materials design

UGM 2020 Training Series

Exploring Molecular Crystal Polymorphs with *MedeA*: Applications in the Pharmaceutical Industry.

Materials Design

November 5th, 2020

Materials Design UGM

Training & Support Team

Siwen Wang
presenter

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moderator

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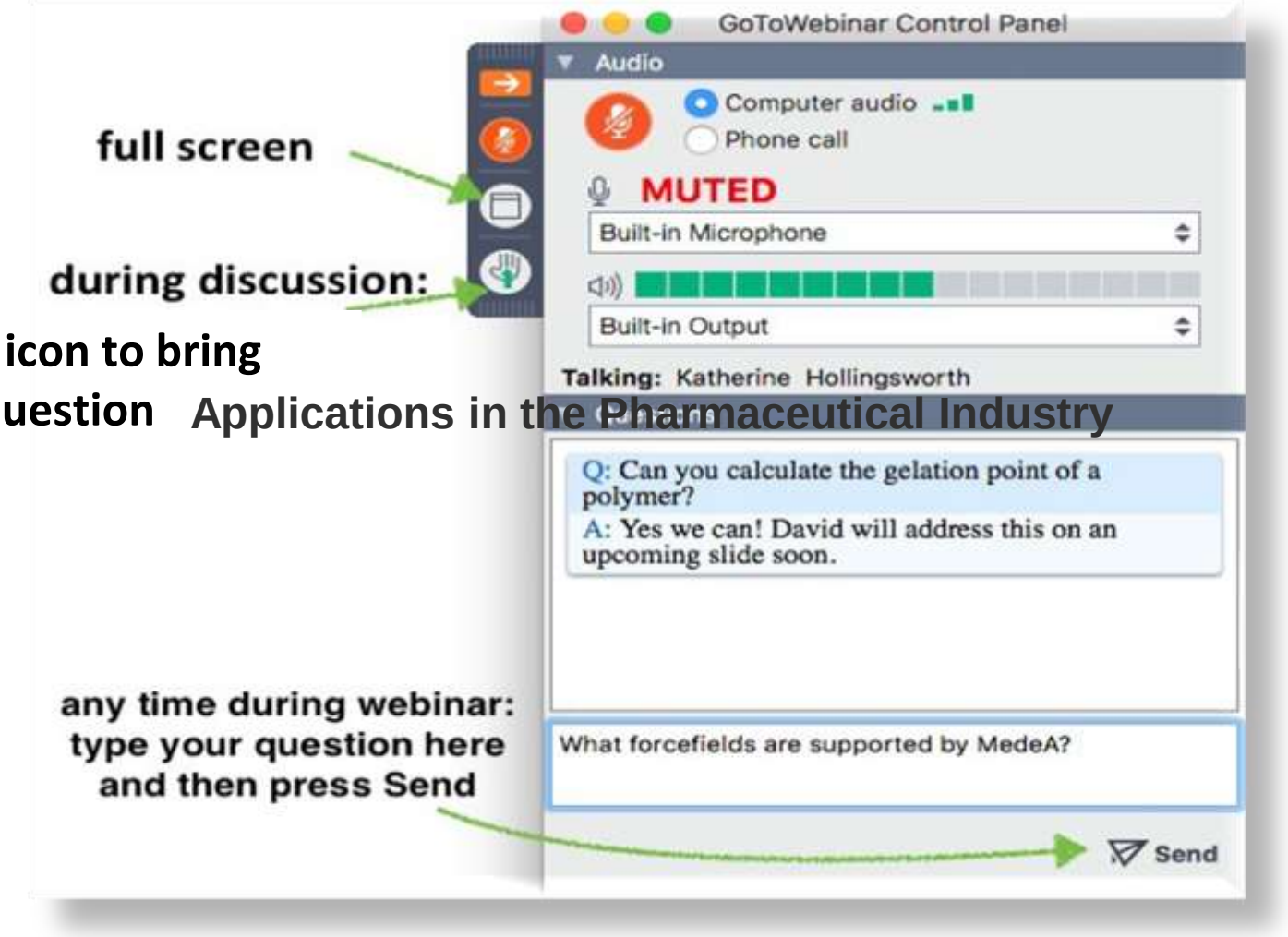
Ray Shan

Please Ask Questions!



Use the raise hand icon to bring attention to your question

any time during webinar: type your question here and then press Send

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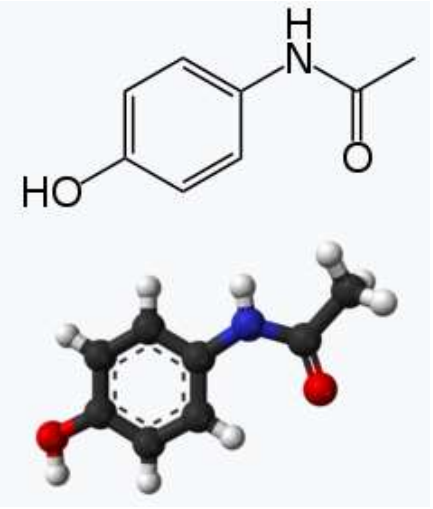
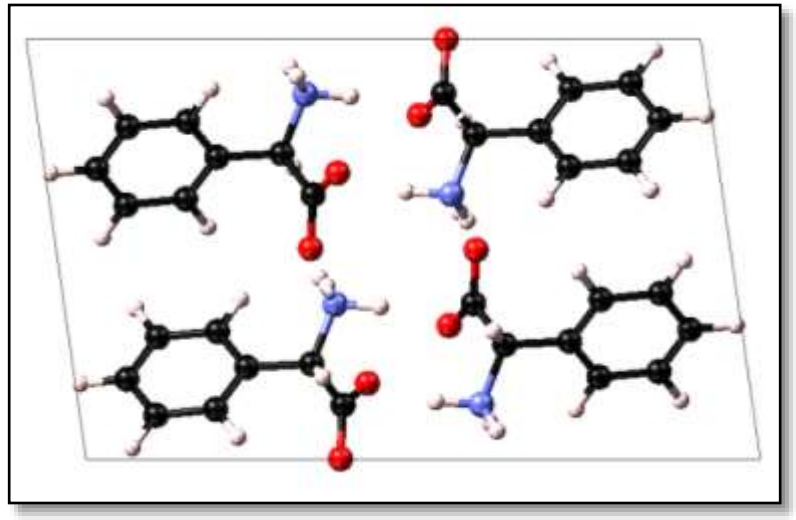
Drug Discovery and Development



Drug Discovery



Drug Development

Molecule:
- Binding
- Toxicity
- Metabolism

…

Crystal:
- Thermal stability
- Solubility
- Physical stability

…

Tablet:
- Efficacy
- Dose adjustment
- Clinical trial

…

Outline

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01 Structure Property

Optimize molecular crystals with *MedeA* VASP

02 Elastic Property

Calculate the mechanical properties of molecular crystals with *MedeA* MT

03 Nuclear Magnetic Resonance (NMR) Property

Calculate the NMR properties of molecular crystals with *MedeA* VASP

04 Thermal Property

Calculate Gibbs free energy of molecular crystals with *MedeA* Phonon
Calculate the heat of sublimation of molecular crystals with *MedeA* VASP
Calculate the cohesive energy density with *MedeA* LAMMPS and *MedeA* CED

Databases

Direct access to experimental and calculated structure data gathered over decades – InfoMaticA

Compute Engines

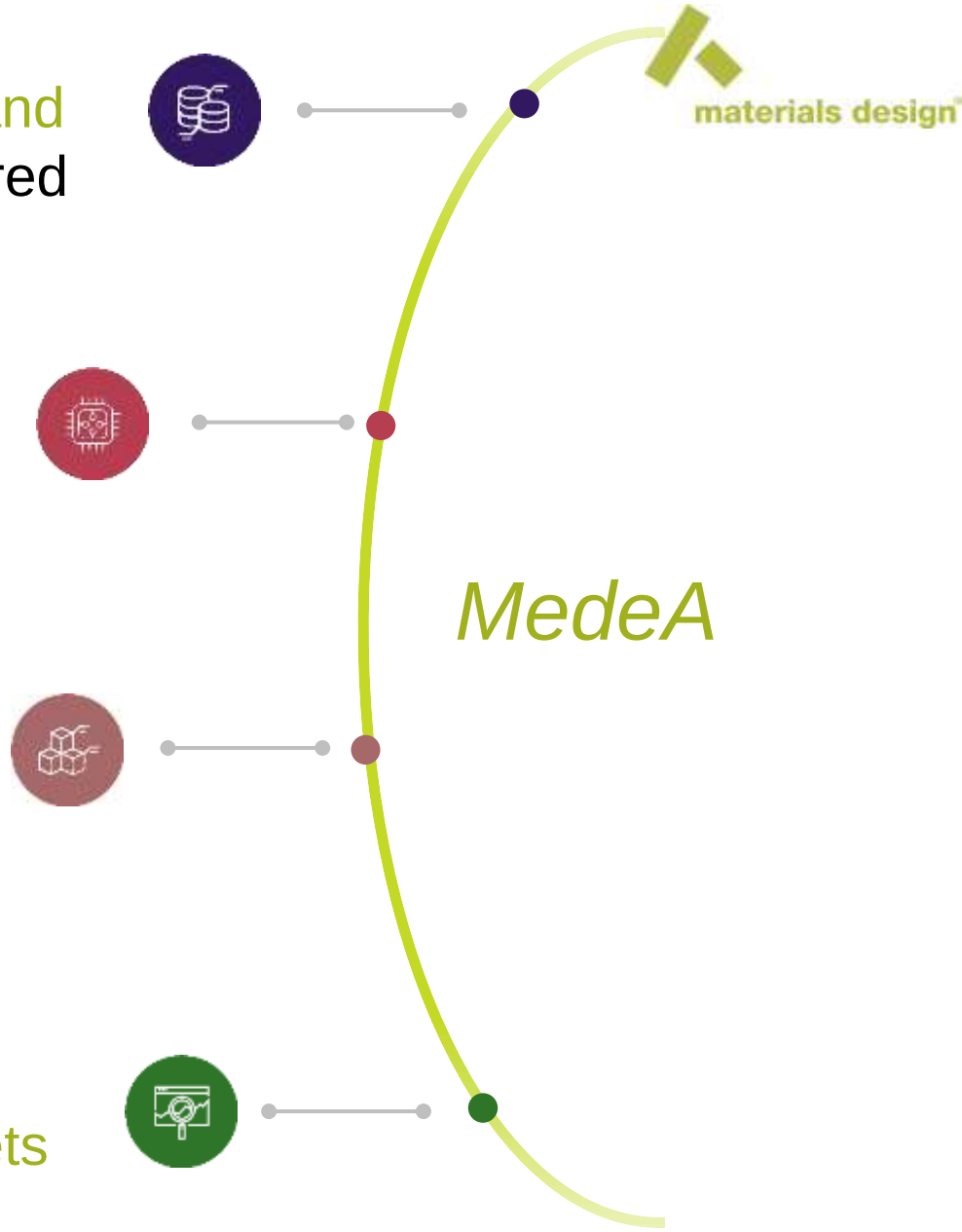
VASP, **LAMMPS**

Property Modules

MT, Phonon, CED, Flowcharts which facilitate modeling, analysis, and property prediction

High Throughput

Generation of large and consistent sets of computed data & descriptors



Introduction

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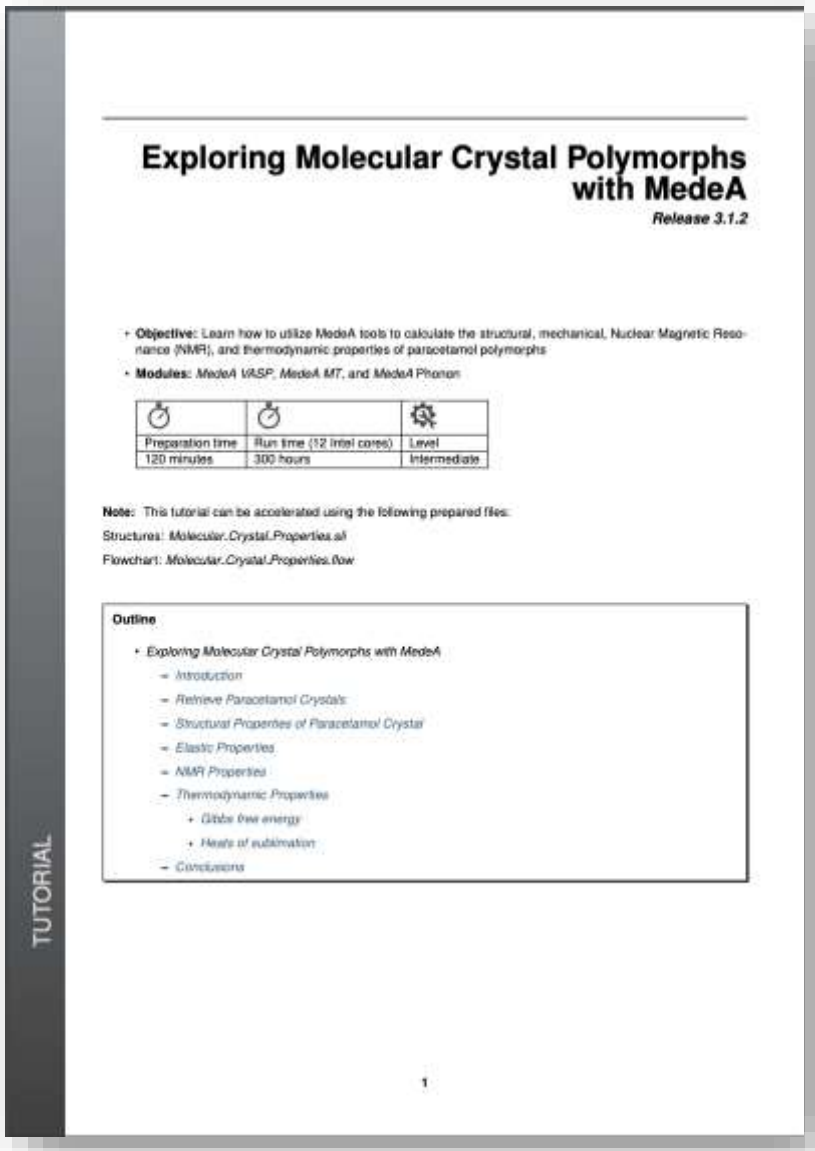
- See *MedeA* tutorial Exploring Molecular Crystal Polymorphs at http://my.materialsdesign.com/tutorials

- **Objective:** Learn how to utilize *MedeA* tools to calculate the structural, mechanical, Nuclear Magnetic Resonance (NMR), and thermodynamic properties of paracetamol polymorphs.

- **Modules:** *MedeA* VASP, *MedeA* MT, and *MedeA* Phonon

Preparation time	Run time (12 Intel cores)	Level
120 minutes	300 hours	Intermediate


TUTORIAL

Exploring Molecular Crystal Polymorphs with MedeA

Release 3.1.2

- **Objective:** Learn how to utilize MedeA tools to calculate the structural, mechanical, Nuclear Magnetic Resonance (NMR), and thermodynamic properties of paracetamol polymorphs
- **Modules:** *MedeA VASP*, *MedeA MT*, and *MedeA* Phonon

Preparation time	Run time (12 Intel cores)	Level
120 minutes	300 hours	Intermediate

Note: This tutorial can be accelerated using the following prepared files:

Structures: *Molecular.Crystal.Properties.sdf*

Flowchart: *Molecular.Crystal.Properties.flow*

Outline

- *Exploring Molecular Crystal Polymorphs with MedeA*
  - *Introduction*
  - *Retrieve Paracetamol Crystals*
  - *Structural Properties of Paracetamol Crystal*
  - *Elastic Properties*
  - *NMR Properties*
  - *Thermodynamic Properties*
    - *Gibbs free energy*
    - *Heats of sublimation*
  - *Conclusions*

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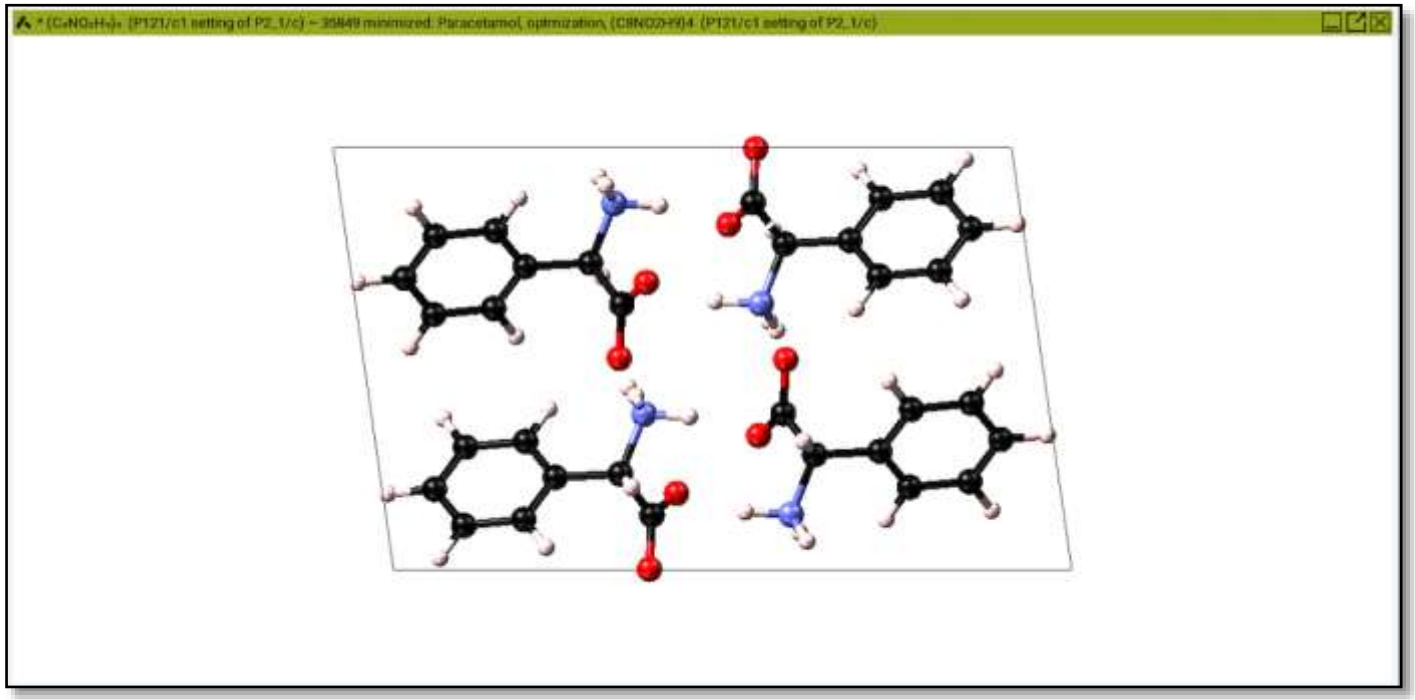
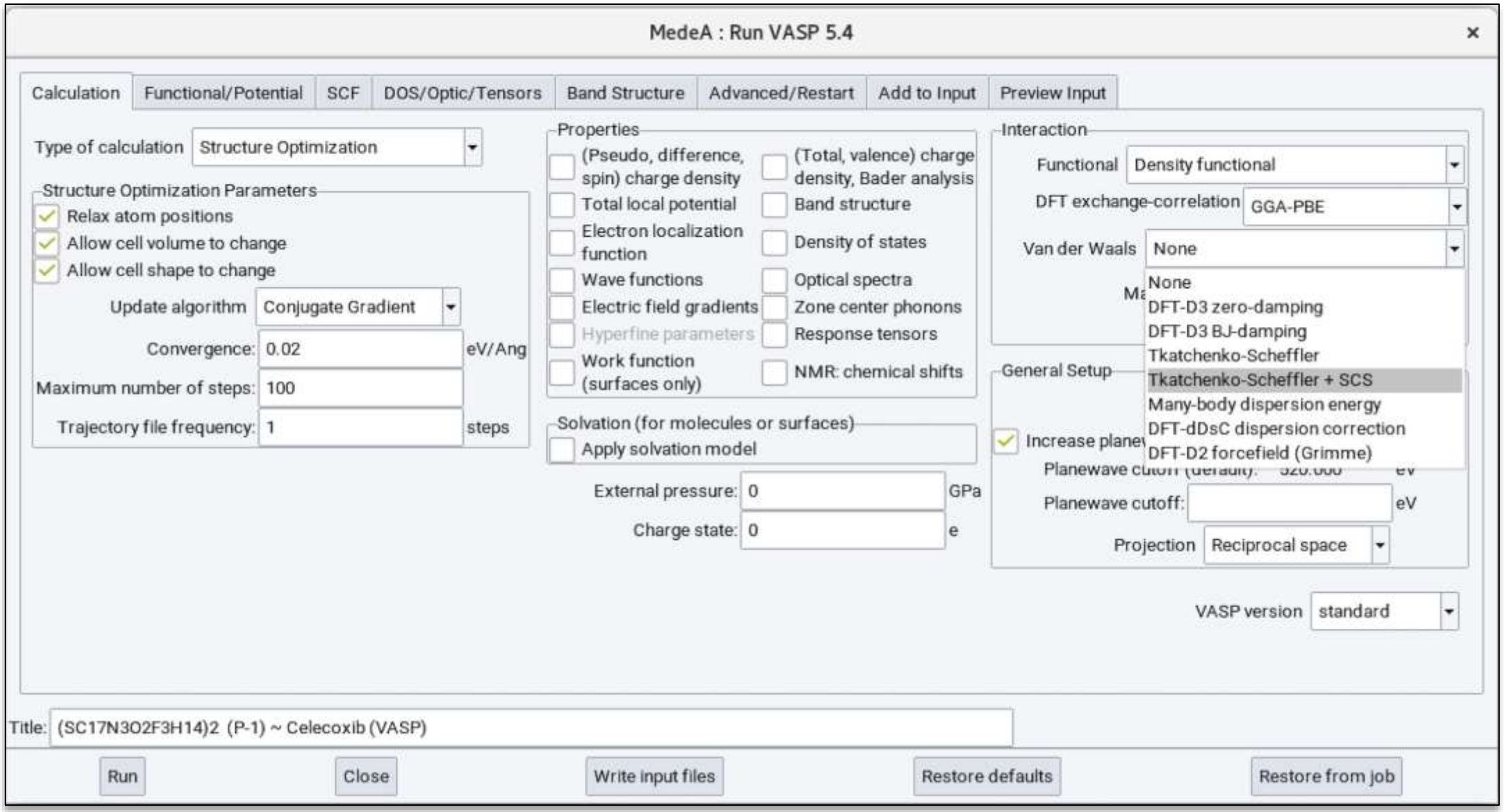
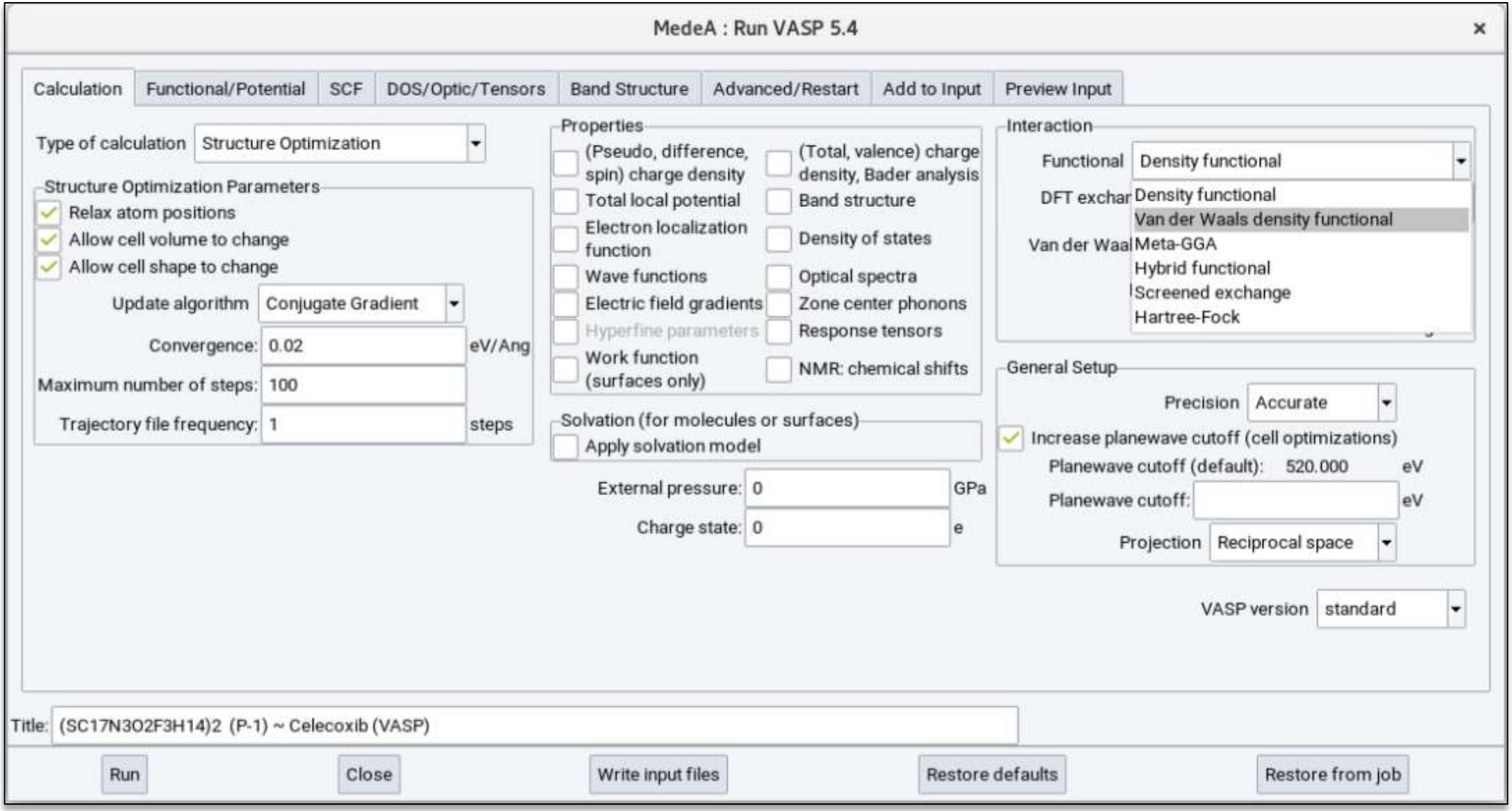
Paracetamol Crystals



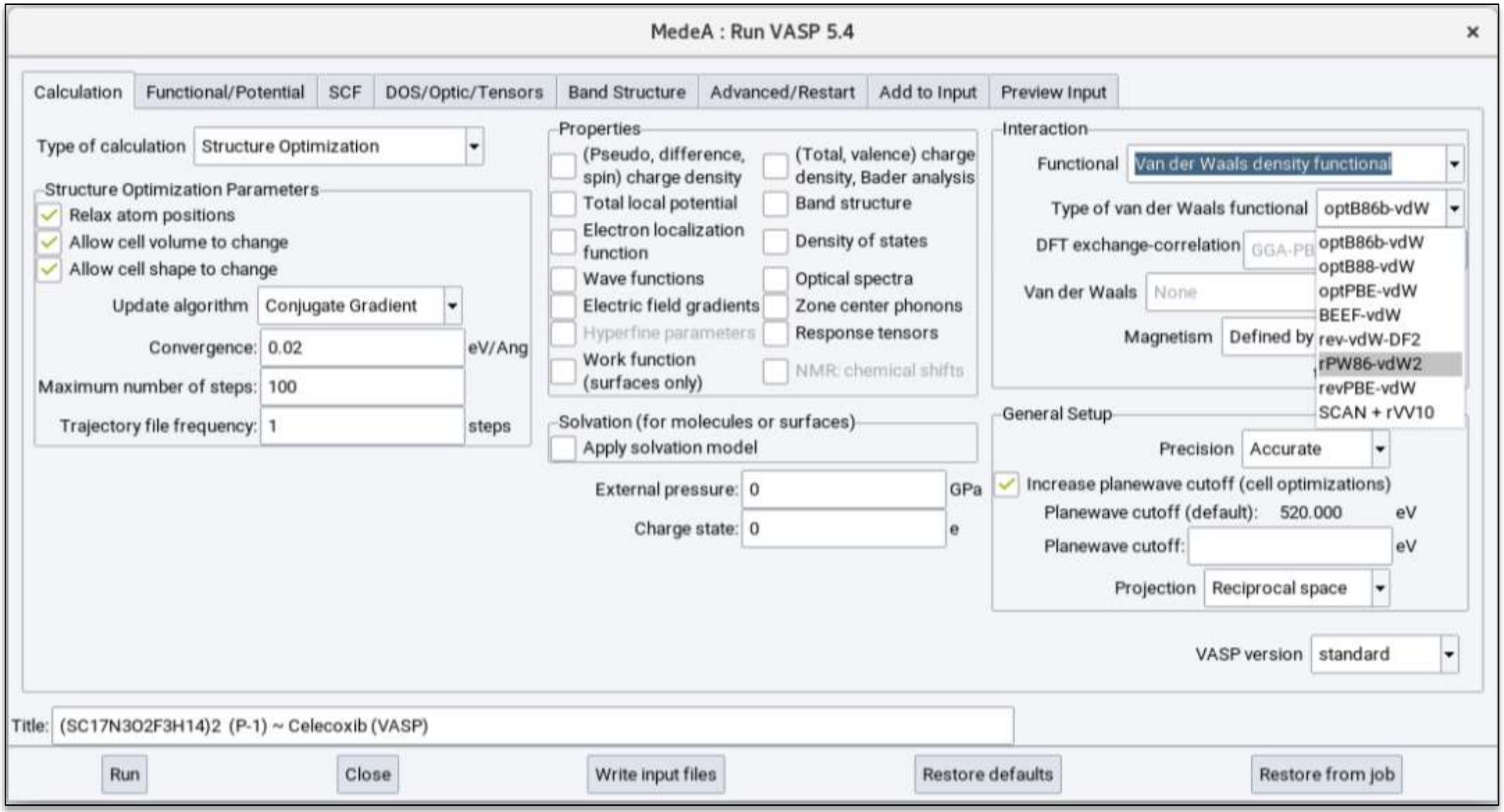
Van der Waals Force Field



Van der Waals Functional



Van der Waals Functional



Van der Waals Interactions in Paracetamol

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Experimental and calculated lattice parameters

Van der Waals forcefield	LDA	PBEsol	PBE	DFT-D3 0-damping	DFT-D3 BJ-damping	Tkatchenko-Scheffler	TkatchenkoScheffler + SCS	DFT-D2	Many-body dispersion energy	DFT-dDsC
Δa (%)	-2.1	0.5	**1.2**	-0.1	-0.1	-0.3	0.1	**0.0**	**-0.1**	**-0.7**
Δb (%)	0.8	7.6	**7.9**	2.8	2.3	2.6	3.6	**-0.1**	**2.5**	**0.5**
Δc (%)	-0.4	1.9	**4.1**	1.5	1.4	1.6	1.8	**0.2**	**1.3**	**0.2**
Δβ (%)	0.2	-0.5	**-0.2**	0.0	0.0	0.4	0.2	**0.3**	**0.1**	**0.4**
ΔV (%)	-1.8	10.4	**13.7**	4.3	3.5	3.8	5.5	**0.0**	**3.6**	**-0.1**

Van der Waals Interactions in Paracetamol

materials design

Experimental and calculated lattice parameters

Van der Waals forcefield	LDA	PBEsol	PBE	DFT-D3 0-damping	DFT-D3 BJ-damping	Tkatchenko-Scheffler	TkatchenkoScheffler + SCS	DFT-D2	Many-body dispersion energy	DFT-dDsC
Δa (%)	-2.1	0.5	**1.2**	-0.1	-0.1	-0.3	0.1	**0.0**	**-0.1**	**-0.7**
Δb (%)	0.8	7.6	**7.9**	2.8	2.3	2.6	3.6	**-0.1**	**2.5**	**0.5**
Δc (%)	-0.4	1.9	**4.1**	1.5	1.4	1.6	1.8	**0.2**	**1.3**	**0.2**
Δβ (%)	0.2	-0.5	**-0.2**	0.0	0.0	0.4	0.2	**0.3**	**0.1**	**0.4**
ΔV (%)	-1.8	10.4	**13.7**	4.3	3.5	3.8	5.5	**0.0**	**3.6**	**-0.1**

Van der Waals func.	optB86b-vdW	optB88-vdW	optPBE-vdW	rPW86-vdW2	revPBE-vdW	BEEF- vdW	rev-vdW-DF2	Experimental data		
Δa (%)	**-0.2**	0.2	1.1	2.3	4.4	**2.7**	**0.2**	6.8850 Å		
Δb (%)	**1.6**	1.5	3.1	2.7	8.3	**6.3**	**1.3**	8.5819 Å		
Δc (%)	**0.8**	0.9	1.8	2.8	4.0	**3.1**	**0.6**	11.519 Å		
Δβ (%)	**0.4**	0.3	0.0	0.2	-0.4	**-0.2**	**0.0**	99.12 deg		
ΔV (%)	**2.1**	2.6	6.1	7.9	17.7	**12.6**	**2.2**	672.01 $Å^3$		

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NMR Chemical Shift

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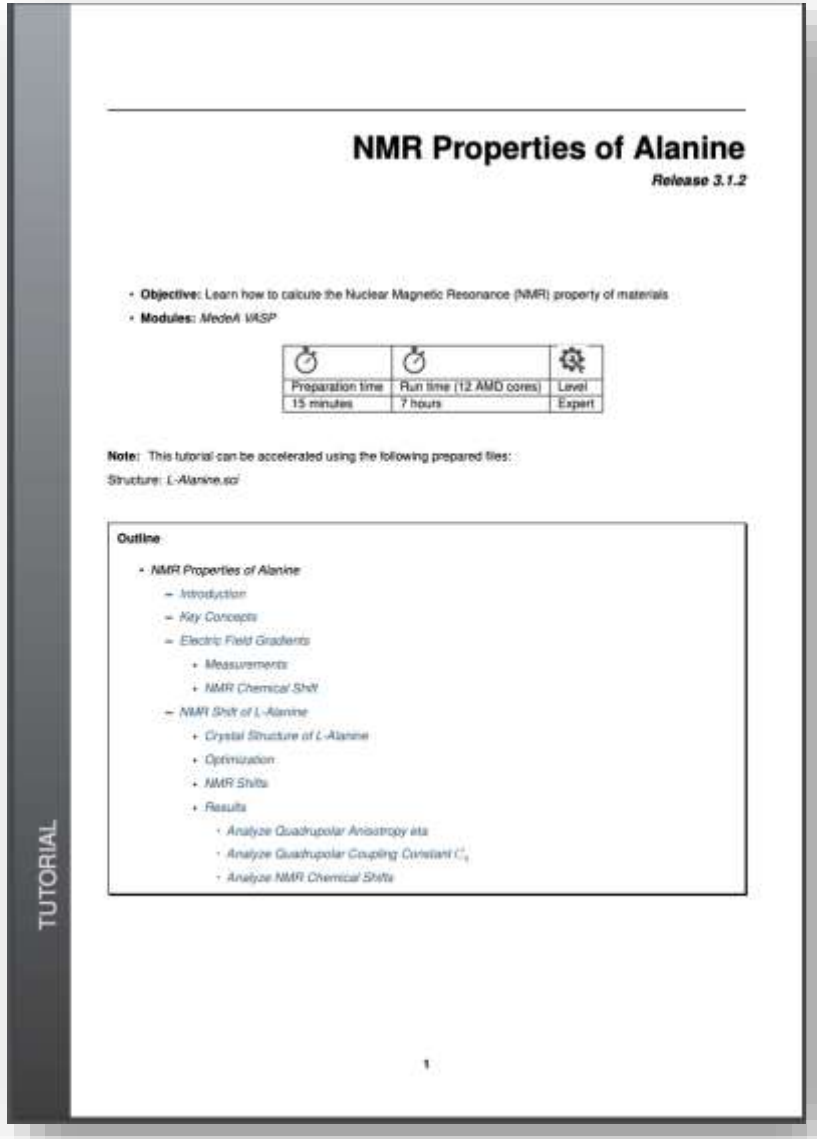
- See *MedeA* tutorial NMR Properties of Alanineat http://my.materialsdesign.com/tutorials

- **Objective:** Learn how to calculate the Nuclear Magnetic Resonance (NMR) property of materials.

Preparation time	Run time (12 AMD cores)	Level
15 minutes	7 hours	Expert


TUTORIAL

NMR Properties of Alanine

Release 3.1.2

- **Objective:** Learn how to calcute the Nuclear Magnetic Resonance (NMR) property of materials
- **Modules:** *MedeA VASP*

Preparation time	Run time (12 AMD cores)	Level
15 minutes	7 hours	Expert

Note: This tutorial can be accelerated using the following prepared files:
Structure: *L-Alanine.sci*

Outline

- *NMR Properties of Alanine*
  - *Introduction*
  - *Key Concepts*
  - *Electric Field Gradients*
    - *Measurements*
    - *NMR Chemical Shift*
  - *NMR Shift of L-Alanine*
    - *Crystal Structure of L-Alanine*
    - *Optimization*
    - *NMR Shifts*
    - *Results*
      - *Analyze Quadrupolar Anisotropy eta*
      - *Analyze Quadrupolar Coupling Constant (C_q)*
      - *Analyze NMR Chemical Shifts*

1

NMR Properties of Paracetamol

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Electric Gradient Field is second derivative of the electrostatic potential generated by the charge distribution of the electrons and nuclei:

$$V_{ij} = \frac{\partial^2 V}{\partial x_i \partial x_j}$$

Asymmetry parameter after diagonalization of Electric Gradient Fields:

$$\eta = \frac{V_{xx} - V_{yy}}{V_{zz}}$$

$$\text{Chemical shift, } \delta = \frac{\text{frequency of signal} - \text{frequency of reference}}{\text{spectrometer frequency}} \times 10^6$$

[1] Angew Chem Int Ed Engl. 2008; 47(38): 7328–7331

NMR Properties of Paracetamol

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Asymmetry parameter after diagonalization of Electric Gradient Fields:

$$\eta = \frac{V_{xx} - V_{yy}}{V_{zz}}$$

$$\text{Chemical shift, } \delta = \frac{\text{frequency of signal} - \text{frequency of reference}}{\text{spectrometer frequency}} \times 10^6$$

Quantity	VASP	EXP[1]
$\delta_{iso}C7(ppm)$	-13.1	171.5
$\delta_{iso}C4(ppm)$	-28.8	154.1
$\delta_{iso}C7 - \delta_{iso}C4$	15.7	17.4

[1] Angew Chem Int Ed Engl. 2008; 47(38): 7328–7331

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materials design

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Calculate the cohesive energy density with *MedeA* LAMMPS and *MedeA* CED

Paracetamol Polymorphs

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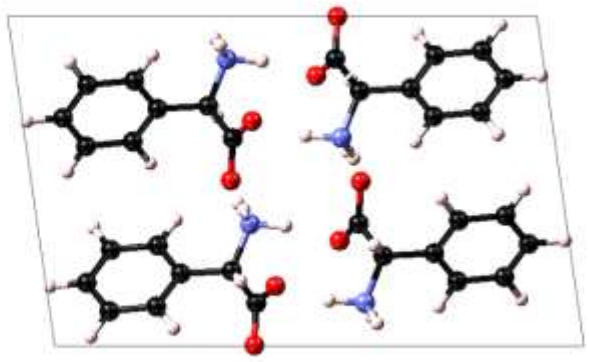
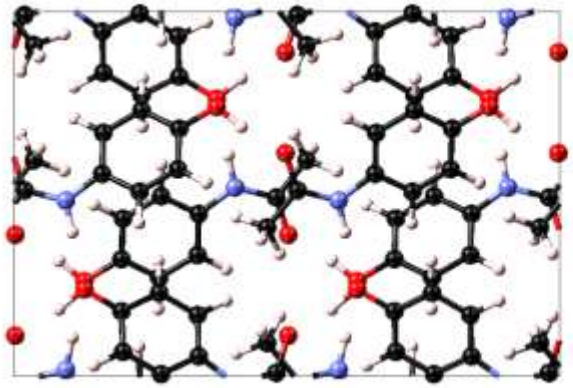
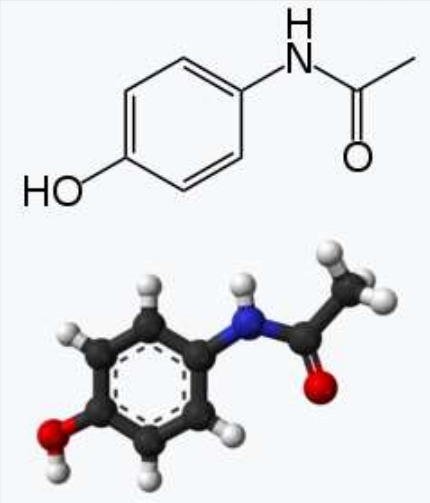
P21/c

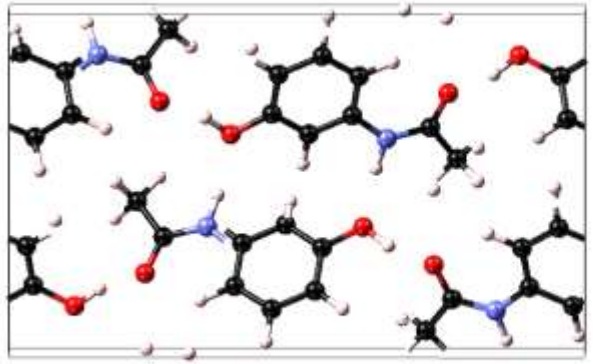


Pbca





Pna21



Gibbs Free Energy

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Thermodynamic functions:

- Cv: heat capacity
- E(T)-E(0): change in vibrational internal energy from 0 K
- S(T): vibrational entropy
- -(A(T)-E(0)): change in the vibrational Helmholtz free energy
- E(T): change in vibrational internal energy plus the ZPE
- A(T): internal energy plus vibrational Helmholtz energy
- alpha: coefficient of linear thermal expansion

Electronic contributions:

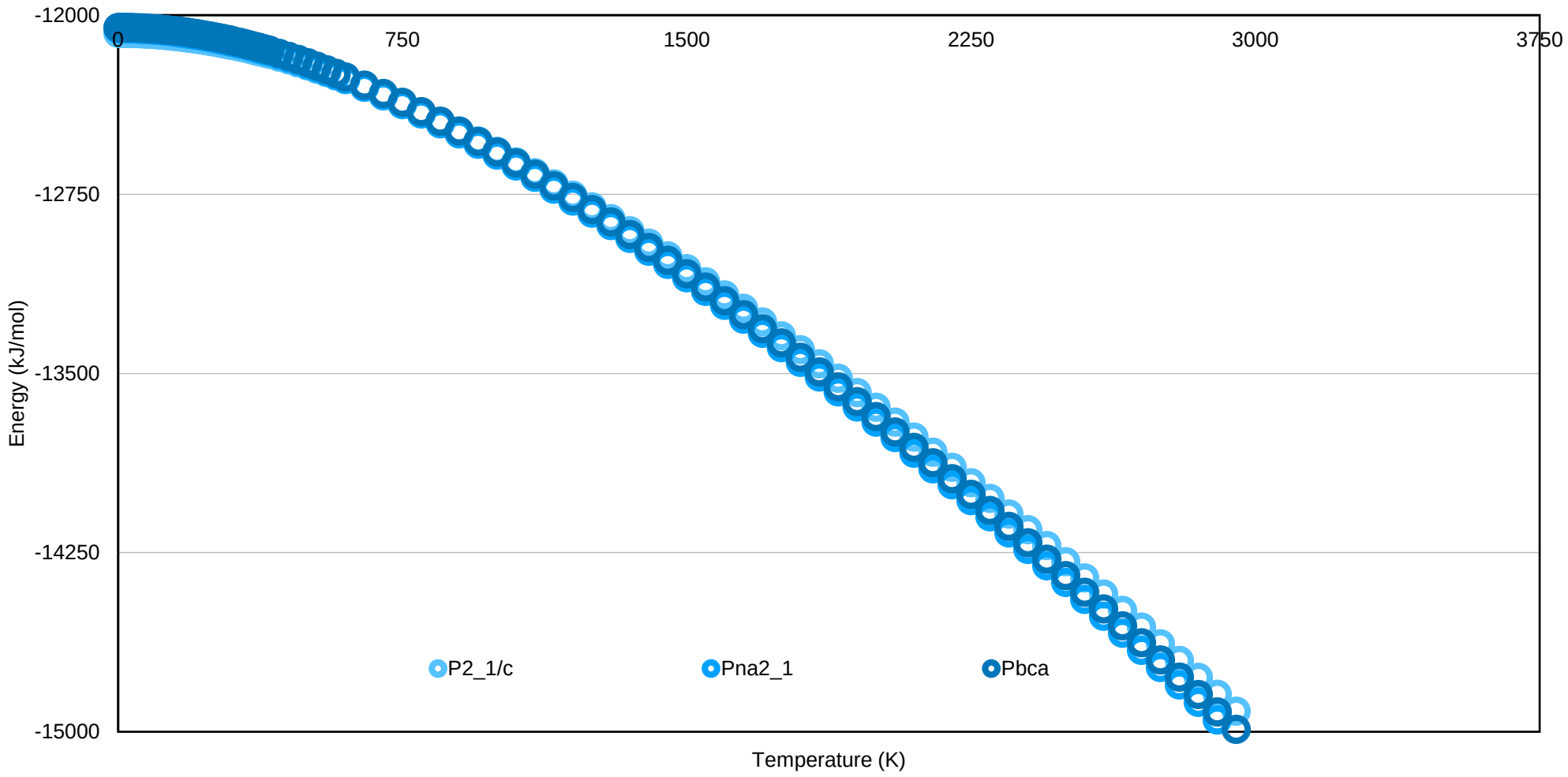
	Empirical Formula C8NO2H9	Cell (C8NO2H9)4
VASP Energy	-129.375591	-517.502362 eV
=	-12482.844	-49931.375 kJ/mol

Gibbs: G(T) = U + ZPE + PV – TS(T)
Helmholtz: F(T) = U + A(T) = G(T) - PV

Electronic energy of formation = 0.00 kJ/mol (referenced to elements in the standard state)
PV term = -0.14 kJ/mol
Zero-point energy = 7.81 kJ/mol

T K	Cv J/K/mol	E(T)-E(0) kJ/mol	S(T) J/K/mol	-(A(T)-E(0)) kJ/mol	E(T) kJ/mol	A(T) kJ/mol	alpha 10^-6/K
1	0.0001	0.0000	0.0000	0.0000	7.8061	7.8061	0.0000
2	0.0004	0.0000	0.0002	0.0000	7.8061	7.8061	0.0002
3	0.0014	0.0000	0.0008	0.0000	7.8061	7.8061	0.0005
4	0.0034	0.0000	0.0020	0.0000	7.8061	7.8061	0.0012
5	0.0067	0.0000	0.0039	0.0000	7.8062	7.8061	0.0024
10	0.0535	0.0001	0.0312	0.0002	7.8063	7.8060	0.0192
15	0.1806	0.0007	0.1053	0.0009	7.8068	7.8052	0.0648
20	0.4281	0.0021	0.2497	0.0029	7.8083	7.8033	0.1537
30	1.4422	0.0108	0.8418	0.0144	7.8170	7.7917	0.5178
40	3.3548	0.0340	1.9699	0.0448	7.8402	7.7614	1.2045
50	6.1852	0.0810	3.6940	0.1037	7.8872	7.7025	2.2206
60	9.6652	0.1599	5.9342	0.1962	7.9660	7.6100	3.4701
70	13.4234	0.2752	8.5353	0.3222	8.0814	7.4839	4.8194
80	17.1509	0.4282	11.3416	0.4791	8.2344	7.3271	6.1576
90	20.6532	0.6175	14.2314	0.6633	8.4236	7.1428	7.4150
100	23.8350	0.8402	17.1220	0.8720	8.6464	6.9342	8.5574
125	30.2835	1.5211	24.0663	1.4872	9.3272	6.3189	10.8726
150	34.8860	2.3390	30.4110	2.2227	10.1451	5.5835	12.5250
175	38.1606	3.2543	36.1390	3.0700	11.0605	4.7362	13.7007
200	40.5264	4.2395	41.3186	4.0243	12.0456	3.7819	14.5500
225	42.2715	5.2755	46.0293	5.0811	13.0817	2.7251	15.1766
250	43.5865	6.3495	50.3418	6.2360	14.1556	1.5702	15.6487
273	44.5255	7.3632	54.0084	7.3811	15.1693	0.4250	15.9858
275	44.5974	7.4523	54.3149	7.4843	15.2585	0.3219	16.0116
298	45.3321	8.4868	57.7118	8.7113	16.2929	-0.9052	16.2754
300	45.3888	8.5775	57.9966	8.8215	16.3837	-1.0153	16.2958
350	46.5274	10.8775	64.6349	11.7448	18.6836	-3.9386	16.7046
400	47.2884	13.2240	70.4929	14.9731	21.0302	-7.1670	16.9778
450	47.8204	15.6025	75.7343	18.4779	23.4087	-10.6718	17.1688
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
2800	49.8466	132.0716	162.4221	322.7102	139.8777	-314.9041	17.8963
2850	49.8486	134.5639	163.2891	330.8100	142.3701	-323.0038	17.8969
2900	49.8504	137.0564	164.1413	338.9533	144.8626	-331.1472	17.8976
2950	49.8521	139.5490	164.9792	347.1396	147.3551	-339.3335	17.8982
3000	49.8538	142.0416	165.8032	355.3681	149.8478	-347.5619	17.8988

Gibbs Free Energy



Heats of Sublimation

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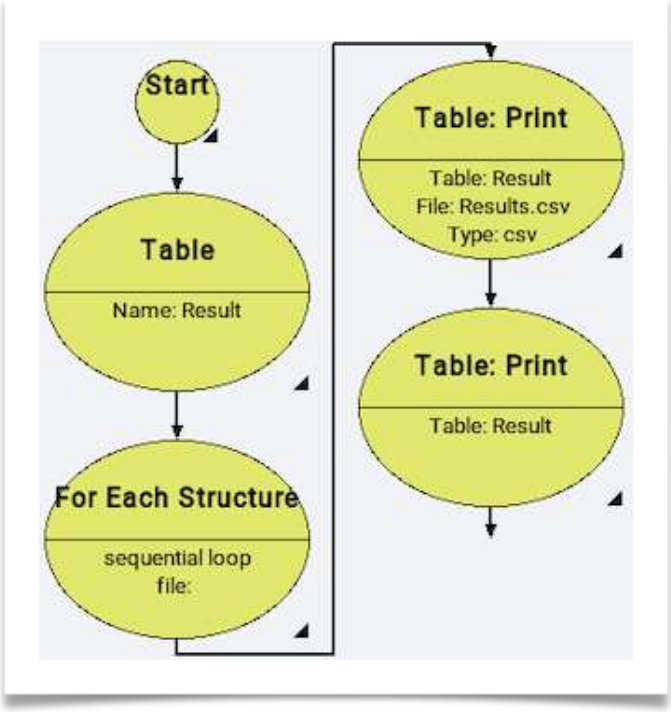
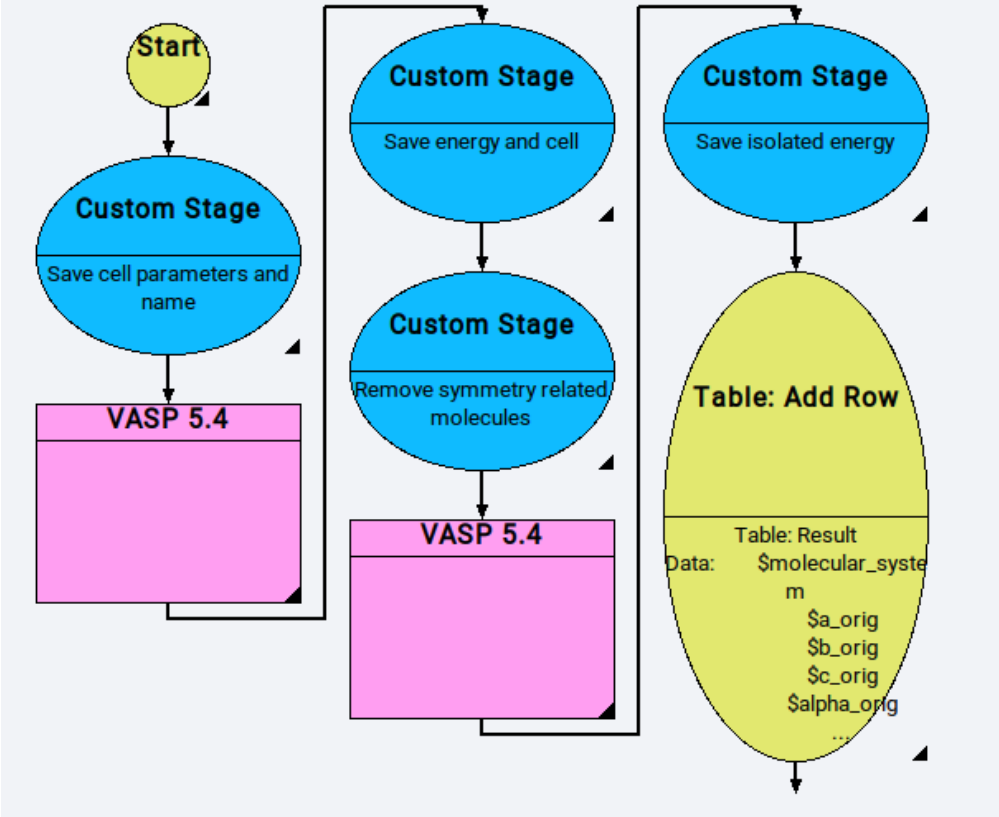
of molecular crystals:
Energy of bringing a molecule from the solid state into the gas phase

$$\Delta E_{subl} = E(\text{molecule, gas phase}) - E(\text{molecule, solid})$$

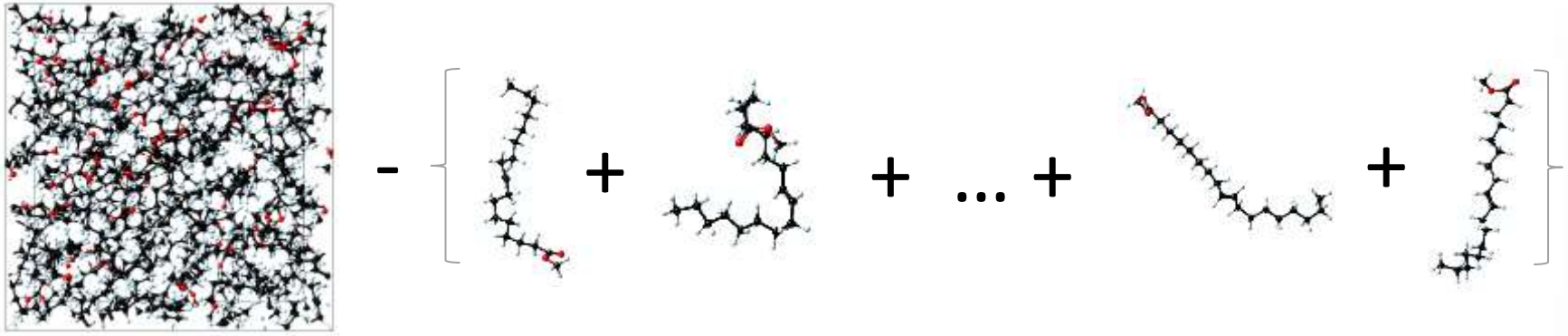
Automated with the Flowchart

- Jobs >> New Job… >> Open Library
  - `Flowcharts.kit/VASP/Calculate sublimation energies of molecular crystals.flow`





MedeA CED



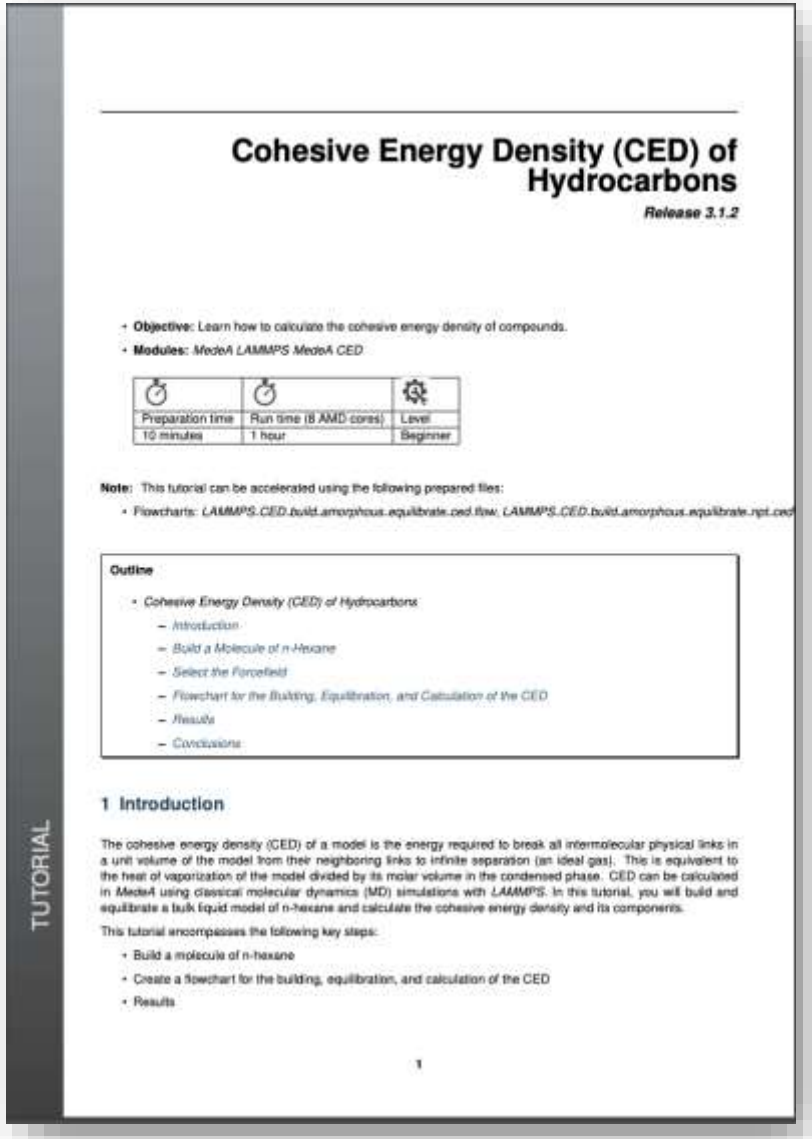
$E_{tot}(n, V_P, T)$ E_1 E_2 E_{n-1} E_n

$$CED = \frac{E_{tot}(n, V_P, T) - \sum_{i=1}^{n} E_i}{V_{molar}}$$

$E_{tot}(n, V, T)$: energy of a configuration obtained from a NVT molecular dynamic trajectory at T with V_P corresponding to a volume containing n molecules and fixed by density obtained for a pressure P

E_i : intramolecular energy of the i^{th} molecule, extracted from V as evaluated in the vacuum

V_{molar} : molar volume of liquid at T and P



TUTORIAL

Cohesive Energy Density (CED) of Hydrocarbons

Release 3.1.2

- **Objective:** Learn how to calculate the cohesive energy density of compounds.
- **Modules:** *MedeA LAMMPS MedeA CED*

Preparation time	Run time (8 AMD cores)	Level
10 minutes	1 hour	Beginner

Note: This tutorial can be accelerated using the following prepared files:

- Flowcharts: *LAMMPS.CED.build.amorphous.equilibrate.ced.flow*; *LAMMPS.CED.build.amorphous.equilibrate.npt.ced*

Outline

1 Introduction

The cohesive energy density (CED) of a model is the energy required to break all intermolecular physical links in a unit volume of the model from their neighboring links to infinite separation (an ideal gas). This is equivalent to the heat of vaporization of the model divided by its molar volume in the condensed phase. CED can be calculated in *MedeA* using classical molecular dynamics (MD) simulations with *LAMMPS*. In this tutorial, you will build and equilibrate a bulk liquid model of n-hexane and calculate the cohesive energy density and its components.

This tutorial encompasses the following key steps:

- Build a molecule of n-hexane
- Create a flowchart for the building, equilibration, and calculation of the CED
- Results

Conclusions

- *MedeA* VASP can capture lattice constants of Paracetamol very well via considering Van de Waals interaction.
- It's handy to:
  I. Utilize *MedeA* MT to calculate elastic properties.
  II. Utilize *MedeA* VASP to calculate NMR properties.
  III. Utilize *MedeA* Phonon to calculate Gibbs free energy.
  IV. Utilize flowcharts and *MedeA* CED to calculate energy of sublimation.
- *MedeA*'s high-throughput calculations enable leveraging today's unprecedented compute power

List of Resources

- Tutorials:
  - Exploring Molecular Crystal Polymorphs with MedeA (pdf, zip): Learn how to utilize MedeA® tools to calculate the structural, mechanical, Nuclear Magnetic Resonance (NMR), and thermodynamic properties of paracetamol polymorphs.
  - Introduction to MedeA VASP (pdf, zip): Learn how to set up and run VASP first principles calculations with MedeA®.
  - Phase Stability of ZrO2 (pdf, zip): Learn how to calculate the phase stability of ZrO2 phases from Gibbs free energies using MedeA Phonon.
  - NMR Properties of Alanine (pdf, zip): Learn how to calcute the Nuclear Magnetic Resonance (NMR) property of materials with MedeA VASP.
  - Introduction to MedeA MT: Elastic Properties of TaN (pdf, zip): Learn how to calculate the mechanical properties of crystals with MedeA MT and MedeA VASP.
  - Phase stability of molecular crystal polymorphs: Learn how to calculate the phase stability of paracetamol polymorphs from Gibbs free energies using MedeA Phonon.
  - Cohesive Energy Density (CED) of Hydrocarbons (pdf, zip): Learn how to calculate the cohesive energy density of compounds with MedeA LAMMPS and MedeA CED.
- Webinars:
  - https://www.materialsdesign.com/webinars/recorded/ VASP in MedeA: A Fast Way- From Models to Reliable Results
  - https://www.materialsdesign.com/webinars/recorded/ Predicting Elastic Properties Using Ab Initio and Forcefield Based Simulations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UGM Plenary Talks and Trainings

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From National Security to Energy Security: How Computational Chemistry is Defining Science at SRNL by Dr. Lindsay Roy

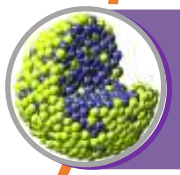
Getting to know the *MedeA* Software Environment by Dr. Taylor Juran, Dr. Marianna Yiannourakou

Interatomic Potentials - Why We Still Need Them and How Can We Improve Them by Prof. Richard Catlow FRS

MedeA LAMMPS: Robust Gateway to Molecular Dynamics by Dr. Ray Shan

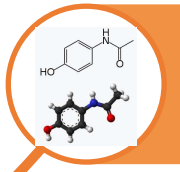
The Random Phase Approximation: A Practical Method Beyond DFT by Prof. Georg Kresse

MedeA VASP 6: Random Phase Approximation, Electron-Phonon Coupling, GW by Dr. David Reith



Modelling Catalyst Deactivation; Multiscale Modeling of Zeolite Catalysis by Prof. Rutger van Santen

MedeA Transition State Search: Calculating Energy Barriers of Chemical Reactions and Diffusion Processes with Ease by Dr. Rene Windiks



Computational Pharmaceutical Science: Guiding Experiments in a Sea of Variables by Dr. Kevin J. Gagnon

Exploring Molecular Crystal Polymorphs with *MedeA*: Applications in the Pharmaceutical Industry by Dr. Siwen Wang

https://www.materialsdesign.com/webinars

Q & A

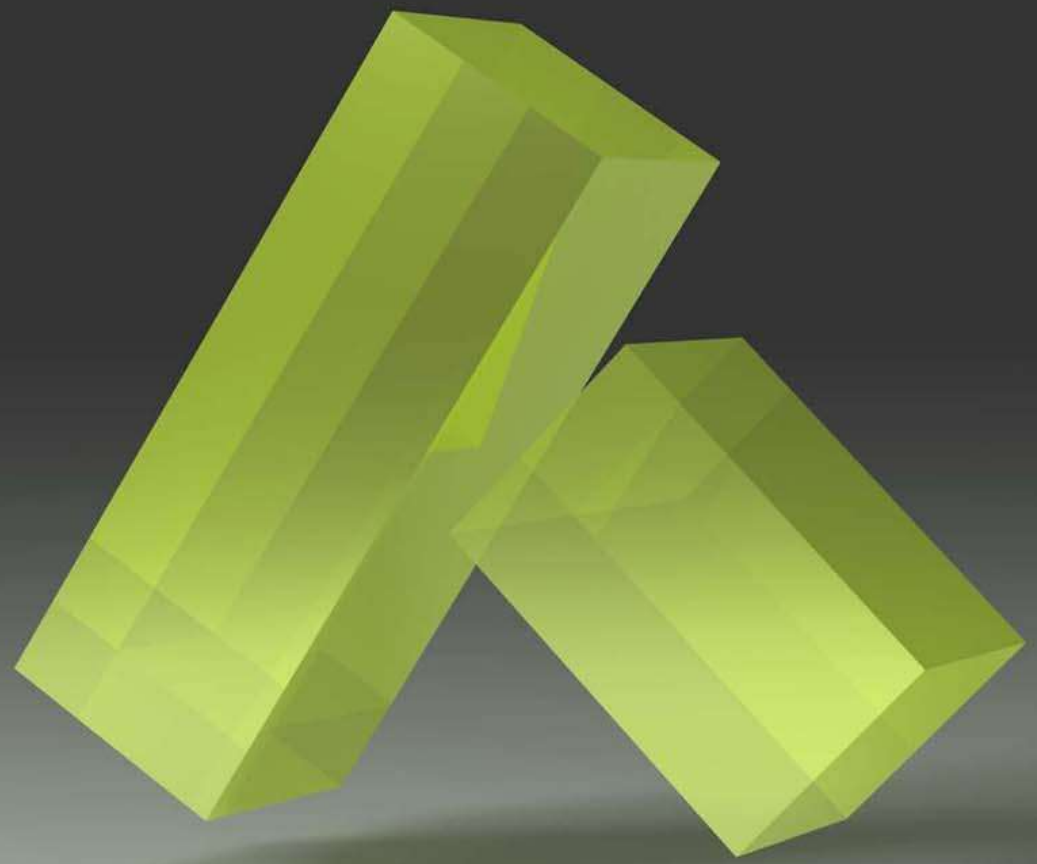
Siwen Wang
presenter

Taylor Juran
moderator

David Reith

René Windiks

Ray Shan



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Innovation by Simulation