

SUPPLEMENTARY DATA

DEFINING THE UNIQUE CRYSTAL CONFORMATIONS

As Figure 16 illustrates there are many possible combinations of Torsions 1-4, as such a series of descriptors were drawn up to aid with the identification of unique loratadine conformations in the crystal structures. Using a letter to identify each torsion four characters resulted: starting with Form I (conformer 1) as the baseline, each torsion exhibited in Form I was defaulted to AAAA and the order was decided by sequentially going from the top of the molecule down (head, body, tail); Torsions 1-4, resulting in 11 accessible unique conformations of loratadine.

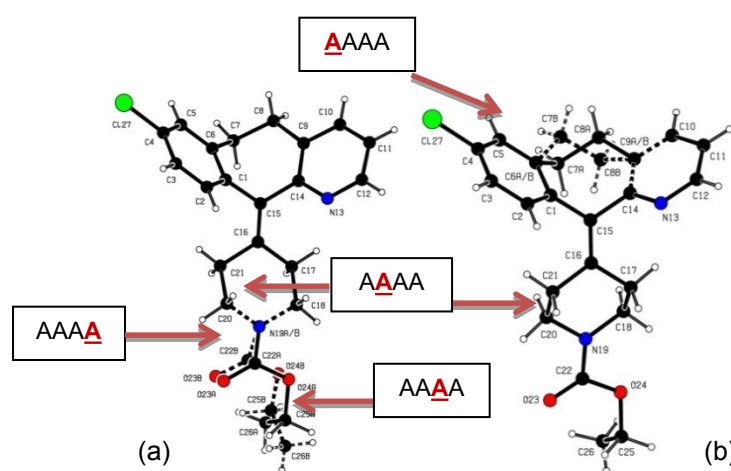


Figure 16. Illustration of how the descriptors were defined: (a) Form I (b) Form II; asymmetric units

Figure 16(a) shows Form I conformer 1 (AAAA) in bold lines and conformer 2 (AABA) with the hashed lines, as the difference between conformer 1 and 2 involves a rotation around Torsion 3 the third letter of the descriptor changed. Figure 16(b) shows Form II conformer 1 (ABAA) in bold lines and conformer 2 (BBAA) with the hashed lines, as the difference between conformer 1 and 2 involves a ring flip on Torsion 1 the first letter of the descriptor changed. To further illustrate how the unique descriptors were attributed and to provide a visual representation with the dihedral angles, six examples are provided in Figure 17(a-f) and Figure 18(a-f) where the molecular diagrams are placed face on and side on respectively.

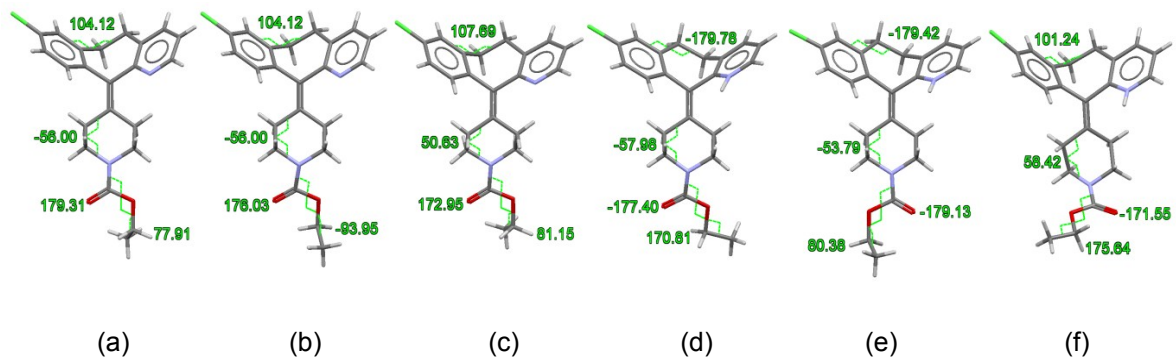


Figure 17. Face on where a-f are AAAA; AABA; ABAA; BACA; BABB; ACDB respectively

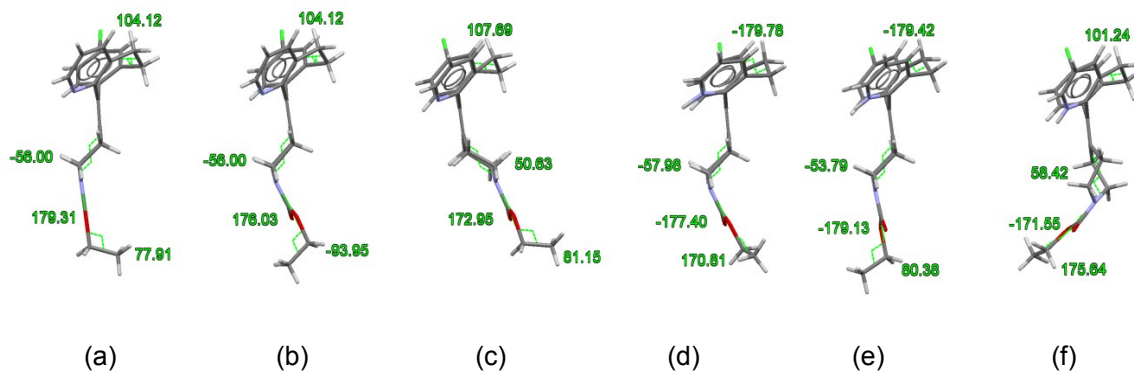


Figure 18. Side on where a-f are AAAA; AABA; ABAA; BACA; BABB; ACDB respectively

Table 6. 62 Energy ranked structures of loratadine with relative energy, Z', space group, unique conformer identifier and notable comment

Energy ranked structure	Rel. energy [kcal/mol]	Z'	Space group	Descriptor	Descriptor	Comment
1	0.000	1	C2/c	ABAA		Form II conformer 1
2	0.279	2	P2 ₁ /c	ABAA	ABAA	
3	0.293	1	C2/c	ABAA		
4	0.293	2	P-1	ABAA	ABAA	
5	0.348	2	P-1	AAAA	AABA	Form I: both conformers 1&2
6	0.433	2	P2 ₁ /c	AAAA	AABA	Form I: both conformers 1&2
7	0.449	2	P2 ₁ /c	AAAA	AABA	Form I: both conformers 1&2
8	0.467	2	Cc	AAAA	AABA	Form I: both conformers 1&2
9	0.480	1	C2/c	ABAA		
10	0.588	2	C2/c	ABAA	ABAA	
11	0.610	1	C2/c	AAAA		Form I conformer 1
12	0.612	2	P-1	ABAA	BBAA	Form II: both conformers 1&2
13	0.623	1	P2 ₁ /c	BABB		C=O flip to right
14	0.657	1	C2/c	AACA		
15	0.660	2	P2 ₁ /c	ABAA	BBAA	
16	0.707	2	P-1	AAAA	ABAA	Form I & Form II conformers
17	0.708	2	P2 ₁ /c	AABA	ABAA	Form I & Form II conformers
18	0.712	2	C2/c	ABAA	ABAA	
19	0.719	2	P2 ₁ /c	ABAA	ABAA	
20	0.757	1	P2 ₁ /c	ABAA		
21	0.769	2	P-1	AABA	ABAA	Form I & Form II conformers
22	0.790	2	P2 ₁ /c	AABA	AACA	
23	0.797	2	P-1	AAAA	AACA	

Energy ranked structure	Rel. energy [kcal/mol]	Z'	Space group	Descriptor	Descriptor	Comment
24	0.800	2	C2/c	AAAA	AAAA	
25	0.814	2	Cc	AACA	ABAA	Form I & II like conformers
26	0.818	2	P-1	AABA	AACA	
27	0.828	2	P-1	AAAA	AABA	Form I: both conformers 1&2
28	0.842	1	P-1	BACA		
29	0.845	2	C2/c	AACA	BACA	
30	0.848	2	P-1	AAAA	AABA	Form I: both conformers 1&2
31	0.859	2	P2 ₁ /c	AACA	ABAA	Form I & II like conformers
32	0.861	2	C2/c	AACA	AACA	
33	0.877	1	P-1	AACA		
34	0.877	2	C2/c	ABAA	BACA	Form I & II like conformers
35	0.880	2	P2 ₁ /c	AABA	AACA	
36	0.890	2	P-1	AACA	ABAA	Form I & II like conformers
37	0.891	2	C2/c	AABA	AACA	
38	0.895	2	P-1	AAAA	AABA	Form I: both conformers 1&2
39	0.896	2	Cc	AABA	ABAA	Form I & Form II conformers
40	0.902	2	P-1	AAAA	AABA	Form I: both conformers 1&2
41	0.909	2	Cc	AABA	AACA	
42	0.913	2	P2 ₁ /c	AABA	ABAA	Form I & Form II conformers
43	0.926	1	P2 ₁ /c	ABAA		
44	0.966	1	P2 ₁	ABDB		C=O flip to right
45	0.976	1	C2/c	AABA		Form I conformer 2
46	0.988	2	P2 ₁ /c	AAAA	ABAA	Form I & Form II conformers
47	0.997	1	P-1	ABAA		
48	0.998	2	P-1	AAAA	AACA	

Energy ranked structure	Rel. energy [kcal/mol]	Z'	Space group	Descriptor	Descriptor	Comment
49	1.003	2	P2 ₁ /c	AACA	AACA	
50	1.011	1	P2 ₁ /c	BADB		C=O flip to right
51	1.014	1	P2 ₁ /c	AAAA		
52	1.018	2	P-1	AAAA	AACA	
53	1.037	1	P2 ₁ /c	ABAB		C=O flip to right
54	1.041	2	P-1	AAAA	AACA	
55	1.103	1	C2	ABAA		
56	1.172	1	P-1	BABA		
57	1.192	1	P2 ₁ /c	AACA		
58	1.230	1	C2/c	BBAA		Form II conformer 2
59	1.240	1	Pbcn	BBAA		
60	1.267	1	P2 ₁ 2 ₁ 2 ₁	ABDB		C=O flip to right
61	1.280	1	P2 ₁ /c	AABA		
62	1.284	1	P2 ₁ 2 ₁ 2 ₁	ABDB		C=O flip to right

There are 38 Z' = 2 structures within the top 62 energy ranked structures, giving rise to 100 conformers of loratadine which were assessed and processed in Table 6. The occurrences of individual conformers are enumerated in Table 7.

Table 7. Summary of the individual conformers from the 62 energy ranked structures

AAAA	18
AABA	19
AACA	20
ABAA	29
ABAB	1
ABDB	3
BABA	1
BABB	1
BACA	3
BADB	1
BBAA	4

Form I conformers 1 and 2 were found 18 and 19 times respectively. Of those 18 times conformer 1 (AAAA) coincided with a second conformer 1 within a $Z' = 2$ structure just once (i.e. AAAA & AAAA). Whereas eight out of the 38 $Z' = 2$ structures contain both Form I conformer 1 and 2 (AAAA & AABA) suggesting that the low energy structures containing both conformers 1 and 2 result in a thermodynamically stable product, owing to the number of times they were generated *ab initio*. Additionally all of the AAAA & AABA structures are within 0.90 kcal/mol of the lowest energy structure.

Conversely Form II conformer 1 and 2 appear together in a $Z' = 2$ structure just once (ABAA & BBAA) in rank 12, highlighting that the structure is stable at only 0.61 kcal/mol higher in energy than rank 1, however, not as significant as the Form I AAAA & AABA configuration.

Of the 100 conformers 90 have Torsion 1 at $\sim 104^\circ$ (C7 in the back orientation (conformer 1)). 63 have Torsion 2 at $\sim -56^\circ$ (Form I-like piperidine orientation) and 37 have Torsion 2 at $\sim -51^\circ$ (Form II-like piperidine orientation), there are just two defined chair orientations of the piperidine ring and two defined twisted boat positions of the cycloheptane ring.

Torsion 3 is found to be $\sim 90^\circ$ 52 times (conformer 1; with the carbamate tail backwards), $\sim -90^\circ$ 21 times (conformer 2; forwards), $\sim 166^\circ$ 23 times (conformer 3; facing right) and $\sim -167^\circ$ 4 times (conformer 4; facing left). In each of those latter four times and in two further instances Torsion 4 is found at $\sim 175^\circ$ (conformer 2; with the carbonyl facing right), the remaining 94 times the carbonyl faces left with Torsion 4 $\pm 180^\circ$ (conformer 1).

The CSD search of Torsion 3 described the prevalence of the $\pm 180^\circ$ orientation, yet it is the specific packing environment of loratadine that gives rise to the number of times that Torsion 3 is found as conformer 1 or 2 (73/100).

FORM II SYMMETRY-ADAPTED ENSEMBLE THEORY DERIVED DATA

Form II is not a thermodynamic equilibrium property. The energy values provided in Table 8 show that the energetic cost of a transition is 2.5 ± 0.5 kcal/mol regardless of the actual configuration. Accordingly, the symmetry-adapted ensemble approach yield an occupancy of the rank 58 configuration of 0.029 that is in good agreement with the value of 0.031 obtained from the isolated-site model. The rank 58 configuration is not favoured by a collective effect in the 121 supercell used here.

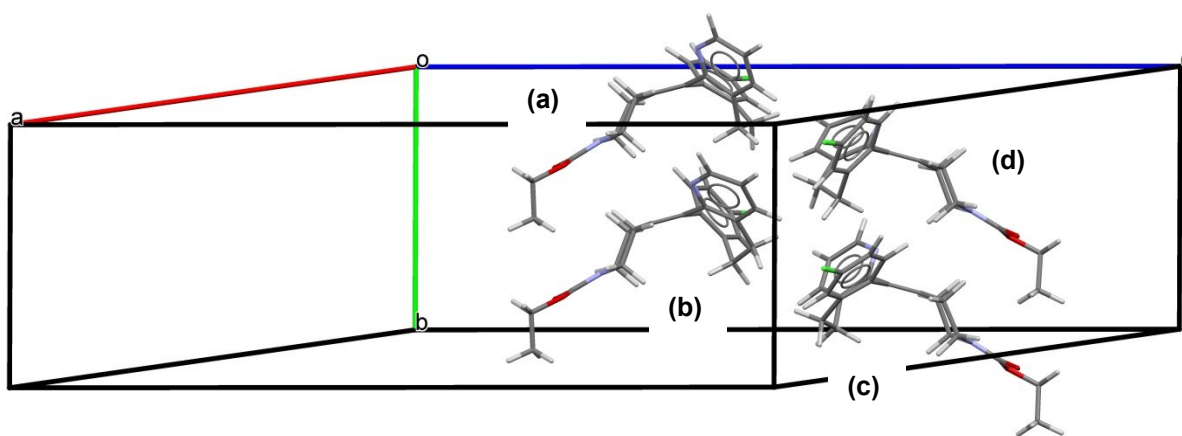


Figure 19. 1D rod of interacting molecules in 1x2x1 supercell of Form II. Molecules not belonging to the rod have been omitted for clarity

Table 8. Form II supercell models with energies

Sites with rank 58 configuration	Multiplicity	Number of sites with rank 58 configuration	Rel energy [kcal/mol]
-	1	0	0
a	4	1	2.0
ab	2	2	6.18
ac	2	2	4.708
ad	2	2	4.5
abc	4	3	7.044
abcd	1	4	10.088

OCCUPATION OF LORATADINE CONFORMER 1 : 2 AS A FUNCTION OF SCXRD COLLECTION TEMPERATURE

In order to determine if the variation of occupancy with temperature was significant an independent refinement was performed by Richard I. Cooper (University of Oxford) using CRYSTALS. The number of parameters and restraints were kept the same at all temperatures in order to enable meaningful comparisons of the results. Hydrogen atom positions were refined using a riding model.

All occupancies were found to be equivalent whether refined by T.W. or R.I.C. using SHELXTL or CRYSTALS respectively within three times the estimated standard deviation (i.e. 99.73% of the data assuming a normal distribution). The occupation of the minor component is plotted as a function of SCXRD collection temperature including the associated errors in Figure 20.

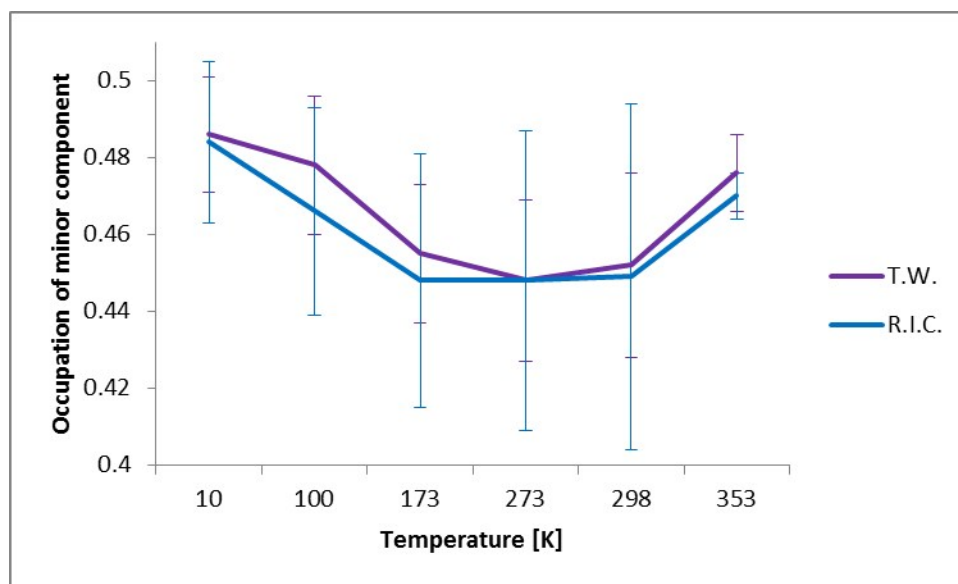


Figure 20. Plot of experimentally determined occupation of conformer 2 in loratadine Form I as a function of SCXRD collection temperature, from two independent refinements plotted with ± 3 times e.s.d. Shown to illustrate the trend of the minor component occupancy decreasing with increasing temperature; evident from 10-273 K