

The Polymorphs of ROY: A Computational Study of Lattice Energies and Conformational Energy Differences*

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The remarkable structural diversity observed in polymorphs of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (commonly known as ROY) challenges computational attempts to predict or rationalize their relative stability. This modest study explores the applicability of CE-B3LYP model energy calculation of lattice energies (using experimental crystal structures), supplemented by a systematic approach to account for conformational energy differences. The CE-B3LYP model provides sensible estimates of absolute and relative lattice energies for the polymorphs, provided care is taken to achieve convergence in the summation of pairwise terms. Conformational energy differences based on density functional theory (DFT) energies are shown to be unreliable, but MP2 energies based on DFT-optimized structures show considerable promise.

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Introduction

5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (Fig. 1) exhibits one of the largest numbers of crystalline polymorphs of any molecular system. Named ROY after the red, orange, and yellow colours of three of its crystal forms, it is known to crystallize in 10 polymorphs, 7 of which have been characterized in detail by single-crystal X-ray diffraction.^[1–5] Of particular interest is the fact that the molecule has a different conformation, described by the torsion angles θ_{thio} , θ_{phen} , and θ_{nitro} (Fig. 1), in each of the seven known crystal structures. This structural diversity, both crystalline and conformational, coupled with careful experimental determination of the relative thermodynamic stability of the polymorphs,^[1,3] makes ROY an excellent – but extremely challenging – system for crystal structure prediction (CSP) of conformationally flexible molecules,^[6,7] or the computational estimation of relative polymorph stability through calculation of lattice energies.^[8,9]

We have recently demonstrated that lattice energies of molecular crystals computed with CE-B3LYP model energies^[10,11] compare very well with benchmark estimates derived from sublimation enthalpies, in many cases being comparable with the results from more computationally demanding approaches.^[12] Although the mean absolute deviation from experimentally derived lattice energies for a set of 110 molecular crystals is found to be only 6.4 kJ mol^{–1} in that work, a recent report by Nyman and Day^[13] noted that ‘polymorphic lattice energy differences are typically very small: over half of polymorph pairs are separated by less than 2 kJ mol^{–1} and lattice energy differences exceed 7.2 kJ mol^{–1} in only 5 % of cases’.

This of course suggests that CE-B3LYP lattice energies (as well as many of those from more sophisticated computational approaches) are unlikely to provide reliable estimates of relative polymorph stability. But computing lattice energy differences between polymorphs avoids some of the problems inherent in comparisons with benchmark values (e.g. the typical uncertainty in sublimation enthalpies of ~5 kJ mol^{–1}, and the need to consider geometry relaxation from crystal to gas), and we have shown elsewhere that meaningful estimates can be obtained for rigid molecules such as 1,4-diiodobenzene and 5-fluorouracil.

In a logical development of that research, we have been exploring the applicability of CE-B3LYP model energies to

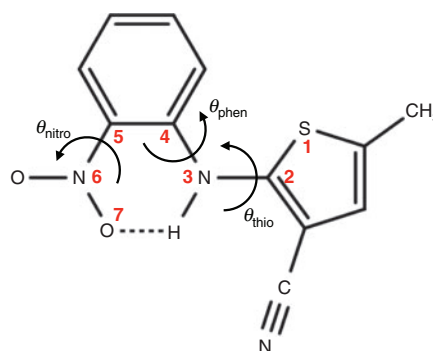


Fig. 1. Molecular structure of ROY showing the key torsion angles θ_{thio} , θ_{phen} , and θ_{nitro} . Across the seven polymorphs, θ_{thio} differs by more than 91°, θ_{phen} by 25°, and θ_{nitro} by 17°.

*Dedicated to Graham Chandler, Honours and PhD supervisor, wise mentor, wonderful colleague, and much loved and valued friend to MAS for over 40 years, on the occasion of his 80th birthday.

estimating the lattice energy differences between polymorphs of some common pharmaceutical compounds. Conformational polymorphism is common in pharmaceutical compounds, a consequence of their considerable internal flexibility,^[14] and any attempt to estimate relative polymorph stability must also incorporate the energy differences between the different conformations found in the polymorphs. The ability to provide meaningful estimates of relative polymorph stability through an approach of this kind would not only further validate the reliability of the CE-B3LYP model energies, but also the relationship between pairwise intermolecular interactions, their topology in the crystal, and bulk properties such as softness, brittleness, cleavage, and bending.^[15,16]

The objectives of the present work are therefore two-fold: (i) to establish if CE-B3LYP energies can provide reliable predictions of lattice energy differences between conformational polymorphs of drug-like molecules; and (ii) to determine an economical approach to the reliable estimation of conformational energy differences, bearing in mind the inherent limitations of (i). The seven polymorphs of ROY represent an ideal system for these studies.

Results and Discussion

Lattice Energies: Estimating the Intermolecular Energy in the Crystal

The CE-B3LYP energy model^[10,11] is based on B3LYP/6–31G(d,p) quantum mechanical charge distributions for unperturbed monomers, and can be applied with confidence to molecular crystals, metal coordination compounds, organic salts, solvates, and open-shell molecules. The total interaction energy between pairs of molecules or ions is separated into electrostatic, polarization, dispersion, and exchange–repulsion terms,

$$E_{\text{tot}} = k_{\text{ele}}E'_{\text{ele}} + k_{\text{pol}}E'_{\text{pol}} + k_{\text{dis}}E'_{\text{dis}} + k_{\text{rep}}E'_{\text{rep}} \quad (1)$$

Details on the individual terms E'_{ele} , E'_{pol} , etc. are given elsewhere,^[10,11] and optimum values of the scale factors k_{ele} , etc., in Eqn 1 have been determined by calibration against counterpoise-corrected B3LYP-D2/6–31G(d,p) interaction energies for 1794 molecule or ion pairs extracted from 171 crystal structures. The mean absolute deviation (MAD) of these CE-B3LYP model energies from the density functional theory (DFT) benchmark values is 2.4 kJ mol^{−1} for energies of molecule or ion pairs that span a range of 3.75 MJ mol^{−1}.^[11]

For the present purposes, CE-B3LYP lattice energies are estimated by direct summation of pair interaction energies over molecules B interacting with a central molecule A until E_{lat} is converged to better than 1 kJ mol^{−1}, using a summation limit based on the separation of molecular centroids, R_{AB} .

$$E_{\text{lat}} = \frac{1}{2} \sum_{R_{\text{AB}} < R} E_{\text{tot}}^{\text{AB}} \quad (2)$$

As in all of our previous work, experimental geometries are used, with bond lengths to hydrogen atoms set to standard values from neutron diffraction studies.^[17] Polarization, dispersion, and repulsion energy terms in Eqn 2 converge quite rapidly, but the electrostatic energy is much longer-range, and especially for dipolar compounds like ROY, where molecular dipole moments calculated at the experimental geometry range between 6.08 and 7.12 D, depending on θ_{thio} (Table 1). For this reason, E'_{ele} is

Table 1. Crystal structure data, principal torsion angle θ_{thio} , MP2/6–31G(d,p) dipole moment μ , and CE-B3LYP lattice energy components E for the seven ROY polymorphs

	CSD refcode ^A	θ_{thio} [°]	$ \mu $ [D]	E_{ele}	E_{pol}	E_{dis}	E_{rep}	$E_{\text{lat}}^{\text{B}}$
						[kJ mol ^{−1}]		
R	QAXMEH02	21.7	7.10	−44.9	−17.4	−139.0	81.1	−131.7
ORP	QAXMEH05	39.4	7.12	−39.9	−17.6	−132.2	70.9	−126.8
OP	QAXMEH03	46.1	7.02	−46.6	−18.6	−137.1	86.4	−129.4
ON	QAXMEH	52.6	6.94	−41.0	−16.8	−139.9	84.4	−125.7
YN	QAXMEH04	104.1	6.08	−46.5	−16.0	−136.4	83.8	−128.3
Y	QAXMEH01	104.7	6.19	−52.1	−18.6	−138.4	84.9	−137.2
YT04	QAXMEH12	112.8	6.17	−43.6	−18.0	−145.3	88.5	−131.6

^AFrom the Cambridge Structural Database (CSD).^[21] All crystal structures were determined at room temperature,^[1,3] and a convenient summary of crystal structure data for all seven polymorphs can be found in table 1 of ref. [5].

^BThe total lattice energy is the sum of scaled terms: $E_{\text{lat}} = 1.057 E_{\text{ele}} + 0.740 E_{\text{pol}} + 0.871 E_{\text{dis}} + 0.618 E_{\text{rep}}$, as described in ref. [11].

computed using a distributed multipole model of the electron density for molecules separated by more than 12 Å, which makes the calculation faster, but, as can be seen in Fig. 2, the lattice energies only approach satisfactory convergence for ROY polymorphs when the separation between molecular centroids is beyond 35 Å. (This can be understood by recognizing that the classical interaction energy for two dipoles^[18] of 7.0 D at 35-Å separation can be as much as ± 0.14 kJ mol^{−1}, depending on their relative orientation. Moreover, the number of neighbouring molecules increases dramatically with the radial distance, resulting in a considerable contribution from such small long-range electrostatic contributions.)

The identification codes for the polymorphs are indicative of the colour (and in some cases morphology) exhibited by their crystals: Y and YT04 – yellow prisms, R – red prism, OP – orange plate, ON – orange needle, YN – yellow needle, and ORP – orange-red plate.^[5] Fig. 2 shows the convergence behaviour of CE-B3LYP lattice energies for the ROY polymorphs, plotted as partial sums including pairs of molecules within a specific radius (separation of centroids). Although convergence is not smooth, reflecting the nature of the distribution of molecules in successive 1-Å shells in each of the polymorphs, the figure suggests that the confidence interval for the final values (Table 1) is better than 0.5 kJ mol^{−1}, and probably as small as 0.2 kJ mol^{−1}. Fig. 2 makes it clear that Y has by far the lowest CE-B3LYP lattice energy, and the ranking of ON, ORP, YN, and OP (in terms of lattice energy) is well defined, but also that R and YT04 have almost identical lattice energies. Table 1 provides a breakdown of the lattice energies into separate sums reflecting the terms in Eqn 1, and it is notable that the present electrostatic energies are almost identical to those obtained with Gavezzotti's PIXEL approach.^[8] As observed by those authors, the greater stability of Y appears to be largely due to the electrostatic energy sum, but this cannot be attributed to any specific intermolecular interactions (or syn-thons). We can see this by examining the partial sums of electrostatic energies for a cut-off radius of 12 Å (which includes the closest 20 to 30 molecule pairs). These differ from the converged values by less than 3 kJ mol^{−1} for all polymorphs except Y, for which the 12-Å partial sum is almost 12 kJ mol^{−1} from the converged result. Clearly, long-range electrostatic interactions are unusually important for the Y polymorph.

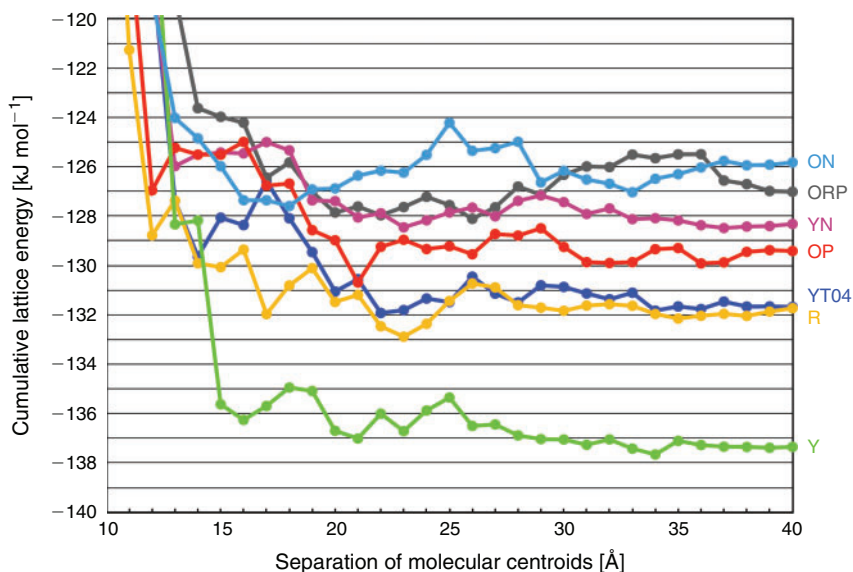


Fig. 2. Convergence of CE-B3LYP lattice energies for ROY polymorphs. The lattice energy is plotted as a partial sum against the largest separation between molecular centroids involved in that sum (at 1-Å intervals), and the horizontal lines are 1 kJ mol⁻¹ apart.

Conformational Energies: Estimating the Difference in Intramolecular Energies

A systematic approach to combine estimates of conformational energy differences for flexible molecules like ROY with CE-B3LYP lattice energy sums must recognize the inherent limitations of the CE-B3LYP model energies used to obtain the lattice energies. As our goal is to introduce the correction term associated with the conformational differences between polymorphs, moderate-sized basis sets are used for these calculations. To pursue this objective, we explored four approaches to computing energies for the different molecular geometries observed in the ROY polymorphs, presented and discussed in order of increasing computational demands:

- Experimental heavy-atom geometries with X–H bonds set to standard neutron distances.^[17] This is the simplest approach, and uses the same molecular geometries that were used for the lattice energy calculation, but, as noted by Chen et al.^[3] ‘residual errors in crystallographic determination of atomic coordinates can cause anomalously high single-point energies’. MP2 single-point calculations were explored with this approach, and the relative energies are summarized in Table 2. MP2/6–31G(d,p) energies predict R to have the lowest energy conformation, and ORP the highest (26.0 kJ mol⁻¹ higher than R). Use of a more flexible basis set does not significantly change this prediction of unreasonably large conformational energy differences.
- Experimental heavy-atom geometries with H atom positions optimized. This is more demanding than A, but corrects for any errors in assigning H atom positions, especially for hydrogen bonds. MP2/6–31G(d,p) optimizations were performed, but relaxation of H atom positions still results in a conformational energy difference of 13.3 kJ mol⁻¹ between the seven polymorphs (Table 2).
- Molecular geometries optimized with torsion angle θ_{thio} frozen at experimental values. Other workers have performed geometry optimizations fixing two or all three torsion angles (Fig. 1), but here, we decided to fix only

Table 2. Computed relative conformational energies (kJ mol⁻¹) for molecules of ROY in each of the seven polymorphs

Energies are relative to the lowest energy conformer in each row, indicated by **0.0** in bold

Method	Y	YT04	R	OP	ON	YN	ORP
A: Normalized bonds to H atoms							
MP2/6–31G(d,p)	3.9	0.7	0.0	6.4	4.9	11.3	26.0
MP2/6–31+G(2df,p)	3.4	0.0	2.7	7.7	6.7	10.0	26.7
B: Optimized H atom positions							
MP2/6–31G(d,p)	4.5	0.4	0.0	4.3	4.1	8.2	13.3
C: Optimization with θ_{thio} fixed							
B3LYP/6–31G(d,p)	2.6	2.0	0.6	0.2	0.6	2.7	0.0
B3LYP-D3BJ/6–31G(d,p)	1.5	0.5	0.2	0.4	0.9	1.6	0.0
B97-D/cc-pVTZ	1.3	0.0	0.8	0.4	0.7	1.5	0.1
MP2/6–31G(d,p)	0.3	0.0	3.6	1.9	1.9	0.3	2.2
D: MP2/6–31G(d,p) energies at optimized geometries from C							
//B3LYP/6–31G(d,p)	0.4	0.0	3.7	1.5	1.3	0.4	1.7
//B3LYP-D3BJ/6–31G(d,p)	0.4	0.0	4.5	2.2	2.1	0.4	2.5
//B97-D/cc-pVTZ	0.3	0.0	4.1	2.3	2.0	0.4	2.4
‘Best estimate’ ^A	0.4	0.0	4.0	2.0	1.8	0.4	2.2
s.d. of ‘best estimate’ ^A	0.0	0.0	0.4	0.4	0.4	0.1	0.3

^AMD and s.d. of MP2/6–31G(d,p) energies from the last four rows of the table.

θ_{thio} as it varies over the greatest range, and to see how much the optimized geometries, in particular θ_{phen} and θ_{nitro} , differed from those observed experimentally. Geometry optimizations were undertaken with three different DFT approaches (B3LYP, B3LYP-D3BJ, and B97-D) as well as MP2. All four computational methodologies predict much smaller energy differences than A or B above (less than 4 kJ mol⁻¹), but importantly, there is no consensus in the ranking of the seven geometries. To explore this further, Table 3 summarizes differences between experimental

Table 3. Differences between experimental torsion angles θ_{phen} and θ_{nitro} and those obtained in geometry optimizations with torsion angle θ_{thio} fixed at experimental values

All angles are in degrees, and their signs are defined by the sequence of numbered atoms in Fig. 1: $\theta_{\text{thio}}(\text{S}_1\text{--C}_2\text{--N}_3\text{--C}_4)$, $\theta_{\text{phen}}(\text{C}_2\text{--N}_3\text{--C}_4\text{--C}_5)$, and $\theta_{\text{nitro}}(\text{C}_4\text{--C}_5\text{--N}_6\text{--O}_7)$

	B3LYP ^A		B3LYP-D3BJ ^A	B97-D ^B	MP2 ^A
	$\theta_{\text{phen,exp}}$		$\Delta\theta_{\text{phen}} = \theta_{\text{phen,opt}} - \theta_{\text{phen,exp}}$		
R	−150.0	−11.5	−11.4	−8.9	5.2
ORP	−174.4	8.0	7.5	10.1	21.4
OP	−167.3	−1.8	−2.4	−1.4	10.6
ON	173.3	−2.2	−1.4	−2.4	−12.5
YN	−175.2	−1.9	−1.4	0.8	−3.3
Y	175.0	2.0	1.8	−0.2	3.9
YT04	169.7	10.6	10.1	12.0	6.7
MD ± s.d. ^C	2.1 ± 7.3		2.3 ± 7.1	2.6 ± 7.3	−1.3 ± 10.6
	$\theta_{\text{nitro,exp}}$		$\Delta\theta_{\text{nitro}} = \theta_{\text{nitro,opt}} - \theta_{\text{nitro,exp}}$		
R	−18.3	10.0	9.9	6.1	−3.9
ORP	−3.6	−4.0	−4.0	−7.8	−16.1
OP	−18.7	11.8	11.7	8.3	−0.3
ON	4.5	2.0	2.1	5.6	14.0
YN	−3.6	6.0	6.3	8.2	17.8
Y	1.7	−4.3	−4.6	−6.8	−15.9
YT04	14.7	−10.7	−10.4	−8.2	0.3
MD ± s.d. ^C	−1.8 ± 8.3		−1.7 ± 8.2	−0.3 ± 7.9	4.1 ± 13.2

^A6–31G(d,p) basis set.

^Bcc-pVTZ basis set.

^CMean deviation (MD) and standard deviation from the mean (s.d.).

values of θ_{phen} and θ_{nitro} and those obtained by geometry optimization. These results show that all three DFT approaches predict similar geometries, with strikingly similar patterns of differences for θ_{phen} and θ_{nitro} . MP2-optimized geometries show overall a greater range of deviations from the experimental torsion angles. Interestingly, all levels of theory predict θ_{nitro} to be quite different from zero, which means the experimentally observed non-planarity of the nitro group and the phenyl ring is not solely due to intermolecular interactions. We conclude from these results that DFT approaches appear to provide reliable and useful molecular geometries, but unreliable conformational energy differences.

- (D) Single-point MP2/6–31G(d,p) energies computed at the optimized geometries from C. These MP2 energies (i.e. the last four rows in Table 2) are remarkably consistent. They all predict YT04 to have the lowest energy; Y and YN to be very close and just above YT04; OP, ON, and ORP to be close together; and R by far the highest, with the range of energies consistently within 3 to 4 kJ mol^{−1}. Based on this consistency, we derived a ‘best estimate’ for the ranking of conformational energies by simply averaging the results for these sets of MP2 energies obtained from four different geometry optimizations. The standard deviations from these mean values suggest that the interpretation of differences in polymorph stability incorporating CE-B3LYP lattice energies and these conformational energy differences is limited to 0.5 kJ mol^{−1} at best.

The results from strategies C and D above led us to question the potential energy curve for ROY reported by Cruz-Cabeza

and Bernstein,^[14] which was based on DFT energies obtained with the same B97-D/cc-pVTZ optimization strategy pursued in C. The potential curve in fig. 4 of that work shows two local minima separated by a barrier of ~6 kJ mol^{−1}, one at $\theta_{\text{thio}} \sim 40^\circ$ and another 2 kJ mol^{−1} lower at $\theta_{\text{thio}} \sim 140^\circ$. It predicts Y, YN, and YT04 to lie well above (between 2 and 4 kJ mol^{−1}) the global minimum of that curve, which seemed to us rather puzzling as this means there are no known polymorphs with conformations near the global minimum. To explore this point further, we performed scans of the θ_{thio} potential surface for ROY at 10° intervals, with full MP2/6–31G(d,p) and B3LYP/6–31G(d,p) optimizations at each frozen torsion angle. Fig. 3 shows the resulting potential energy curves, as well as one obtained using MP2/6–31G(d,p) energies computed at the B3LYP/6–31G(d,p) optimized geometries. The results reinforce the conclusions above that the DFT energies are likely to be unreliable for estimating conformational energies. The B3LYP curve predicts a minimum at $\theta_{\text{thio}} \sim 40^\circ$ and another ~1.5 kJ mol^{−1} higher at $\theta_{\text{thio}} \sim 130^\circ$. However, both curves based on MP2 energies show the opposite result, with the global minimum at $\theta_{\text{thio}} \sim 120^\circ$ and a higher and shallower minimum at $\theta_{\text{thio}} \sim 50^\circ$. These curves also show that the conformations observed in the two most stable polymorphs, Y and YT04, lie very close in energy to the global minimum at this level of theory.

Combining CE-B3LYP Lattice Energies with Conformational Energy Differences

Table 4 compares the final estimates of relative stability of the ROY polymorphs with previous computational results, and with the experimentally determined enthalpy differences. Our combined results show Y to be the most stable polymorph, YT04 next but ~5 kJ mol^{−1} higher, with R, YN, and OP within 0.5 kJ mol^{−1} of one another, and ON and ORP the least stable and separated by ~0.5 kJ mol^{−1}. The difference between Y and ON is ~13 kJ mol^{−1}. Although there is agreement with experiment that Y is lowest, followed by YT04, and ORP one of the highest in energy, this differs from experiment in that the overall range observed is only ~4 kJ mol^{−1}. However, the present estimates are somewhat better than those provided in the CSP study by Vasileiadis et al.,^[6] where YN is estimated to be the most stable, followed by Y and YT04 ~R, and ON the least stable. The predicted lattice energies span a range of 10.3 kJ mol^{−1}. This CSP study on ROY was revisited by Habgood et al.^[7] using an improved global search algorithm, and the best lattice energy predictions from that study (labelled ‘CrystalOptimizer’ in table 2 of that work) are also given in Table 4. Although the range of lattice energies is much reduced (and at 3.3 kJ mol^{−1} smaller than that observed experimentally), agreement with the observed ranking is still poor. The polymorph ranking of Li et al.,^[9] who used optimized crystal structures from a periodic B3LYP/6–31G(d,p) approach ‘empirically augmented’ to account for dispersion, has ORP the most stable and YT04 the least stable, in substantial disagreement with experiment. Finally, the PIXEL-based predictions by Dunitz and Gavezzotti^[8] (whose study preceded the crystal structure report for YT04) are in some respects similar to the present ones, with Y lowest and ORP the highest, but with a much greater range of 22 kJ mol^{−1}. This difference is not only much greater than the experimental enthalpy differences, but, as noted by Yu,^[5] the enthalpy of the liquid is only 18 kJ mol^{−1} above that of the Y polymorph.

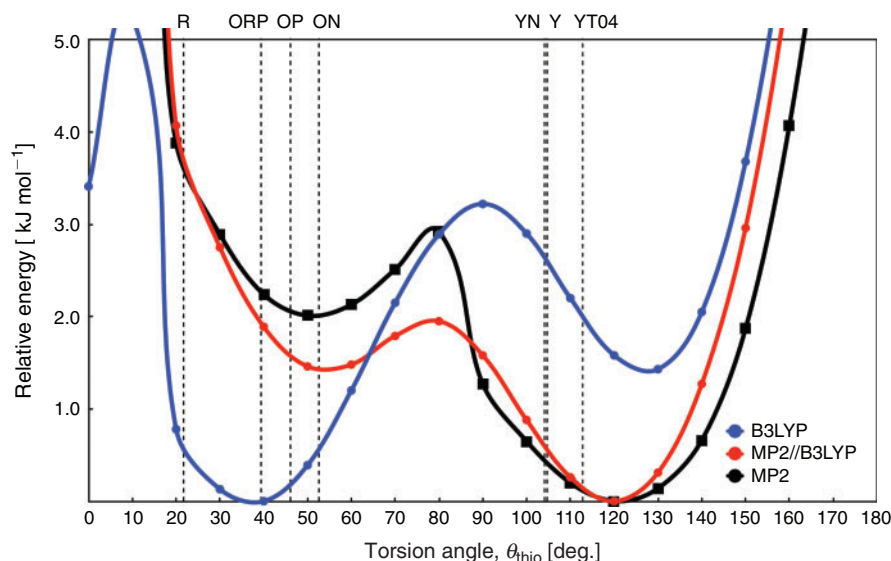


Fig. 3. Potential curves for ROY as a function of the torsion angle θ_{thio} . B3LYP (blue) and MP2 (black) curves were obtained by full optimization at each 10° interval with fixed θ_{thio} , using the 6–31G(d,p) basis set. The red curve is based on MP2 energies computed at the B3LYP optimized geometries. Vertical dashed lines indicate θ_{thio} values for the seven ROY conformations observed experimentally.

Table 4. Computed relative stabilities (kJ mol^{-1}) for the seven polymorphs of ROY

All energies are given relative to Y, the lowest-energy conformer from experiment, and the row order follows the experimental ranking of stability

Method	Y	YT04	R	OP	ON	YN	ORP
Dunitz and Gavezzotti ^[8]	0	–	7	16	8	18	22
E_{latt} from Li et al. ^[9]	0.0	9.5	2.7	3.6	–4.1	7.8	–7.7
E_{cryst} from Li et al. ^[9]	0.0	8.5	3.4	10.1	3.6	7.2	5.2
Vasileiadis et al. ^[6]	0.0	2.3	2.1	3.3	9.3	–1.0	7.6
Habgood et al. ^[7]	0.0	2.4	–0.9	0.6	2.1	–0.6	2.0
Present work ^A	0.0	5.2	9.1	9.4	12.9	8.9	12.2
Experimental enthalpies ^[1,3,4]	0.0	0.9	1.4	1.9	2.6	3.0	4.1

^ACE-B3LYP lattice energies corrected for conformational energy differences.

Conclusion

This fairly modest study on a challenging polymorphic crystal system was undertaken as a proof-of-concept – an attempt to determine the quality of predictions that could be made with a model energy calculation of lattice energies (using experimental crystal structures) augmented with a reliable and systematic approach to account for conformational energy differences. The present CE-B3LYP model seems capable of providing sensible estimates of absolute and relative lattice energies for polymorphs, provided care is taken to achieve convergence of the summation of pairwise terms. For estimating conformational energy differences, DFT energies have been shown to be unreliable, but MP2 energies based on DFT-optimized structures show considerable promise, and we will explore this economical combined approach in our future work on polymorphism of pharmaceutical compounds.

The present study is perhaps the first on ROY to examine the performance of DFT versus MP2 energies for determining energy differences between conformers. Although far from a comprehensive analysis, our conclusion that DFT energy

differences are unreliable for this purpose, with MP2 energies more consistent and preferable (even based on DFT geometries), has potentially far-reaching implications for CSP studies of conformationally flexible molecules. The two CSP studies on ROY by Vasileiadis et al.^[6] and Habgood et al.^[7] estimated conformational energy differences at the B3LYP/6–31G(d,p) level. The difference between MP2/6–31G(d,p) and B3LYP/6–31G(d,p) conformational energies can be as much as 3 kJ mol^{-1} (Table 2 and Fig. 3), and correcting for these differences radically alters (and significantly improves) the predicted rankings compared with experiment.

It is of course important to recognize that the present computational approach, in common with all previous ones, yields energy differences relevant to 0 K. As such, these differences reflect only part of the enthalpy differences measured experimentally; they are missing the important vibrational energy term, which includes both zero point and thermal contributions. The careful study by Nyman and Day^[13] showed that the difference in vibrational energies between polymorphic pairs is typically of the order of 1 kJ mol^{-1} , and greater than 2 kJ mol^{-1} in less than 6 % of pairs they studied. Although these vibrational energy differences are small, Nyman and Day concluded that lattice and vibrational energy differences ‘are of opposite sign in the majority of cases; vibrational contributions in general decrease the energy difference between polymorphs’.

The present study and the comparisons with previous computational and experimental results certainly underscore the comment made by Yu^[5] in his 2010 review that studies like this demonstrate ‘the difficulty of calculating small energy differences between polymorphs and the importance of experimental data for testing computational methods’. Although they do not alter his important conclusion at that time that ‘there is no satisfactory agreement between experiment and theory and between the various computational methods’, we believe that the approach outlined in the present study gives reason for optimism. There can be little doubt that what we set out to achieve here was quite ambitious, but given the approximations

and levels of theory involved, we could hardly expect a better outcome than that we obtained. Estimating the relative stabilities of polymorphs exhibited by molecular crystals will continue to be a challenge for computational chemists and experimentalists alike.

Computational Methods

Lattice energy calculations employed the CE-B3LYP model intermolecular interaction energies incorporated in *CrystalExplorer17*,^[19] and DFT and *ab initio* calculations were carried out with the *Gaussian 09* program suite.^[20]

Conflicts of Interest

The authors declare no conflicts of interest.

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