. The provided form factors must cover a greater variety of Miller indices than would be needed in the spherical case (due to (ii)). In other words, form factors must be provided for all Miller indices $\mathbf{h}$ with recorded reflections and all symmetry equivalents $R\mathbf{h}$, for $(R, \mathbf{t})$ appearing in $\boldsymbol{S}$ (see (1)). This is also relevant for dealing with twin laws.

Validation Part:

Measurement details

The results presented here involve the comparison of the results obtained through HAR using *Tonto* and HAR using *NoSpherA2* for the following X-ray datasets:

- Glycyl-*L*-alanine, at 12K, λ= 0.5259 (2) Å, data set taken from ref. S5
- Glycyl-*L*-alanine, at 50K, λ= 0.5259 (2) Å, data set taken from ref. S5
- Glycyl-*L*-alanine, at 100K, λ= 0.5259 (2) Å, data set taken from ref. S5
- Glycyl-*L*-alanine, at 150K, λ= 0.5259 (2) Å, data set taken from ref. S5
- Glycyl-*L*-alanine, at 295K, λ= 0.5259 (2) Å, data set taken from ref. S5
- *L*-Alanine, at 23K, λ= 0.71073 Å, data set taken from ref. S6
- *L*-Alanine, at 100K, λ= 0.71073 Å, results taken from ref. S7
- *L*-Alanine, at 150K, λ= 0.71073 Å, results taken from ref. S7

Neutron-diffraction data sets are available for all structures except for L-alanine and glycyl-*L*-alanine at 100K.

- Glycyl-*L*-alanine, at 12K, λ= 0.8313(2) Å, data set taken from ref. S8
- Glycyl-*L*-alanine, at 50K, λ= 0.8313(2) Å, data set taken from ref. S8
- Glycyl-*L*-alanine, at 150K, λ= 0.8313(2) Å, data set taken from ref. S8
- Glycyl-*L*-alanine, at 295K, λ= 0.8313(2) Å, data set taken from ref. S8
- *L*-Alanine, at 23K, λ= 0.750 to 1.500 Å (Laue), results taken from ref. S7
- *L*-Alanine, at 150K, λ= 0.750 to 1.500 Å (Laue), results taken from ref. S7

Refinement results

The R factor was calculated on the basis of manually edited *.hkl* files containing an unusual cut-off criterion of 2.1 I/σ(I) to ensure neither *olex2.refine* nor *Tonto* would disregard any reflections during refinement, statistics preparation or residual density calculation. R-factor and Goodness of Fit (S) were taken from CIFs, but the residual density was calculated using *Olex2* using *.fcf* files.

HARs of Gly-L-Ala (CCDC-2035148)

Table S2: Refinements against X-ray data for Gly-*L*-Ala at 12 K

	Tonto	**NoSpherA2**	**Olex2.refine IAM**
$R[F^2>2.1\sigma(F^2)]$, S	0.016, 1.26	0.016, 1.29	0.024, 2.45
No. of reflections	2374	2374	2374
No. of parameters	181	181	131
H-atom treatment	All H-atom parameters refined (anisotropically)	All H-atom parameters refined (anisotropically)	H atoms refined isotropically
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.151, -0.194	0.152, -0.194	0.289, -0.253

Table S3: Refinements against X-ray data for Gly-*L*-Ala at 50 K

	Tonto	**NoSpherA2**	**Olex2.refine IAM**
$R[F^2>2.1\sigma(F^2)]$, S	0.018, 1.21	0.018, 2.24	0.025, 2.16
No. of reflections	2261	2261	2261
No. of parameters	181	181	131
H-atom treatment	All H-atom parameters refined (anisotropically)	All H-atom parameters refined (anisotropically)	H atoms refined isotropically
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.137, -0.180	0.137, -0.166	0.259, -0.232

Table S4: Refinements against X-ray data for Gly-*L*-Ala at 100 K

	Tonto	**NoSpherA2**	**Olex2.refine IAM**
$R[F^2>2.1\sigma(F^2)]$, S	0.018, 1.57	0.018, 1.59	0.026, 3.11
No. of reflections	2430	2430	2430
No. of parameters	181	181	131
H-atom treatment	All H-atom parameters refined (anisotropically)	All H-atom parameters refined (anisotropically)	H atoms refined isotropically
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.136, -0.254	0.135, -0.254	0.267, -0.257

Table S5: Refinements against X-ray data for Gly-*L*-Ala at 150 K

	Tonto	**NoSpherA2**	**Olex2.refine IAM**
R*[F^2>2.1σ(F^2)], *S	0.016, 1.54	0.016, 1.57	0.025, 3.13
No. of reflections	2391	2391	2391
No. of parameters	181	181	131
H-atom treatment	All H-atom parameters refined (anisotropically)	All H-atom parameters refined (anisotropically)	H atoms refined isotropically
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.124, -0.196	0.124, -0.196	0.221, -0.227

Table S6: Refinements against X-ray data for Gly-*L*-Ala at 295 K

	Tonto	**NoSpherA2**	**Olex2.refine IAM**
R*[F^2>2.1σ(F^2)], *S	0.019, 1.44	0.019, 1.47	0.030, 2.81
No. of reflections	2265	2265	2265
No. of parameters	181	181	131
H-atom treatment	All H-atom parameters refined (anisotropically)	All H-atom parameters refined (anisotropically)	H atoms refined isotropically
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.132, -0.184	0.132, -0.184	0.191, -0.214

HARs of L-Alanine (CCDC-2035147)

Table S7: Refinements against X-ray data for *L*-Ala at 23 K

	Tonto	**NoSpherA2**	**Olex2.refine IAM**
R*[F^2>2.1σ(F^2)], *S	0.019, 1.18	0.019, 1.18	0.028, 2.31
No. of reflections	2387	2387	2387
No. of parameters	118	118	83
H-atom treatment	All H-atom parameters refined (anisotropically)	All H-atom parameters refined (anisotropically)	H atoms refined isotropically
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.112, -0.127	0.113, -0.126	0.349, -0.209

Table S8: Refinements against X-ray data for *L*-Ala at 100 K

	Tonto	**NoSpherA2**	**Olex2.refine IAM**
R*[F^2>2.1σ(F^2)], *S	0.019, 2.08	0.019, 2.09	0.027, 4.16
No. of reflections	4549	4549	4549
No. of parameters	118	118	83
H-atom treatment	All H-atom parameters refined (anisotropically)	All H-atom parameters refined (anisotropically)	H atoms refined isotropically
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.159, -0.330	0.159, -0.327	0.379, -0.255

Table S9: Refinements against X-ray data for *L*-Ala at 150 K

	HAR	**NoSpherA2**	**Olex2.refine IAM**
R(F)*[F^2>2.1σ(F^2)], *S	0.020, 1.76	0.020, 1.75	0.028, 2.62
No. of reflections	2584	2584	2584
No. of parameters	118	118	83
H-atom treatment	All H-atom parameters refined (anisotropically)	All H-atom parameters refined (anisotropically)	H atoms refined isotropically
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.233, -0.197	0.232, -0.199	0.495, -0.238

Methodology for validation of NoSpherA2

To be comparable with previous studies [S6], the same level of theory was chosen in *Tonto* and *NoSpherA2*: RHF/6-311G(d,p) without cluster charges and dipoles.

Three types of agreement statistics were used in the following:

1) Mean ratios of values X in two models A and B, denoted by $\langle \mathbf{X}_A/\mathbf{X}_B \rangle$
2) Mean absolute differences of two quantities $\langle |\Delta \mathbf{X}_{\mathbf{A-B}}| \rangle$
3) Root mean square differences of $\mathbf{X}$ weighted by combined standard uncertainties $\boldsymbol{\sigma}$.

The wRMSD is calculated as:

$$wRMSD = \langle \frac{(X_A - X_B)^2}{\sigma(X_A)^2 + \sigma(X_B)^2} \rangle^{\frac{1}{2}}$$

For a perfect agreement between two models one would expect the ratio of all parameters to become 1. The mean absolute difference should be 0 for perfect agreement, but this does not say anything about the spread of the values around this mean point. The wRMSD becomes 0 for identical numerical values (as $(X_A - X_B)^2$ becomes 0), and close to 1 for statistical agreement.

Model names (compare to Table 2 in the main document):

ID	Type	Program	QM	Partitioning	Weighting	Model name for the SI
i	IAM	olex2.refine	--	--	$1/\sigma^2(F^2)$	IAM
ii	HAR	Tonto	Tonto	Tonto	$1/\sigma(F)$	Tonto
iii	HAR	NoSpherA2	Tonto	Tonto	$1/\sigma^2(F^2)$	NoSpherA2 - T
iv	HAR	NoSpherA2	ORCA	Tonto	$1/\sigma^2(F^2)$	NoSpherA2 - O
v	HAR	NoSpherA2	ORCA	Tonto	Shelxl-type	NoSpherA2 - w
vi	HAR	NoSpherA2	ORCA	NoSpherA2	$1/\sigma^2(F^2)$	NoSpherA2 - Q

The results show almost perfect agreement between Tonto and NoSpherA2 refinements. The differences in bond lengths (Table S9) for *Gly-L-Ala* are at a maximum of 0.002 Å, while the smallest standard uncertainty of any of the bond distances is 0.005 Å. This difference can be due to numerical differences in the least-squares implementation, since HAR in *Tonto* is performed on F, while *olex2.refine* uses F^2. In the case of *L-Ala*, the maximum bond distance difference is 0.008 Å, while standard uncertainties for HAR and NoSpherA2 are 0.009 Å and 0.011 Å, respectively.
For hydrogen atom ADPs in *Gly-L-Ala*, the biggest difference between Tonto and NoSpherA2 refinements in all temperatures is 0.0031 $Å^2$ in U^{11}, while the standard uncertainties are 0.0123 $Å^2$ and 0.0124 $Å^2$, respectively. For non-hydrogen atom ADPs, the biggest difference is 0.000068 $Å^2$ for U^{22}, while the standard uncertainties in both methods for this particular ADP are 0.00025 $Å^2$ and 0.00026 $Å^2$.

In *L*-Ala the biggest difference in any hydrogen atom ADP for any considered temperature is 0.0086 $Å^2$ for U^{23}, while the standard uncertainties are 0.0044 $Å^2$ and 0.0053 $Å^2$. Non hydrogen atoms have a maximum difference of 0.00046 $Å^2$ for U^{13} while the standard uncertainties are 0.00010 $Å^2$ and 0.00012 $Å^2$. All these maximum differences appeared at the highest temperature, as the absolute value is higher and therefore statistical and numerical differences would be bigger.

To visualize the validation results, Figures S5 – S10 were prepared by using the data in Tables S10-S21.

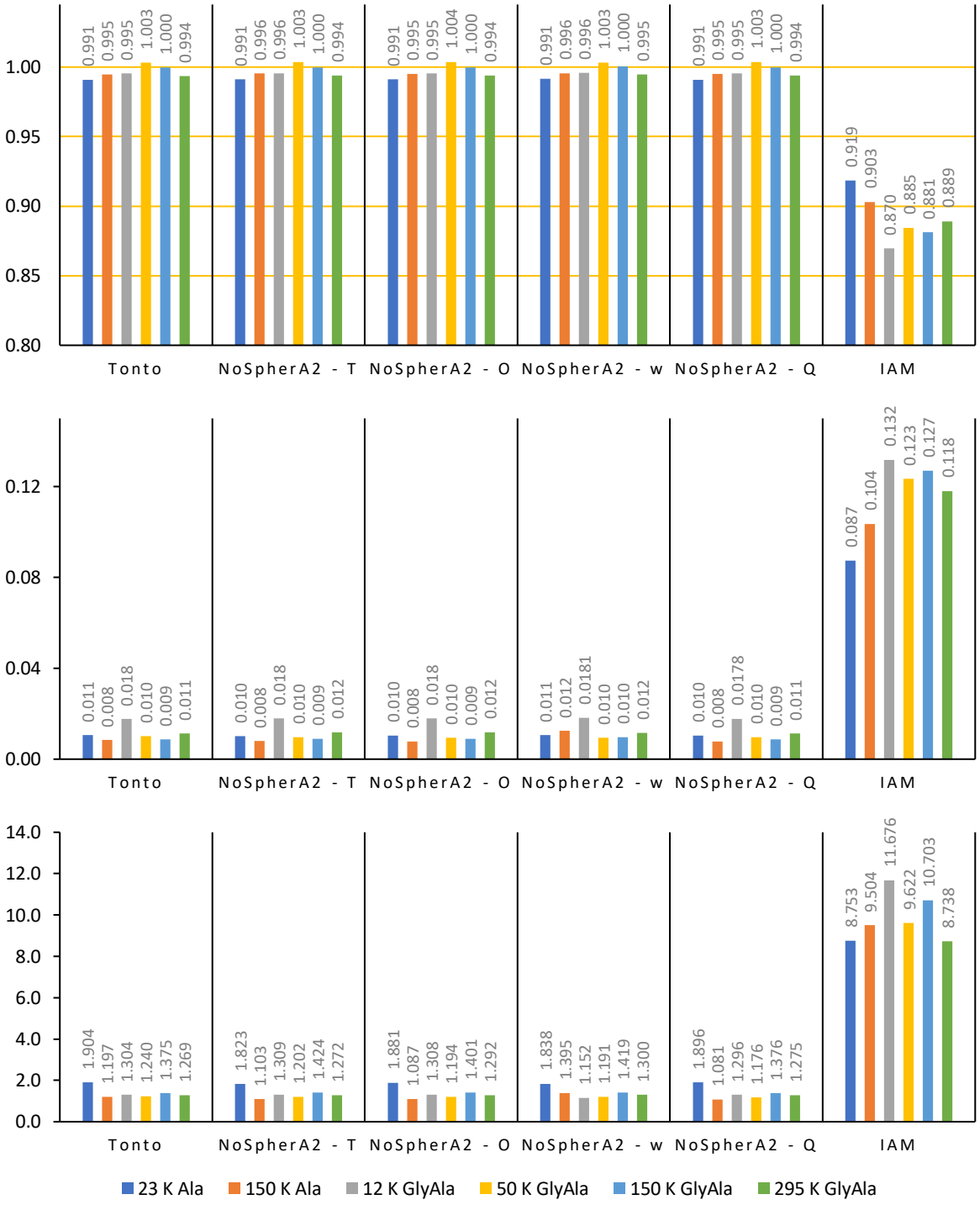

Figure S5: Plots of agreement in X-H bond lengths (Å) between different HAR models and neutron data. Top: $\langle r_A/r_{Neutron} \rangle$ (1 is best), middle: $\langle |\Delta r_{A\text{-}Neutron}| \rangle$ (0 is best), bottom: wRMSD (0 is best, 1 is statistical agreement)

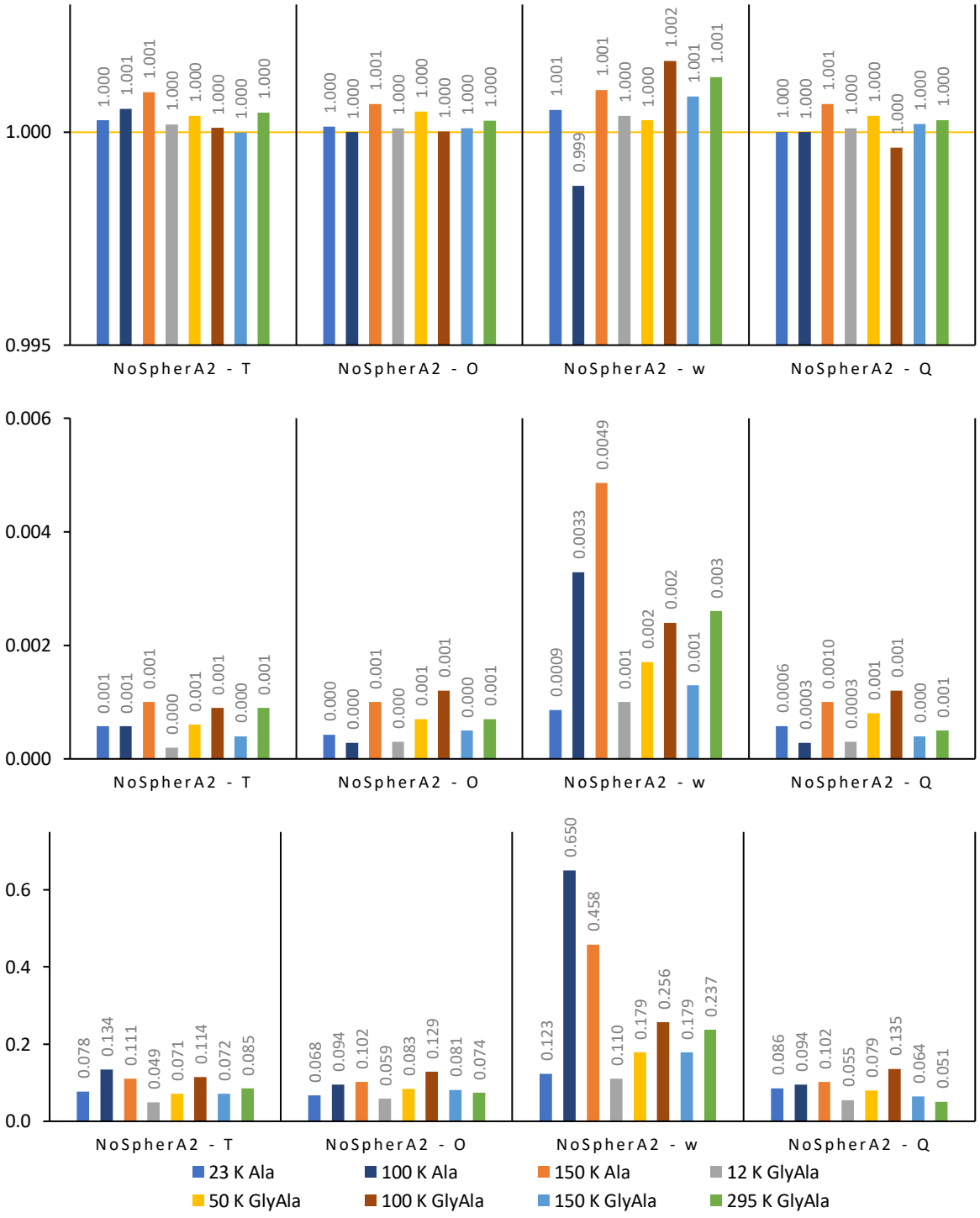

Figure S6: Plots of agreement in X-H bond lengths (Å) between different NoSpherA2 HAR models and HAR in Tonto. Top: $\langle r_A/r_{HAR} \rangle$ (1 is best), middle: $\langle |\Delta r_{A\text{-}HAR}| \rangle$ (0 is best), bottom: wRMSD (0 is best, 1 is statistical agreement)

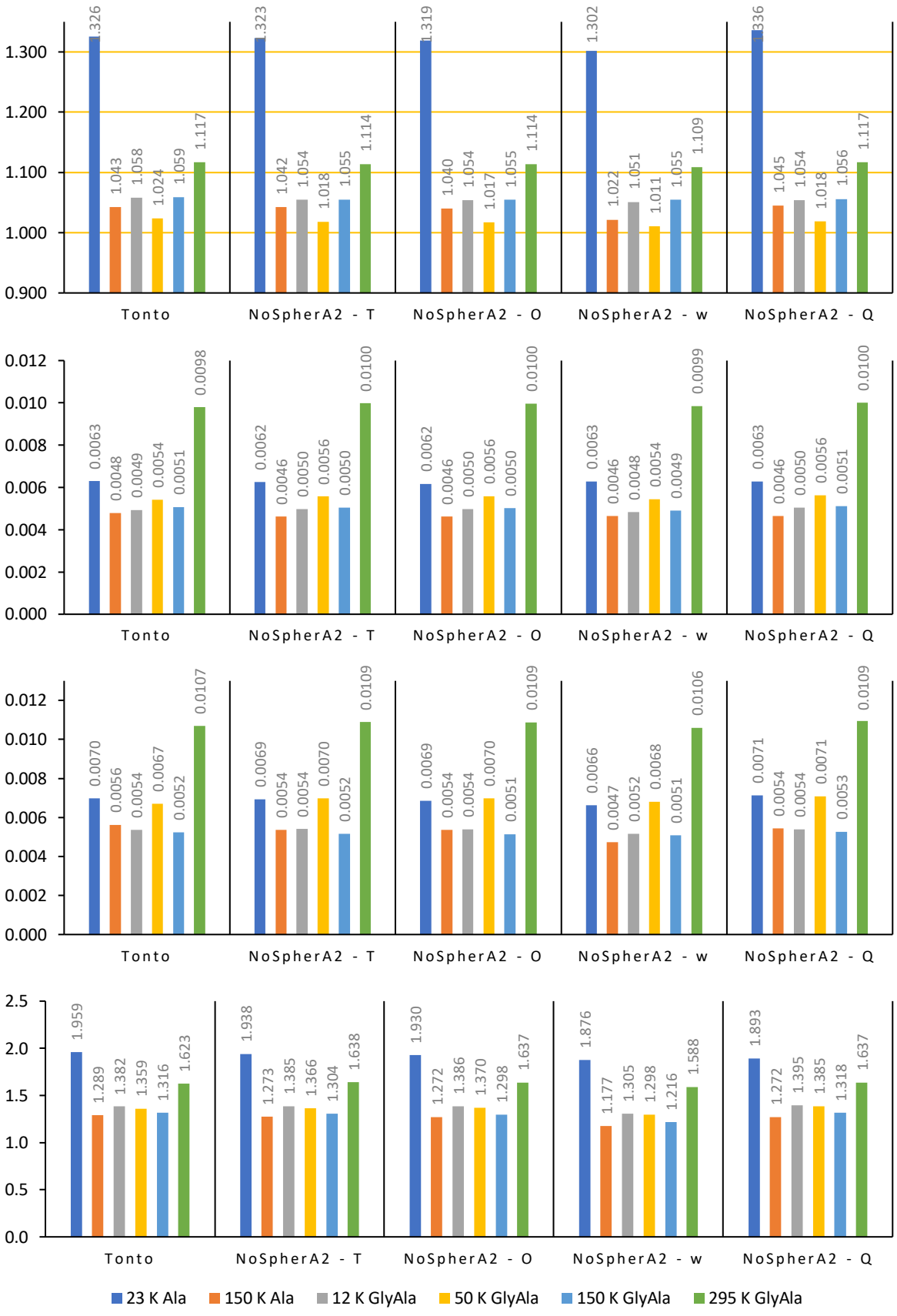

Figure S7: Plots of agreement in U^{ij} (Å^2) of hydrogen atoms between different HAR models and neutron data. From top to bottom: $\langle U^{ii}_{A}/U^{ii}_{Neutron} \rangle$ (1 is best), $\langle |\Delta U^{ij}_{\text{A-Neutron}}| \rangle$ (0 is best), $\langle |\Delta U^{ii}_{\text{A-Neutron}}| \rangle$ (0 is best), wRMSD (0 is best, 1 is statistical agreement)

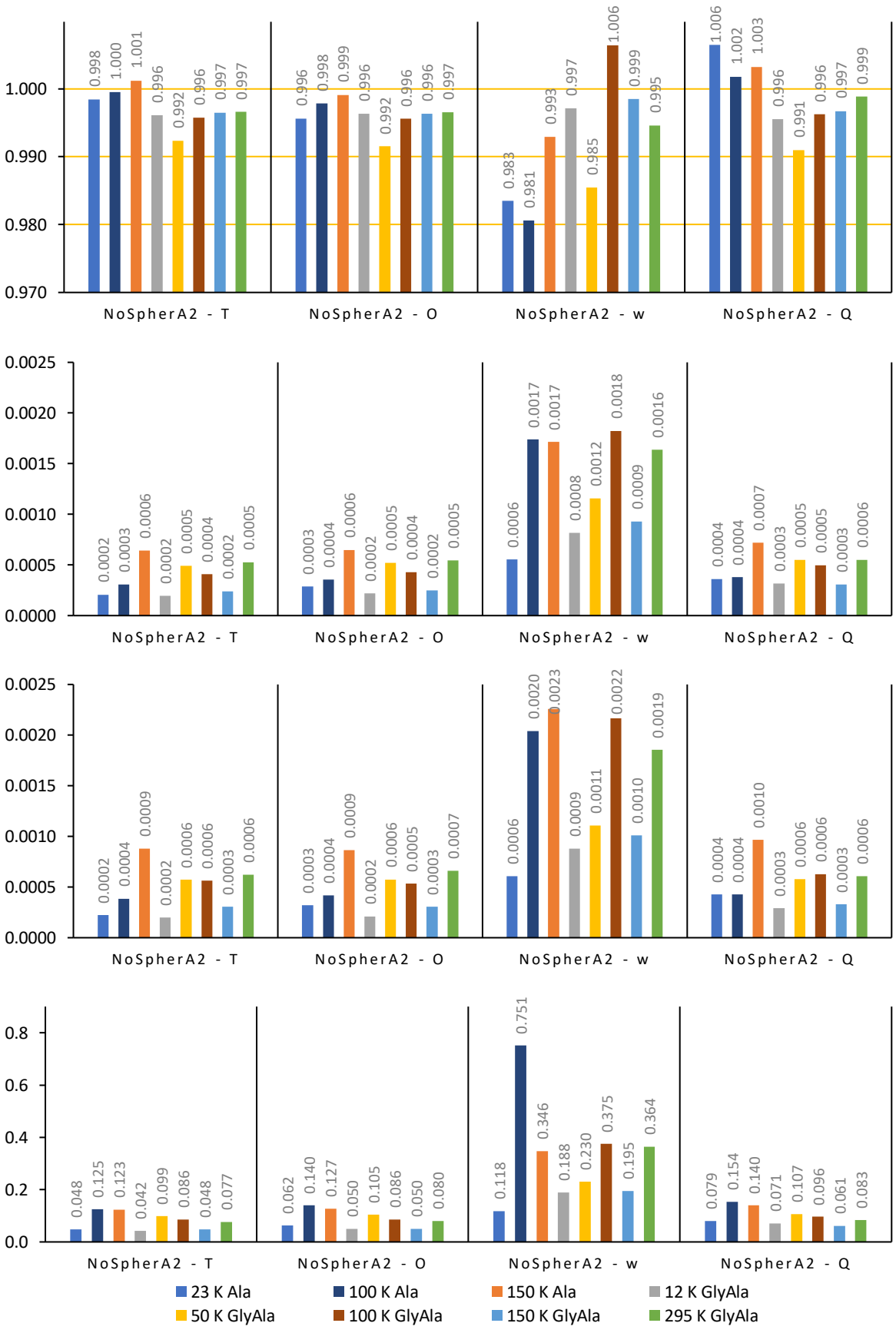

Figure S8: Plots of agreement in U^{ij} (Å^2) of hydrogen atoms between different NoSpherA2 HAR models and HAR in Tonto. From top to bottom: $\langle U^{ii}_A/U^{ii}_{HAR}\rangle$ (1 is best), $\langle|\Delta U^{ij}{}_{\text{A-HAR}}|\rangle$ (0 is best), $\langle|\Delta U^{ii}{}_{\text{A-HAR}}|\rangle$ (0 is best), wRMSD (0 is best, 1 is statistical agreement)

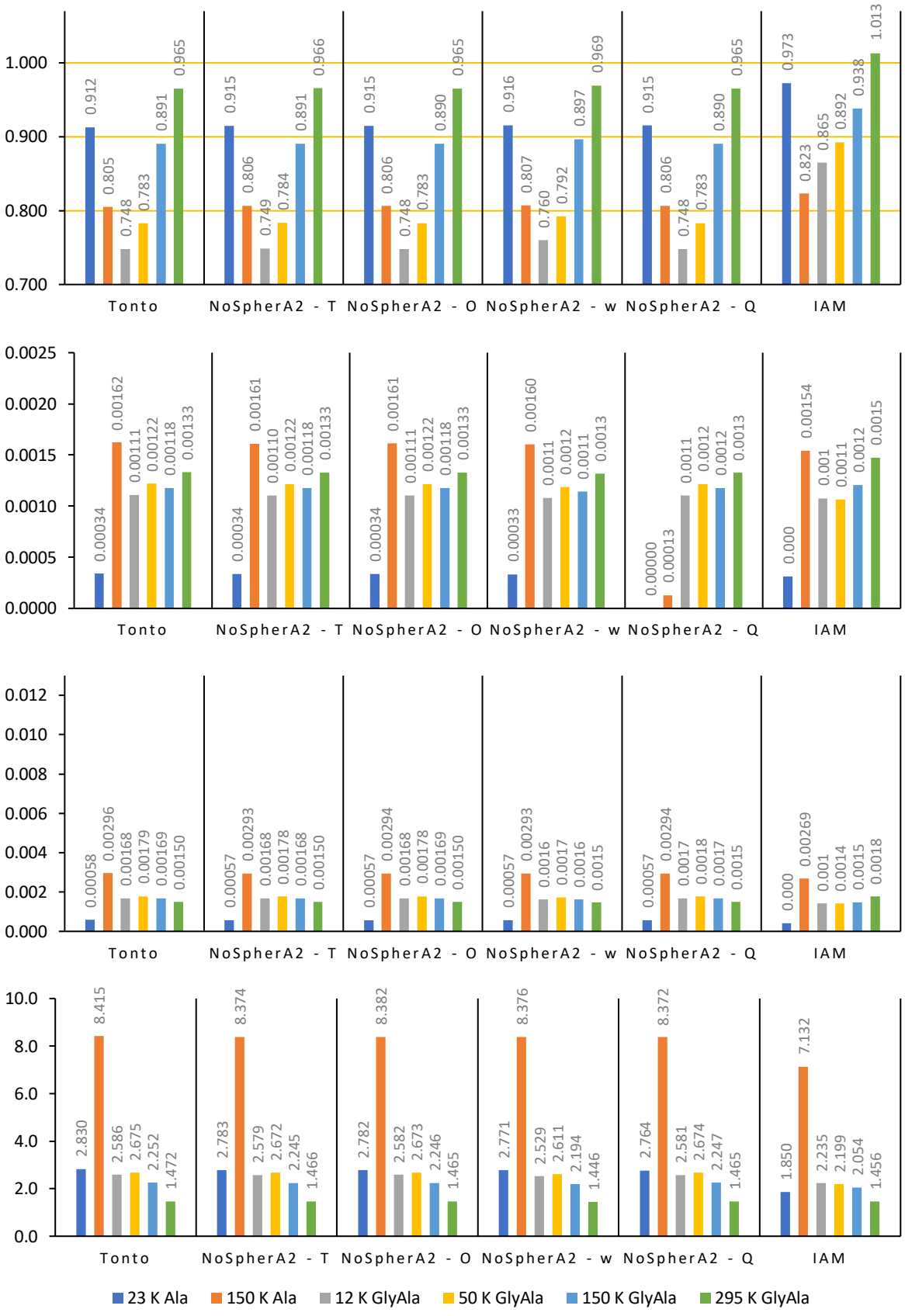

Figure S9: Plots of agreement in U^{ij} (Å^2) of non-hydrogen atoms between different HAR models and neutron data. From top to bottom: $\langle U^{ii}_{A}/U^{ii}_{Neutron} \rangle$ (1 is best), $\langle |\Delta U^{ij}_{\text{A-Neutron}}| \rangle$ (0 is best), $\langle |\Delta U^{ii}_{\text{A-Neutron}}| \rangle$ (0 is best), wRMSD (0 is best, 1 is statistical agreement)

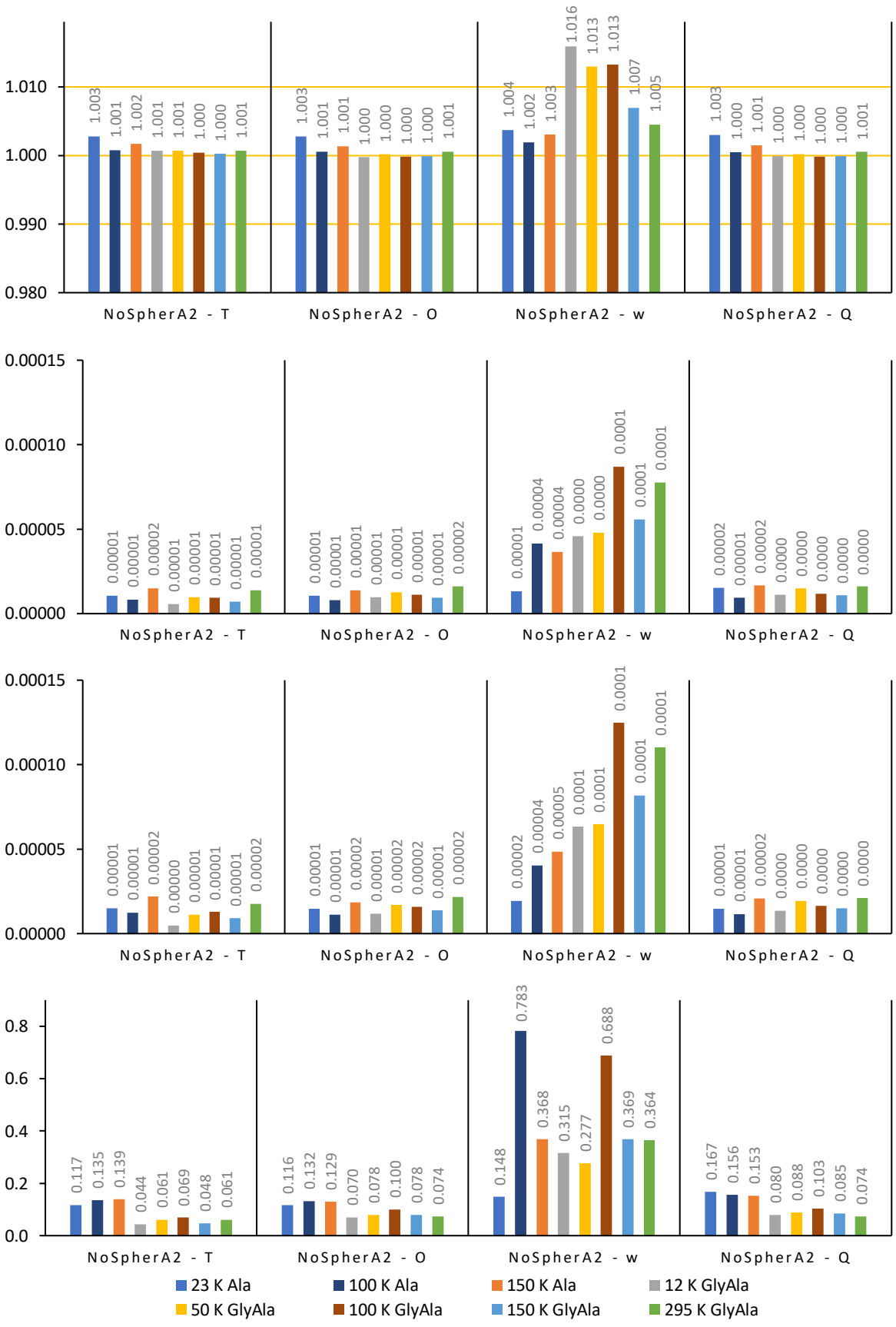

Figure S10: Plots of agreement in U^{ij} (Å^2) of non-hydrogen atoms between different NoSpherA2 HAR models and HAR in Tonto. From top to bottom: $\langle U^{ii}_{A}/U^{ii}_{HAR} \rangle$ (1 is best), $\langle |\Delta U^{ij}_{\text{A-HAR}}| \rangle$ (0 is best), $\langle |\Delta U^{ii}_{\text{A-HAR}}| \rangle$ (0 is best), wRMSD (0 is best, 1 is statistical agreement)

Table S10: Bond-length statistics for X-H distances, averaged among all bonds for Gly-*L*-Ala.

Temp.	Method (A / B)	$\langle r_A/r_B \rangle$	$\langle \lvert \Delta r_{A-B} \rvert \rangle$ / Å	wRMSD
	Tonto / Neutron	0.995	0.018	1.304
	NoSpherA2 – T / Neutron	0.996	0.018	1.309
	NoSpherA2 – O / Neutron	0.995	0.018	1.308
12K	IAM / Neutron	0.870	0.132	11.676
	Tonto / NoSpherA2 – T	1.000	0.000	0.049
	Tonto / NoSpherA2 – O	1.000	0.000	0.059
	NoSpherA2 – O / NoSpherA2 – T	1.000	0.000	0.032
	Tonto / Neutron	1.003	0.010	1.240
	NoSpherA2 – T / Neutron	1.003	0.010	1.202
	NoSpherA2 – O / Neutron	1.004	0.010	1.194
50K	IAM / Neutron	0.885	0.123	9.622
	Tonto / NoSpherA2 – T	1.000	0.001	0.071
	Tonto / NoSpherA2 – O	1.000	0.001	0.083
	NoSpherA2 – O / NoSpherA2 – T	1.000	0.000	0.025
	Tonto / Neutron	--	--	--
	NoSpherA2 – T / Neutron	--	--	--
	NoSpherA2 – O / Neutron	--	--	--
100K	IAM / Neutron	--	--	--
	Tonto / NoSpherA2 – T	1.000	0.001	0.114
	Tonto / NoSpherA2 – O	1.000	0.001	0.129
	NoSpherA2 – O / NoSpherA2 – T	1.000	0.000	0.060
	Tonto / Neutron	1.000	0.009	1.375
	NoSpherA2 – T / Neutron	1.000	0.009	1.424
	NoSpherA2 – O / Neutron	1.000	0.009	1.401
150K	IAM / Neutron	0.881	0.127	10.703
	Tonto / NoSpherA2 – T	1.000	0.000	0.072
	Tonto / NoSpherA2 – O	1.000	0.000	0.081
	NoSpherA2 – O / NoSpherA2 – T	1.000	0.000	0.037
	Tonto / Neutron	0.994	0.011	1.269
	NoSpherA2 – T / Neutron	0.994	0.012	1.272
	NoSpherA2 – O / Neutron	0.994	0.012	1.292
295K	IAM / Neutron	0.889	0.118	8.738
	Tonto / NoSpherA2 – T	1.000	0.001	0.085
	Tonto / NoSpherA2 – O	1.000	0.001	0.074
	NoSpherA2 – O / NoSpherA2 – T	1.000	0.000	0.042

Table S11: Bond-length statistics for X-H distances, averaged among all bonds for *L*-Ala.

Temp.	Method (A / B)	$\langle r_A/r_B \rangle$	$\langle \lvert \Delta r_{A-B} \rvert \rangle$ / Å	wRMSD
23K	Tonto / Neutron	0.991	0.011	1.904
	NoSpherA2 – T / Neutron	0.991	0.010	1.823
	NoSpherA2 – O / Neutron	0.991	0.010	1.881
	IAM / Neutron	0.919	0.087	8.753
	Tonto / NoSpherA2 – T	1.000	0.001	0.078
	Tonto / NoSpherA2 – O	1.000	0.000	0.068
	NoSpherA2 – O / NoSpherA2 – T	1.000	0.000	0.066
100K	Tonto / Neutron	--	--	--
	NoSpherA2 – T / Neutron	--	--	--
	NoSpherA2 – O / Neutron	--	--	--
	IAM / Neutron	--	--	--
	Tonto / NoSpherA2 – T	1.001	0.001	0.134
	Tonto / NoSpherA2 – O	1.000	0.000	0.094
	NoSpherA2 – O / NoSpherA2 – T	0.999	0.001	0.134
150K	Tonto / Neutron	0.995	0.008	1.197
	NoSpherA2 – T / Neutron	0.996	0.008	1.103
	NoSpherA2 – O / Neutron	0.995	0.008	1.087
	IAM / Neutron	0.903	0.104	9.504
	Tonto / NoSpherA2 – T	1.001	0.001	0.111
	Tonto / NoSpherA2 – O	1.001	0.001	0.102
	NoSpherA2 – O / NoSpherA2 – T	1.000	0.000	0.042

Table S12: Statistical results for hydrogen atom ADPs for Gly-*L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	$< U^{ii}_A / U^{ii}_B >$	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	wRMSD
12 K	Tonto/Neutron	1.058	0.0049	0.0054	1.382
	NoSpherA2 - T/Neutron	1.054	0.0050	0.0054	1.385
	NoSpherA2 - O/Neutron	1.054	0.0050	0.0054	1.386
	NoSpherA2 - T/Tonto	0.996	0.0002	0.0002	0.042
	NoSpherA2 - O/Tonto	0.996	0.0002	0.0002	0.050
	NoSpherA2 - O/T	1.000	0.0001	0.0001	0.026
50 K	Tonto/Neutron	1.024	0.0054	0.0067	1.359
	NoSpherA2 - T/Neutron	1.018	0.0056	0.0070	1.366
	NoSpherA2 - O/Neutron	1.017	0.0056	0.0070	1.370
	NoSpherA2 - T/Tonto	0.992	0.0005	0.0006	0.099
	NoSpherA2 - O/Tonto	0.992	0.0005	0.0006	0.105
	NoSpherA2 - O/T	0.999	0.0001	0.0001	0.023
100 K	Tonto/Neutron	--	--	--	--
	NoSpherA2 - T/Neutron	--	--	--	--
	NoSpherA2 - O/Neutron	--	--	--	--
	NoSpherA2 - T/Tonto	0.996	0.0004	0.0006	0.086
	NoSpherA2 - O/Tonto	0.996	0.0004	0.0005	0.086
	NoSpherA2 - O/T	1.000	0.0001	0.0001	0.026
150 K	Tonto/Neutron	1.059	0.0051	0.0052	1.316
	NoSpherA2 - T/Neutron	1.055	0.0050	0.0052	1.304
	NoSpherA2 - O/Neutron	1.055	0.0050	0.0051	1.298
	NoSpherA2 - T/Tonto	0.997	0.0002	0.0003	0.048
	NoSpherA2 - O/Tonto	0.996	0.0002	0.0003	0.050
	NoSpherA2 - O/T	1.000	0.0001	0.0001	0.025
295 K	Tonto/Neutron	1.117	0.0098	0.0107	1.623
	NoSpherA2 - T/Neutron	1.114	0.0100	0.0109	1.638
	NoSpherA2 - O/Neutron	1.114	0.0100	0.0109	1.637
	NoSpherA2 - T/Tonto	0.997	0.0005	0.0006	0.077
	NoSpherA2 - O/Tonto	0.997	0.0005	0.0007	0.080
	NoSpherA2 - O/T	1.000	0.0001	0.0001	0.025

Table S13: Statistical results for non-hydrogen atom ADPs for Gly-*L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	$< U^{ii}_A / U^{ii}_B >$	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	wRMSD
	Tonto/Neutron	0.748	0.00111	0.00168	2.586
	NoSpherA2 - T/Neutron	0.749	0.00110	0.00168	2.579
	NoSpherA2 - O/Neutron	0.748	0.00111	0.00168	2.582
12 K	IAM/Neutron	0.865	0.00108	0.00141	2.235
	NoSpherA2 - T/Tonto	1.001	0.00001	0.00000	0.044
	NoSpherA2 - O/Tonto	1.000	0.00001	0.00001	0.070
	NoSpherA2 – O/T	0.999	0.00001	0.00001	0.060
	Tonto/Neutron	0.783	0.00122	0.00179	2.675
	NoSpherA2 - T/Neutron	0.784	0.00122	0.00178	2.672
	NoSpherA2 - O/Neutron	0.783	0.00122	0.00178	2.673
50 K	IAM/Neutron	0.892	0.00106	0.00142	2.199
	NoSpherA2 - T/Tonto	1.001	0.00001	0.00001	0.061
	NoSpherA2 - O/Tonto	1.000	0.00001	0.00002	0.078
	NoSpherA2 – O/T	0.999	0.00001	0.00001	0.052
	Tonto/Neutron	-	-	-	-
	NoSpherA2 - T/Neutron	-	-	-	-
	NoSpherA2 - O/Neutron	-	-	-	-
100 K	IAM/Neutron	-	-	-	-
	NoSpherA2 - T/Tonto	1.000	0.00001	0.00001	0.069
	NoSpherA2 - O/Tonto	1.000	0.00001	0.00002	0.100
	NoSpherA2 – O/T	0.999	0.00001	0.00001	0.062
	Tonto/Neutron	0.891	0.00118	0.00169	2.252
	NoSpherA2 - T/Neutron	0.891	0.00118	0.00168	2.245
	NoSpherA2 - O/Neutron	0.890	0.00118	0.00169	2.246
150 K	IAM/Neutron	0.938	0.00121	0.00149	2.054
	NoSpherA2 - T/Tonto	1.000	0.00001	0.00001	0.048
	NoSpherA2 - O/Tonto	1.000	0.00001	0.00001	0.078
	NoSpherA2 – O/T	1.000	0.00001	0.00001	0.064
	Tonto/Neutron	0.965	0.00133	0.00150	1.472
	NoSpherA2 - T/Neutron	0.966	0.00133	0.00150	1.466
	NoSpherA2 - O/Neutron	0.965	0.00133	0.00150	1.465
295 K	IAM/Neutron	1.013	0.00148	0.00178	1.456
	NoSpherA2 - T/Tonto	1.001	0.00001	0.00002	0.061
	NoSpherA2 - O/Tonto	1.001	0.00002	0.00002	0.074
	NoSpherA2 – O/T	1.000	0.00001	0.00001	0.052

Table S14: Statistical results for hydrogen atom ADPs for *L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	$< U^{ii}_A / U^{ii}_B >$	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	wRMSD
23 K	Tonto/Neutron	1.326	0.0063	0.0070	1.959
	NoSpherA2 - T/Neutron	1.323	0.0062	0.0069	1.938
	NoSpherA2 - O/Neutron	1.319	0.0062	0.0069	1.930
	NoSpherA2 - T/HAR	0.998	0.0002	0.0002	0.048
	NoSpherA2 - O/HAR	0.996	0.0003	0.0003	0.062
	NoSpherA2 – O/T	0.997	0.0001	0.0002	0.040
100 K	HAR/Neutron	--	--	--	--
	NoSpherA2 - T/Neutron	--	--	--	--
	NoSpherA2 - O/Neutron	--	--	--	--
	NoSpherA2 - T/HAR	1.000	0.0003	0.0004	0.125
	NoSpherA2 - O/HAR	0.998	0.0004	0.0004	0.140
	NoSpherA2 – O/T	0.998	0.0001	0.0001	0.054
150 K	HAR/Neutron	1.043	0.0048	0.0056	1.289
	NoSpherA2 - T/Neutron	1.042	0.0046	0.0054	1.273
	NoSpherA2 - O/Neutron	1.040	0.0046	0.0054	1.272
	NoSpherA2 - T/HAR	1.001	0.0006	0.0009	0.123
	NoSpherA2 - O/HAR	0.999	0.0006	0.0009	0.127
	NoSpherA2 – O/T	0.998	0.0001	0.0001	0.026

Table S15: Statistical results for non-hydrogen atom ADPs for *L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	$< U^{ii}_A / U^{ii}_B >$	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	wRMSD
	HAR/Neutron	0.912	0.00034	0.00058	2.830
	NoSpherA2 - T/Neutron	0.915	0.00034	0.00057	2.783
	NoSpherA2 - O/Neutron	0.915	0.00034	0.00057	2.782
23 K	IAM/Neutron	0.973	0.00032	0.00041	1.850
	NoSpherA2 - T/HAR	1.003	0.00001	0.00001	0.117
	NoSpherA2 - O/HAR	1.003	0.00001	0.00001	0.116
	NoSpherA2 – O/T	1.000	0.00000	0.00000	0.016
	HAR/Neutron	--	--	--	--
	NoSpherA2 - T/Neutron	--	--	--	--
	NoSpherA2 - O/Neutron	--	--	--	--
100 K	IAM/Neutron	--	--	--	--
	NoSpherA2 - T/HAR	1.001	0.00001	0.00001	0.135
	NoSpherA2 - O/HAR	1.001	0.00001	0.00001	0.132
	NoSpherA2 – O/T	1.000	0.00000	0.00001	0.086
	HAR/Neutron	0.805	0.00162	0.00296	8.415
	NoSpherA2 - T/Neutron	0.806	0.00161	0.00293	8.374
	NoSpherA2 - O/Neutron	0.806	0.00161	0.00294	8.382
150 K	IAM/Neutron	0.823	0.00154	0.00269	7.132
	NoSpherA2 - T/HAR	1.002	0.00002	0.00002	0.139
	NoSpherA2 - O/HAR	1.001	0.00001	0.00002	0.129
	NoSpherA2 – O/T	1.000	0.00000	0.00001	0.042

Since NoSpherA2-HAR using ORCA as wavefunction source and Tonto-HAR agree very well, for further comparisons ORCA will be used. This second set of comparisons incorporates updated weighting schemes as one variable, and the use of independent software to calculate .tsc files on the other hand.

Table S16: Bond-length statistics for X-H distances, averaged among all bonds for Gly-*L*-Ala.

Temp.	Method (A / B)	$\langle r_A/r_B \rangle$	$\langle \lvert \Delta r_{A-B} \rvert \rangle$ / Å	wRMSD
12K	Tonto / Neutron	0.995	0.0177	1.304
	NoSpherA2 – w / Neutron	0.996	0.0181	1.152
	NoSpherA2 – Q / Neutron	0.995	0.0178	1.296
	NoSpherA2 - w / Tonto	1.000	0.001	0.110
	NoSpherA2 - Q / Tonto	1.000	0.0003	0.055
50K	Tonto / Neutron	1.003	0.010	1.240
	NoSpherA2 – w / Neutron	1.003	0.010	1.191
	NoSpherA2 – Q / Neutron	1.003	0.010	1.176
	NoSpherA2 - w / Tonto	1.000	0.002	0.179
	NoSpherA2 - Q / Tonto	1.000	0.001	0.079
100K	Tonto / Neutron	-	-	-
	NoSpherA2 – w / Neutron	-	-	-
	NoSpherA2 – Q / Neutron	-	-	-
	NoSpherA2 - w / Tonto	1.002	0.002	0.256
	NoSpherA2 - Q / Tonto	1.000	0.001	0.135
150K	Tonto / Neutron	1.000	0.009	1.375
	NoSpherA2 – w / Neutron	1.000	0.010	1.419
	NoSpherA2 – Q / Neutron	1.000	0.009	1.376
	NoSpherA2 - w / Tonto	1.001	0.001	0.179
	NoSpherA2 - Q / Tonto	1.000	0.000	0.064
295K	Tonto / Neutron	0.994	0.011	1.269
	NoSpherA2 – w / Neutron	0.995	0.012	1.300
	NoSpherA2 – Q / Neutron	0.994	0.011	1.275
	NoSpherA2 - w / Tonto	1.001	0.003	0.237
	NoSpherA2 - Q / Tonto	1.000	0.001	0.051

Table S17: Bond-length statistics for X-H distances, averaged among all bonds for *L*-Ala.

Temp.	Method (A / B)	$\langle r_A/r_B \rangle$	$\langle \lvert \Delta r_{A\text{-}B} \rvert \rangle$ / Å	wRMSD
23K	Tonto / Neutron	0.991	0.011	1.904
	NoSpherA2 – w / Neutron	0.991	0.011	1.838
	NoSpherA2 – Q / Neutron	0.991	0.010	1.896
	Tonto / NoSpherA2 – w	1.001	0.0009	0.123
	Tonto / NoSpherA2 – Q	1.000	0.0006	0.086
100K	Tonto / Neutron	-	-	-
	NoSpherA2 – w / Neutron	-	-	-
	NoSpherA2 – Q / Neutron	-	-	-
	Tonto / NoSpherA2 – w	0.999	0.0033	0.650
	Tonto / NoSpherA2 – Q	1.000	0.0003	0.094
150K	Tonto / Neutron	0.995	0.008	1.197
	NoSpherA2 – w / Neutron	0.996	0.012	1.395
	NoSpherA2 – Q / Neutron	0.995	0.008	1.081
	Tonto / NoSpherA2 – w	1.001	0.0049	0.458
	Tonto / NoSpherA2 – Q	1.001	0.0010	0.102

Table S18: Statistical results for hydrogen atom ADPs for Gly-*L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	$< U^{ii}_A / U^{ii}_B >$	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	wRMSD
12 K	Tonto/Neutron	1.058	0.005	0.005	1.382
	NoSpherA2 - w/Neutron	1.051	0.0048	0.0052	1.305
	NoSpherA2 - Q/Neutron	1.054	0.0050	0.0054	1.395
	NoSpherA2 - w/Tonto	0.997	0.0008	0.0009	0.188
	NoSpherA2 - Q/Tonto	0.996	0.0003	0.0003	0.071
50 K	Tonto/Neutron	1.024	0.0054	0.0067	1.359
	NoSpherA2 - w/Neutron	1.011	0.0054	0.0068	1.298
	NoSpherA2 - Q/Neutron	1.018	0.0056	0.0071	1.385
	NoSpherA2 - w/Tonto	0.985	0.0012	0.0011	0.230
	NoSpherA2 - Q/Tonto	0.991	0.0005	0.0006	0.107
100 K	Tonto/Neutron	-	-	-	-
	NoSpherA2 - w/Neutron	-	-	-	-
	NoSpherA2 - Q/Neutron	-	-	-	-
	NoSpherA2 - w/Tonto	1.006	0.0018	0.0022	0.375
	NoSpherA2 - Q/Tonto	0.996	0.0005	0.0006	0.096
150 K	Tonto/Neutron	1.059	0.0051	0.0052	1.316
	NoSpherA2 - w/Neutron	1.055	0.0049	0.0051	1.216
	NoSpherA2 - Q/Neutron	1.056	0.0051	0.0053	1.318
	NoSpherA2 - w/Tonto	0.999	0.0009	0.0010	0.195
	NoSpherA2 - Q/Tonto	0.997	0.0003	0.0003	0.061
295 K	Tonto/Neutron	1.117	0.0098	0.0107	1.623
	NoSpherA2 - w/Neutron	1.109	0.0099	0.0106	1.588
	NoSpherA2 - Q/Neutron	1.117	0.0100	0.0109	1.637
	NoSpherA2 - w/Tonto	0.995	0.0016	0.0019	0.364
	NoSpherA2 - Q/Tonto	0.999	0.0006	0.0006	0.083

Table S19: Statistical results for non-hydrogen atom ADPs for Gly-*L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	$< U^{ii}_A / U^{ii}_B >$	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	wRMSD
12 K	Tonto/Neutron	0.748	0.001	0.002	2.586
	NoSpherA2 - w/Neutron	0.760	0.0011	0.0016	2.529
	NoSpherA2 - Q/Neutron	0.748	0.0011	0.0017	2.581
	NoSpherA2 - w/Tonto	1.016	0.0000	0.0001	0.315
	NoSpherA2 - Q/Tonto	1.000	0.0000	0.0000	0.080
50 K	Tonto/Neutron	0.783	0.0012	0.0018	2.675
	NoSpherA2 - w/Neutron	0.792	0.0012	0.0017	2.611
	NoSpherA2 - Q/Neutron	0.783	0.0012	0.0018	2.674
	NoSpherA2 - w/Tonto	1.013	0.0000	0.0001	0.277
	NoSpherA2 - Q/Tonto	1.000	0.0000	0.0000	0.088
100 K	Tonto/Neutron	-	-	-	-
	NoSpherA2 - w/Neutron	-	-	-	-
	NoSpherA2 - Q/Neutron	-	-	-	-
	NoSpherA2 - w/Tonto	1.013	0.0001	0.0001	0.688
	NoSpherA2 - Q/Tonto	1.000	0.0000	0.0000	0.103
150 K	Tonto/Neutron	0.891	0.0012	0.0017	2.252
	NoSpherA2 - w/Neutron	0.897	0.0011	0.0016	2.194
	NoSpherA2 - Q/Neutron	0.890	0.0012	0.0017	2.247
	NoSpherA2 - w/Tonto	1.007	0.0001	0.0001	0.369
	NoSpherA2 - Q/Tonto	1.000	0.0000	0.0000	0.085
295 K	Tonto/Neutron	0.965	0.0013	0.0015	1.472
	NoSpherA2 - w/Neutron	0.969	0.0013	0.0015	1.446
	NoSpherA2 - Q/Neutron	0.965	0.0013	0.0015	1.465
	NoSpherA2 - w/Tonto	1.005	0.0001	0.0001	0.364
	NoSpherA2 - Q/Tonto	1.001	0.0000	0.0000	0.074

Table S20: Statistical results for hydrogen atom ADPs for *L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	$< U^{ii}_A / U^{ii}_B >$	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	wRMSD
23 K	Tonto/Neutron	1.326	0.0063	0.0070	1.959
	NoSpherA2 - w/Neutron	1.302	0.0063	0.0066	1.876
	NoSpherA2 - Q/Neutron	1.336	0.0063	0.0071	1.893
	NoSpherA2 - w/Tonto	0.983	0.0006	0.0006	0.118
	NoSpherA2 - Q/Tonto	1.006	0.0004	0.0004	0.079
100 K	Tonto/Neutron	-	-	-	-
	NoSpherA2 - w/Neutron	-	-	-	-
	NoSpherA2 - Q/Neutron	-	-	-	-
	NoSpherA2 - w/Tonto	0.981	0.0017	0.0020	0.751
	NoSpherA2 - Q/Tonto	1.002	0.0004	0.0004	0.154
150 K	Tonto/Neutron	1.043	0.0048	0.0056	1.289
	NoSpherA2 - w/Neutron	1.022	0.0046	0.0047	1.177
	NoSpherA2 - Q/Neutron	1.045	0.0046	0.0054	1.272
	NoSpherA2 - w/Tonto	0.993	0.0017	0.0023	0.346
	NoSpherA2 - Q/Tonto	1.003	0.0007	0.0010	0.140

Table S21: Statistical results for non-hydrogen atom ADPs for *L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	$< U^{ii}_A / U^{ii}_B >$	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	wRMSD
23 K	Tonto/Neutron	0.912	0.000	0.001	2.830
	NoSpherA2 - w/Neutron	0.916	0.00033	0.00057	2.771
	NoSpherA2 - Q/Neutron	0.915	0.00000	0.00057	2.764
	NoSpherA2 - w/Tonto	1.004	0.00001	0.00002	0.148
	NoSpherA2 - Q/Tonto	1.003	0.00002	0.00001	0.167
100 K	Tonto/Neutron	-	-	-	-
	NoSpherA2 - w/Neutron	-	-	-	-
	NoSpherA2 - Q/Neutron	-	-	-	-
	NoSpherA2 - w/Tonto	1.002	0.00004	0.00004	0.783
	NoSpherA2 - Q/Tonto	1.000	0.00001	0.00001	0.156
150 K	Tonto/Neutron	0.805	0.00162	0.00296	8.415
	NoSpherA2 - w/Neutron	0.807	0.00160	0.00293	8.376
	NoSpherA2 - Q/Neutron	0.806	0.00013	0.00294	8.372
	NoSpherA2 - w/Tonto	1.003	0.00004	0.00005	0.368
	NoSpherA2 - Q/Tonto	1.001	0.00002	0.00002	0.153

The refinements and data analysis were repeated *without* the I/σ(I) cutoff to see the difference this makes although inside *olex2.refine* it is normally applied automatically. Most datasets will not have been pruned in such a manner; therefore, the following tables correspond to the situation for the usual data. For comparison of the implementation and numerical reproducibility, the first set of data tables above is more important, but to understand the effect of pruning and cutoff criteria, the second set of table provides additional insight.

Table S22: Bond-length statistics for X-H distances, averaged among all bonds for Gly-*L*-Ala.

Temp.	Method (A / B)	$\langle r_A/r_B \rangle$	$\langle \lvert \Delta r_{A\text{-}B} \rvert \rangle$ / Å	wRMSD
	Tonto / Neutron	0.996	0.006	1.295
	NoSpherA2 – T / Neutron	0.996	0.007	1.304
	NoSpherA2 – O / Neutron	0.996	0.006	1.268
12K	IAM / Neutron	0.871	0.139	11.588
	Tonto / NoSpherA2 – T	1.000	0.0003	0.056
	Tonto / NoSpherA2 – O	1.000	0.0004	0.074
	NoSpherA2 – O / NoSpherA2 – T	1.000	0.0003	0.060
	Tonto / Neutron	1.003	0.010	1.236
	NoSpherA2 – T / Neutron	1.004	0.010	1.187
	NoSpherA2 – O / Neutron	1.003	0.010	1.177
50K	IAM / Neutron	0.883	0.125	12.807
	Tonto / NoSpherA2 – T	1.000	0.001	0.077
	Tonto / NoSpherA2 – O	0.999	0.001	0.101
	NoSpherA2 – O / NoSpherA2 – T	1.000	0.001	0.056
	Tonto / Neutron	-	-	-
	NoSpherA2 – T / Neutron	-	-	-
	NoSpherA2 – O / Neutron	-	-	-
100K	IAM / Neutron	-	-	-
	Tonto / NoSpherA2 – T	1.000	0.001	0.097
	Tonto / NoSpherA2 – O	1.000	0.002	0.290
	NoSpherA2 – O / NoSpherA2 – T	1.000	0.002	0.300
	Tonto / Neutron	1.000	0.008	1.378
	NoSpherA2 – T / Neutron	1.000	0.009	1.416
	NoSpherA2 – O / Neutron	1.000	0.009	1.384
150K	IAM / Neutron	0.880	0.128	10.767
	Tonto / NoSpherA2 – T	1.000	0.001	0.106
	Tonto / NoSpherA2 – O	1.000	0.001	0.094
	NoSpherA2 – O / NoSpherA2 – T	1.000	0.0003	0.055
	Tonto / Neutron	0.994	0.011	1.061
	NoSpherA2 – T / Neutron	0.994	0.011	1.092
	NoSpherA2 – O / Neutron	0.994	0.011	1.105
295K	IAM / Neutron	0.887	0.120	9.113
	Tonto / NoSpherA2 – T	1.000	0.001	0.101
	Tonto / NoSpherA2 – O	1.000	0.001	0.094
	NoSpherA2 – O / NoSpherA2 – T	1.000	0.0003	0.051

Table S23: Bond-length statistics for X-H distances, averaged among all bonds for *L*-Ala.

Temp.	Method (A / B)	$\langle r_A/r_B \rangle$	$\langle \lvert \Delta r_{A\text{-}B} \rvert \rangle$ / Å	wRMSD
23K	Tonto / Neutron	0.991	0.010	1.875
	NoSpherA2 – T / Neutron	0.991	0.010	1.789
	NoSpherA2 – O / Neutron	0.991	0.010	1.841
	IAM / Neutron	0.916	0.090	9.070
	Tonto / NoSpherA2 – T	1.000	0.0009	0.109
	Tonto / NoSpherA2 – O	1.000	0.0007	0.086
	NoSpherA2 – O / NoSpherA2 – T	1.000	0.0004	0.066
100K	Tonto / Neutron	-	-	-
	NoSpherA2 – T / Neutron	-	-	-
	NoSpherA2 – O / Neutron	-	-	-
	IAM / Neutron	-	-	-
	Tonto / NoSpherA2 – T	1.000	0.0003	0.094
	Tonto / NoSpherA2 – O	1.000	0.0004	0.116
	NoSpherA2 – O / NoSpherA2 – T	1.000	0.0004	0.116
150K	Tonto / Neutron	0.995	0.009	1.186
	NoSpherA2 – T / Neutron	0.996	0.007	0.943
	NoSpherA2 – O / Neutron	0.992	0.007	0.974
	IAM / Neutron	0.902	0.105	9.733
	Tonto / NoSpherA2 – T	0.999	0.0036	0.342
	Tonto / NoSpherA2 – O	0.999	0.0034	0.337
	NoSpherA2 – O / NoSpherA2 – T	1.000	0.0001	0.024

Table S24: Statistical results for hydrogen atom ADPs for Gly-*L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	wRMSD	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	$< U^{ii}_A / U^{ii}_B >$
12 K	Tonto/Neutron	1.363	0.0048	0.0053	1.060
	NoSpherA2 - T/Neutron	1.386	0.0049	0.0053	1.056
	NoSpherA2 - O/Neutron	1.387	0.0049	0.0053	1.056
	NoSpherA2 - T/Tonto	0.071	0.0003	0.0004	0.996
	NoSpherA2 - O/Tonto	0.083	0.0003	0.0004	0.996
	NoSpherA2 - O/T	0.026	0.0001	0.0001	1.000
50 K	Tonto/Neutron	1.342	0.0053	0.0067	1.021
	NoSpherA2 - T/Neutron	1.387	0.0055	0.0069	1.015
	NoSpherA2 - O/Neutron	1.375	0.0055	0.0069	1.014
	NoSpherA2 - T/Tonto	0.092	0.0005	0.0006	0.994
	NoSpherA2 - O/Tonto	0.096	0.0005	0.0006	0.993
	NoSpherA2 - O/T	0.023	0.0001	0.0001	0.999
100 K	Tonto/Neutron	-	-	-	-
	NoSpherA2 - T/Neutron	-	-	-	-
	NoSpherA2 - O/Neutron	-	-	-	-
	NoSpherA2 - T/Tonto	0.079	0.0003	0.0004	0.994
	NoSpherA2 - O/Tonto	0.081	0.0003	0.0004	0.994
	NoSpherA2 - O/T	0.027	0.0001	0.0001	1.000
150 K	Tonto/Neutron	1.313	0.0078	0.0051	1.056
	NoSpherA2 - T/Neutron	1.327	0.0050	0.0051	1.053
	NoSpherA2 - O/Neutron	1.321	0.0050	0.0051	1.053
	NoSpherA2 - T/Tonto	0.070	0.0003	0.0003	0.997
	NoSpherA2 - O/Tonto	0.069	0.0003	0.0004	0.997
	NoSpherA2 - O/T	0.026	0.0001	0.0001	1.000
295 K	Tonto/Neutron	1.629	0.0096	0.0106	1.116
	NoSpherA2 - T/Neutron	1.679	0.0099	0.0108	1.113
	NoSpherA2 - O/Neutron	1.678	0.0099	0.0108	1.113
	NoSpherA2 - T/Tonto	0.088	0.0006	0.0006	0.997
	NoSpherA2 - O/Tonto	0.090	0.0006	0.0006	0.996
	NoSpherA2 - O/T	0.027	0.0001	0.0001	1.000

Table S25: Statistical results for non-hydrogen atom ADPs for Gly-*L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	wRMSD	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	$< U^{ii}_A / U^{ii}_B >$
12 K	IAM/Neutron	2.273	0.00108	0.00140	0.863
	Tonto/Neutron	2.578	0.00110	0.00167	0.749
	NoSpherA2 - T/Neutron	2.577	0.00110	0.00168	0.749
	NoSpherA2 - O/Neutron	2.579	0.00111	0.00168	0.749
	NoSpherA2 - T/Tonto	0.057	0.00001	0.00001	1.000
	NoSpherA2 - O/Tonto	0.078	0.00001	0.00001	0.999
	NoSpherA2 - O/T	0.061	0.00001	0.00001	0.999
50 K	IAM/Neutron	2.212	0.00107	0.00144	0.889
	Tonto/Neutron	2.669	0.00122	0.00178	0.784
	NoSpherA2 - T/Neutron	2.666	0.00121	0.00177	0.785
	NoSpherA2 - O/Neutron	2.667	0.00122	0.00178	0.785
	NoSpherA2 - T/Tonto	0.085	0.00001	0.00002	1.001
	NoSpherA2 - O/Tonto	0.101	0.00002	0.00002	1.000
	NoSpherA2 - O/T	0.051	0.00001	0.00001	0.999
100 K	IAM/Neutron	-	-	-	-
	Tonto/Neutron	-	-	-	-
	NoSpherA2 - T/Neutron	-	-	-	-
	NoSpherA2 - O/Neutron	-	-	-	-
	NoSpherA2 - T/Tonto	0.080	0.00001	0.00002	1.000
	NoSpherA2 - O/Tonto	0.103	0.00001	0.00002	1.000
	NoSpherA2 - O/T	0.064	0.00001	0.00001	0.999
150 K	IAM/Neutron	2.068	0.00122	0.00149	0.937
	Tonto/Neutron	2.251	0.00118	0.00168	0.891
	NoSpherA2 - T/Neutron	2.268	0.00118	0.00168	0.891
	NoSpherA2 - O/Neutron	2.271	0.00118	0.00169	0.891
	NoSpherA2 - T/Tonto	0.061	0.00001	0.00001	1.000
	NoSpherA2 - O/Tonto	0.087	0.00001	0.00002	1.000
	NoSpherA2 - O/T	0.065	0.00001	0.00001	1.000
295 K	IAM/Neutron	1.468	0.00147	0.00177	1.011
	Tonto/Neutron	1.468	0.00133	0.00149	0.966
	NoSpherA2 - T/Neutron	1.465	0.00133	0.00149	0.966
	NoSpherA2 - O/Neutron	1.464	0.00133	0.00149	0.966
	NoSpherA2 - T/Tonto	0.069	0.00002	0.00002	1.001
	NoSpherA2 - O/Tonto	0.081	0.00002	0.00002	1.000
	NoSpherA2 - O/T	0.054	0.00001	0.00001	1.000

Table S26: Statistical results for hydrogen atom ADPs for *L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	wRMSD	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	$< U^{ii}_A / U^{ii}_B >$
23 K	Tonto/Neutron	1.957	0.0063	0.0069	1.328
	NoSpherA2 - T/Neutron	1.979	0.0062	0.0069	1.328
	NoSpherA2 - O/Neutron	1.971	0.0061	0.0068	1.324
	NoSpherA2 - T/Tonto	0.141	0.0005	0.0006	1.001
	NoSpherA2 - O/Tonto	0.154	0.0006	0.0007	0.998
	NoSpherA2 - O/T	0.029	0.0002	0.0001	0.997
100 K	Tonto/Neutron	-	-	-	-
	NoSpherA2 - T/Neutron	-	-	-	-
	NoSpherA2 - O/Neutron	-	-	-	-
	NoSpherA2 - T/Tonto	0.182	0.0003	0.0005	1.001
	NoSpherA2 - O/Tonto	0.190	0.0005	0.0005	1.000
	NoSpherA2 - O/T	0.051	0.0001	0.0001	0.998
150 K	Tonto/Neutron	1.282	0.0055	0.0056	1.042
	NoSpherA2 - T/Neutron	1.252	0.0050	0.0058	1.074
	NoSpherA2 - O/Neutron	1.251	0.0050	0.0058	1.072
	NoSpherA2 - T/Tonto	0.513	0.0028	0.0026	1.031
	NoSpherA2 - O/Tonto	0.511	0.0027	0.0026	1.028
	NoSpherA2 - O/T	0.023	0.0001	0.0002	0.998

Table S27: Statistical results for non-hydrogen atom ADPs for *L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	wRMSD	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	$< U^{ii}_A / U^{ii}_B >$
23 K	IAM/Neutron	3.667	0.00032	0.00043	0.967
	Tonto/Neutron	2.818	0.00034	0.00058	0.913
	NoSpherA2 - T/Neutron	2.802	0.00034	0.00057	0.915
	NoSpherA2 - O/Neutron	2.800	0.00034	0.00057	0.915
	NoSpherA2 - T/Tonto	0.136	0.00001	0.00001	1.002
	NoSpherA2 - O/Tonto	0.133	0.00001	0.00001	1.002
	NoSpherA2 - O/T	0.029	0.000002	0.000003	1.000
100 K	IAM/Neutron	-	-	-	-
	Tonto/Neutron	-	-	-	-
	NoSpherA2 - T/Neutron	-	-	-	-
	NoSpherA2 - O/Neutron	-	-	-	-
	NoSpherA2 - T/Tonto	0.432	0.00003	0.00003	1.001
	NoSpherA2 - O/Tonto	0.425	0.00003	0.00003	1.001
	NoSpherA2 - O/T	0.081	0.000005	0.000007	1.000
150 K	IAM/Neutron	51.759	0.00156	0.00272	0.821
	Tonto/Neutron	8.415	0.00162	0.00295	0.805
	NoSpherA2 - T/Neutron	8.120	0.00162	0.00292	0.807
	NoSpherA2 - O/Neutron	8.127	0.00162	0.00292	0.807
	NoSpherA2 - T/Tonto	1.420	0.0002	0.00013	1.003
	NoSpherA2 - O/Tonto	1.421	0.0002	0.00014	1.003
	NoSpherA2 - O/T	0.033	0.000004	0.000006	1.000

Table S28: Bond-length statistics for X-H distances, averaged among all bonds for Gly-*L*-Ala.

Temp.	Method (A / B)	$\langle r_A/r_B \rangle$	$\langle \lvert \Delta r_{A\text{-}B} \rvert \rangle$ / Å	wRMSD
12K	Tonto / Neutron	0.996	0.006	1.295
	NoSpherA2 – w / Neutron	0.996	0.006	1.137
	NoSpherA2 – Q / Neutron	0.996	0.007	1.286
	Tonto / NoSpherA2 – w	1.000	0.0008	0.101
	Tonto / NoSpherA2 – Q	1.000	0.0008	0.117
50K	Tonto / Neutron	1.003	0.010	1.236
	NoSpherA2 – w / Neutron	1.003	0.010	1.189
	NoSpherA2 – Q / Neutron	1.003	0.010	1.209
	Tonto / NoSpherA2 – w	1.000	0.0014	0.141
	Tonto / NoSpherA2 – Q	1.000	0.0003	0.043
100K	Tonto / Neutron	-	-	-
	NoSpherA2 – w / Neutron	-	-	-
	NoSpherA2 – Q / Neutron	-	-	-
	Tonto / NoSpherA2 – w	0.999	0.0022	0.249
	Tonto / NoSpherA2 – Q	1.000	0.0009	0.118
150K	Tonto / Neutron	1.000	0.008	1.378
	NoSpherA2 – w / Neutron	1.000	0.010	1.478
	NoSpherA2 – Q / Neutron	1.000	0.009	1.390
	Tonto / NoSpherA2 – w	1.000	0.0013	0.176
	Tonto / NoSpherA2 – Q	1.000	0.0008	0.111
295K	Tonto / Neutron	0.994	0.011	1.061
	NoSpherA2 – w / Neutron	0.994	0.011	1.092
	NoSpherA2 – Q / Neutron	0.994	0.011	1.048
	Tonto / NoSpherA2 – w	1.000	0.0011	0.101
	Tonto / NoSpherA2 – Q	1.000	0.0008	0.083

Table S29: Bond-length statistics for X-H distances, averaged among all bonds for *L*-Ala.

Temp.	Method (A / B)	$\langle r_A/r_B \rangle$	$\langle \lvert \Delta r_{A-B} \rvert \rangle$ / Å	wRMSD
23K	Tonto / Neutron	0.991	0.010	1.875
	NoSpherA2 – w / Neutron	0.991	0.011	1.835
	NoSpherA2 – Q / Neutron	0.991	0.010	1.729
	Tonto / NoSpherA2 – w	1.000	0.0013	0.172
	Tonto / NoSpherA2 – Q	1.000	0.0009	0.089
100K	Tonto / Neutron	-	-	-
	NoSpherA2 – w / Neutron	-	-	-
	NoSpherA2 – Q / Neutron	-	-	-
	Tonto / NoSpherA2 – w	1.002	0.0033	0.680
	Tonto / NoSpherA2 – Q	1.001	0.0007	0.186
150K	Tonto / Neutron	0.995	0.009	1.186
	NoSpherA2 – w / Neutron	0.996	0.007	0.991
	NoSpherA2 – Q / Neutron	0.996	0.007	0.966
	Tonto / NoSpherA2 – w	0.998	0.0033	0.295
	Tonto / NoSpherA2 – Q	0.999	0.0039	0.358

Table S30: Statistical results for hydrogen atom ADPs for Gly-*L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	wRMSD	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	$< U^{ii}_A / U^{ii}_B >$
12 K	Tonto/Neutron	1.363	0.0048	0.0053	1.060
	NoSpherA2 - w/Neutron	1.308	0.0048	0.0052	1.051
	NoSpherA2 - Q/Neutron	1.382	0.0049	0.0052	1.062
	NoSpherA2 - w/Tonto	0.221	0.0010	0.0011	0.995
	NoSpherA2 - Q/Tonto	0.113	0.0005	0.0006	1.003
50 K	Tonto/Neutron	1.342	0.0053	0.0067	1.021
	NoSpherA2 - w/Neutron	1.303	0.0054	0.0068	1.011
	NoSpherA2 - Q/Neutron	1.369	0.0056	0.0069	1.021
	NoSpherA2 - w/Tonto	0.226	0.0011	0.0012	0.989
	NoSpherA2 - Q/Tonto	0.113	0.0006	0.0007	1.002
100 K	Tonto/Neutron	-	-	-	-
	NoSpherA2 - w/Neutron	-	-	-	-
	NoSpherA2 - Q/Neutron	-	-	-	-
	NoSpherA2 - w/Tonto	0.384	0.0019	0.0021	1.000
	NoSpherA2 - Q/Tonto	0.127	0.0005	0.0006	1.002
150 K	Tonto/Neutron	1.313	0.0078	0.0051	1.056
	NoSpherA2 - w/Neutron	1.235	0.0049	0.0050	1.049
	NoSpherA2 - Q/Neutron	1.323	0.0050	0.0051	1.060
	NoSpherA2 - w/Tonto	0.203	0.0009	0.0010	0.995
	NoSpherA2 - Q/Tonto	0.100	0.0005	0.0005	1.003
295 K	Tonto/Neutron	1.629	0.0096	0.0106	1.116
	NoSpherA2 - w/Neutron	1.623	0.0097	0.0105	1.106
	NoSpherA2 - Q/Neutron	1.679	0.0010	0.0011	1.119
	NoSpherA2 - w/Tonto	0.238	0.0016	0.0018	0.992
	NoSpherA2 - Q/Tonto	0.102	0.0006	0.0006	1.002

Table S31: Statistical results for non-hydrogen atom ADPs for Gly-*L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	wRMSD	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	$< U^{ii}_A / U^{ii}_B >$
12 K	Tonto/Neutron	2.578	0.00110	0.00167	0.749
	NoSpherA2 - w/Neutron	2.520	0.00108	0.00163	0.762
	NoSpherA2 - Q/Neutron	2.575	0.00110	0.00167	0.749
	NoSpherA2 - w/Tonto	0.336	0.00005	0.00007	1.017
	NoSpherA2 - Q/Tonto	0.144	0.00002	0.00002	1.000
50 K	Tonto/Neutron	2.669	0.00122	0.00178	0.784
	NoSpherA2 - w/Neutron	2.594	0.00118	0.00171	0.795
	NoSpherA2 - Q/Neutron	2.665	0.00121	0.00178	0.785
	NoSpherA2 - w/Tonto	0.325	0.00006	0.00008	1.015
	NoSpherA2 - Q/Tonto	0.152	0.00002	0.00003	1.000
100 K	Tonto/Neutron	-	-	-	-
	NoSpherA2 - w/Neutron	-	-	-	-
	NoSpherA2 - Q/Neutron	-	-	-	-
	NoSpherA2 - w/Tonto	0.745	0.00009	0.00013	1.014
	NoSpherA2 - Q/Tonto	0.156	0.00002	0.00002	1.000
150 K	Tonto/Neutron	2.251	0.00118	0.00168	0.891
	NoSpherA2 - w/Neutron	2.226	0.00114	0.00161	0.897
	NoSpherA2 - Q/Neutron	2.270	0.00117	0.00168	0.891
	NoSpherA2 - w/Tonto	0.400	0.00006	0.00009	1.007
	NoSpherA2 - Q/Tonto	0.130	0.00002	0.00002	1.000
295 K	Tonto/Neutron	1.468	0.00133	0.00149	0.966
	NoSpherA2 - w/Neutron	1.445	0.00132	0.00147	0.970
	NoSpherA2 - Q/Neutron	1.464	0.00133	0.00150	0.966
	NoSpherA2 - w/Tonto	0.409	0.00008	0.00012	1.005
	NoSpherA2 - Q/Tonto	0.103	0.00002	0.00003	1.001

Table S32: Statistical results for hydrogen atom ADPs for *L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	wRMSD	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	$< U^{ii}_A / U^{ii}_B >$
23 K	Tonto/Neutron	1.957	0.0063	0.0069	1.328
	NoSpherA2 - w/Neutron	1.925	0.0061	0.0066	1.311
	NoSpherA2 - Q/Neutron	1.826	0.0063	0.0074	1.374
	NoSpherA2 - w/Tonto	0.202	0.0010	0.0010	0.989
	NoSpherA2 - Q/Tonto	0.180	0.0009	0.0011	1.039
100 K	Tonto/Neutron	-	-	-	-
	NoSpherA2 - w/Neutron	-	-	-	-
	NoSpherA2 - Q/Neutron	-	-	-	-
	NoSpherA2 - w/Tonto	0.672	0.0044	0.0020	0.984
	NoSpherA2 - Q/Tonto	0.217	0.0038	0.0007	1.006
150 K	Tonto/Neutron	1.282	0.0055	0.0056	1.042
	NoSpherA2 - w/Neutron	1.230	0.0046	0.0056	1.044
	NoSpherA2 - Q/Neutron	1.179	0.0048	0.0055	1.077
	NoSpherA2 - w/Tonto	0.279	0.0015	0.0017	1.000
	NoSpherA2 - Q/Tonto	0.467	0.0026	0.0026	1.033

Table S33: Statistical results for non-hydrogen atom ADPs for *L*-Ala, units of differences are Å^2.

Temp.	Method (A/B)	wRMSD	$< \lvert U^{ij}_A - U^{ij}_B \rvert >$	$< \lvert U^{ii}_A - U^{ii}_B \rvert >$	$< U^{ii}_A / U^{ii}_B >$
23 K	Tonto/Neutron	2.818	0.00034	0.00058	0.913
	NoSpherA2 - w/Neutron	2.790	0.00033	0.00057	0.916
	NoSpherA2 - Q/Neutron	2.708	0.00033	0.00057	0.917
	NoSpherA2 - w/Tonto	0.156	0.00001	0.00002	1.003
	NoSpherA2 - Q/Tonto	0.311	0.00003	0.00003	1.004
100 K	Tonto/Neutron	-	-	-	-
	NoSpherA2 - w/Neutron	-	-	-	-
	NoSpherA2 - Q/Neutron	-	-	-	-
	NoSpherA2 - w/Tonto	0.904	0.00005	0.00005	1.003
	NoSpherA2 - Q/Tonto	0.439	0.00003	0.00003	1.001
150 K	Tonto/Neutron	8.415	0.00162	0.00295	0.805
	NoSpherA2 - w/Neutron	8.323	0.00161	0.00295	0.806
	NoSpherA2 - Q/Neutron	8.089	0.00162	0.00292	0.808
	NoSpherA2 - w/Tonto	0.358	0.00004	0.00005	1.001
	NoSpherA2 - Q/Tonto	1.429	0.00017	0.00014	1.003

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