Electronic Supplementary Material for CrystEngComm

Supplementary Information

for the article entitled

MMH-2 AS A NEW APPROACH FOR THE PREDICTION OF INTERMOLECULAR INTERACTIONS: THE CRYSTAL PACKING OF ACETAMIDE

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A brief outline of MMH procedures

An appropriate generator of random molecular geometries initially generates a set of *n* molecular cluster configurations, starting from the independently optimized structures of both interacting molecules. Such clusters are fully optimized by standard gradient path minimization, using a semiempirical Hamiltonian in our case. It produces a set of typical cells of local minima in the molecular interaction configuration space. The energy, _*i*, of every *i*th cell of the ensemble is thus obtained. Our attention is focused on finding a reduced set of cells that can represent the most significant contributions to the *i*th state for the whole system. After selecting those cells, we will have model structures for the most important clusters of intermolecular interactions, with real statistical significance because of the previous exploration of the whole space of atomic configurations. Then we can use a Boltzmann distribution to calculate the thermally averaged state of the typical macroscopic system at room temperature. In any case, a partition function should be calculated assuming the appropriate energy scale with respect to a reference value. For this purpose, a conventional state has to be chosen for calculating such reference energy. We can define such a state to exclude all interaction energies among constituent molecules in a given cluster. This means that we consider the translational, rotational, and vibrational states of molecules in the clusters as identical to those in the reference states. Therefore, the association process is considered to be isothermal. In this case, the reference state is taken as a set with the same number of non interacting molecules of the same kind, so that the sum of their total energies is taken as the reference value on our energy scale. Thus, in the reference state q=1.

Accordingly, the *cell* energy with respect to the new reference scale, $\Delta\varepsilon_i$ is:

$$\Delta\varepsilon_i = \varepsilon_i - \varepsilon^{ref}$$

where:

$$\varepsilon^{ref} = \varepsilon_{tot(solute)} + n\varepsilon_{tot(solvent)}$$

Consequently, the molecular partition function in such reference scale is:

$$q^* = \sum g_i e^{-(\Delta\varepsilon_i / RT)} = q e^{\varepsilon^{ref}/RT}$$

Therefore, using common statistical equations we can obtain important thermodynamic quantities of the molecular association process such as: the association energy (E^{assoc}), the association entropy (S^{assoc}), and the free Helmholtz association energy (A^{assoc}) (Eqs. 10-12).

$$E^{assoc} = E - E^{ref} = RT^2 \frac{q^{*'}}{q^*}$$

$$S^{assoc} = S - S^{ref} = R\ln q^* + \frac{E^{assoc}}{T}$$

$$A^{assoc} = A - A^{ref} = -RT\ln q^*$$

Note that this approach can provide, at the same time, important model structures of solute–solvent cluster interactions and energies for these interactions with true statistical significance.

Full author reference 28

(28) Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

Results of MMH-1/AM1 for acetamide dimers

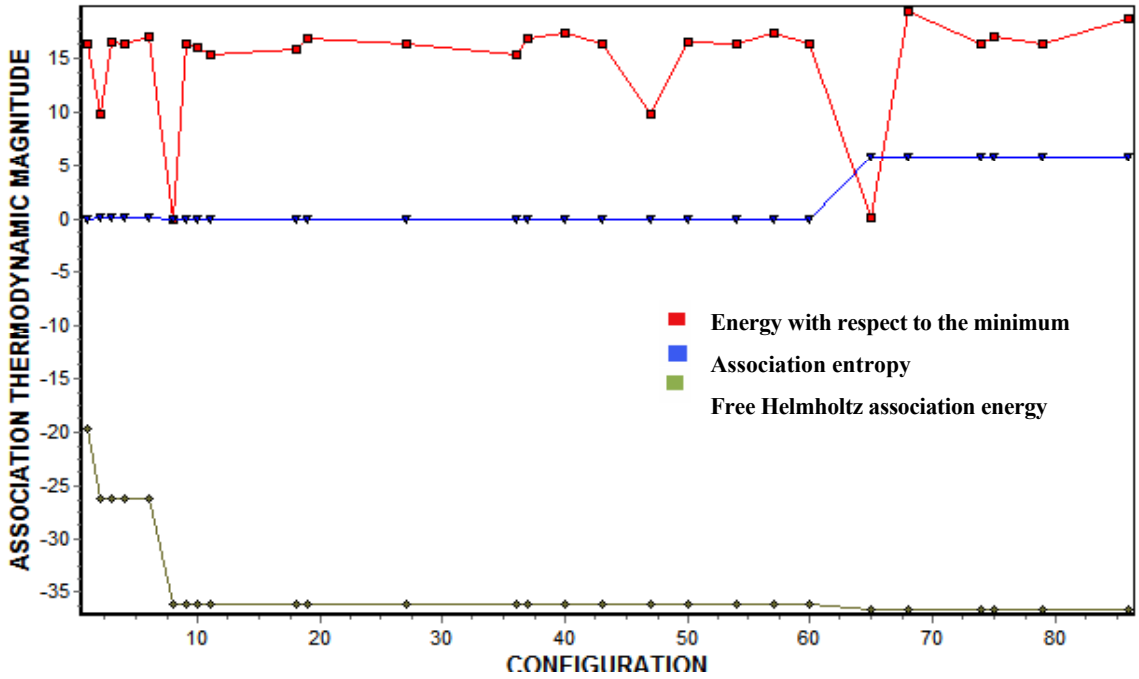


Figure S1. Association thermodynamic magnitudes of acetamide dimers calculated by **MMH-1/AM1**

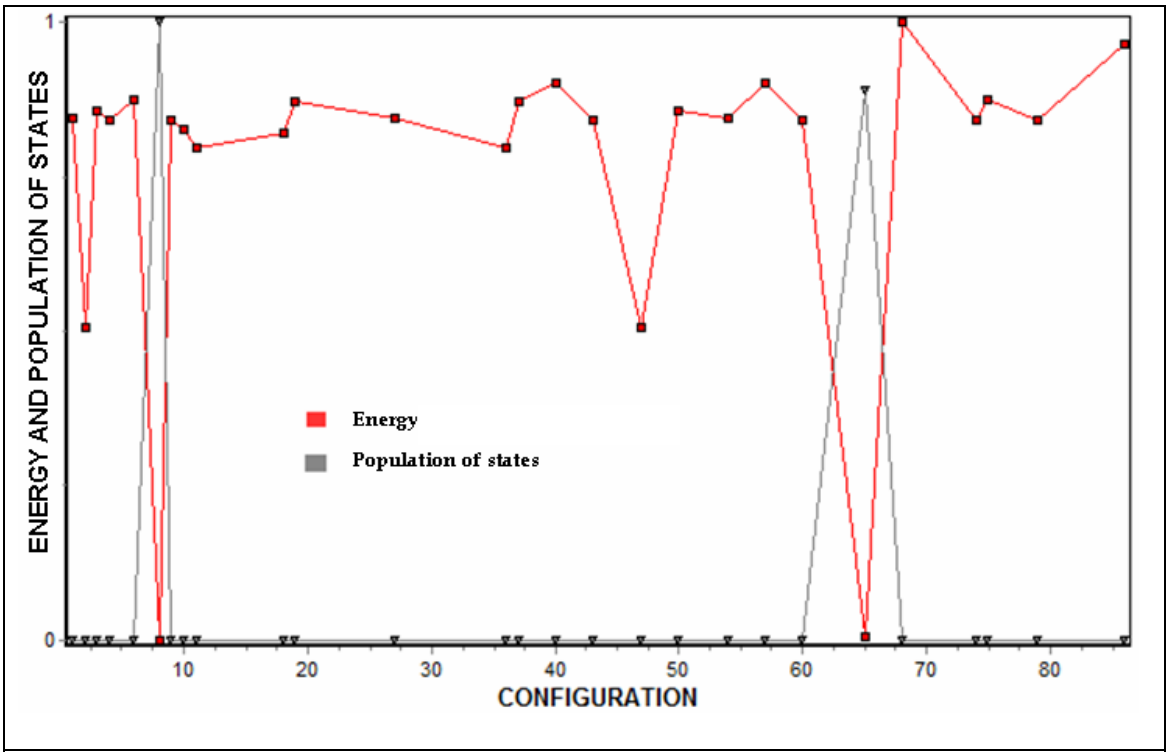
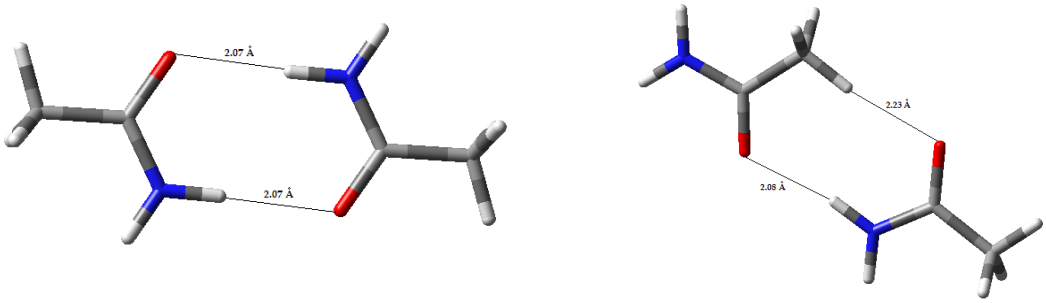


Figure S2. Population of states and configuration energy of acetamide dimers calculated by **MMH-1/AM1**



R 2,2(8) **C1,1(4)**

a b

Figure S3. Acetamide structural motifs found by **MMH-1/AM1**

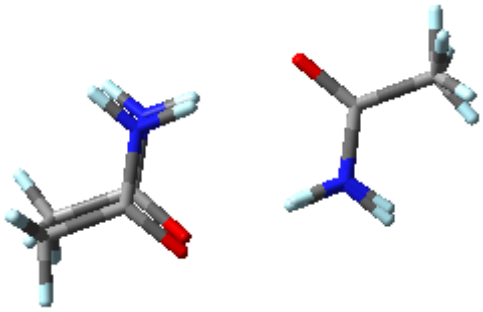
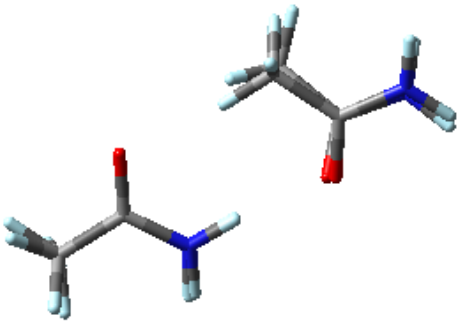
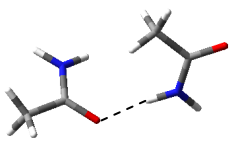
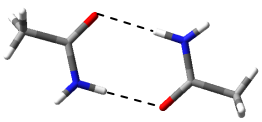
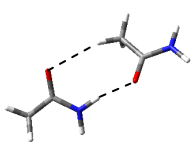
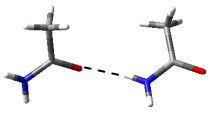
Hydrogen bond motifs obtained by MMH-1/AM1	
	

Figure S4. Superimposed experimental and predicted acetamide dimer structures obtained by **MMH-1/AM1**

Additional results comparing MMH-2/AM1 with MP2 and DFT calculations

Table S1. Different orientations of acetamide dimers after the full optimization

METHOD	d_1	d_2	d_3	d_4
EXP				

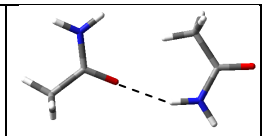
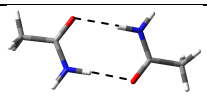
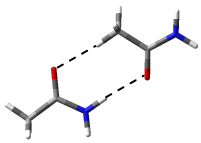
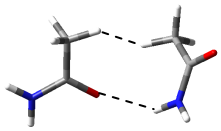
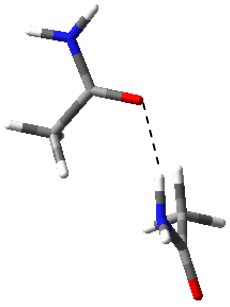
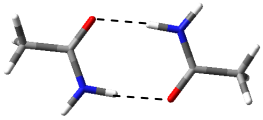
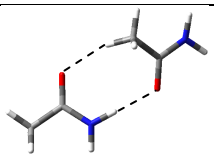
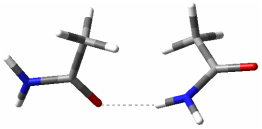
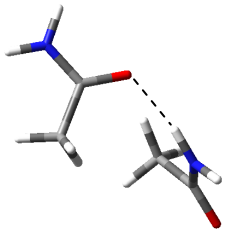
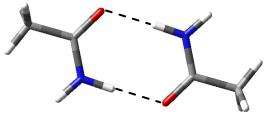
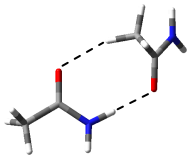
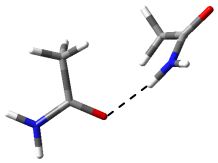
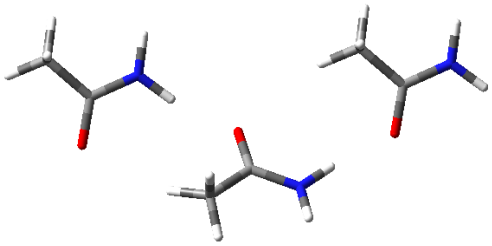
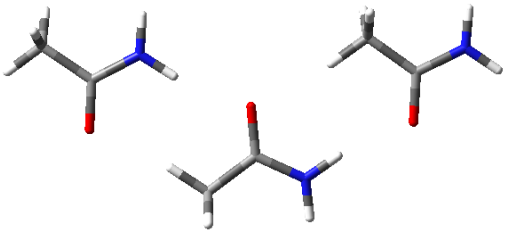
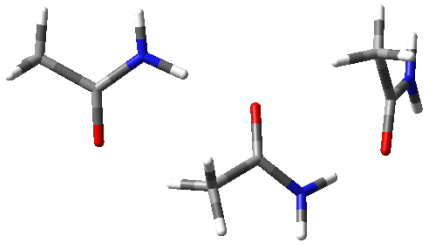
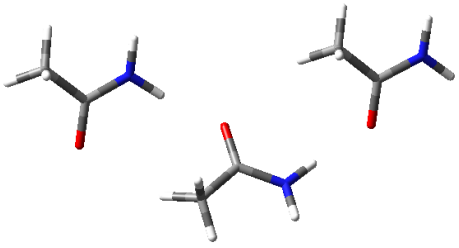
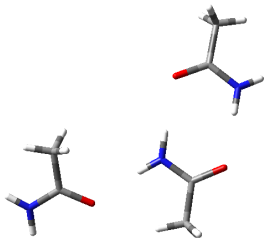
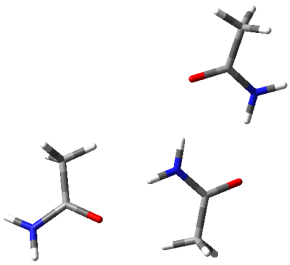
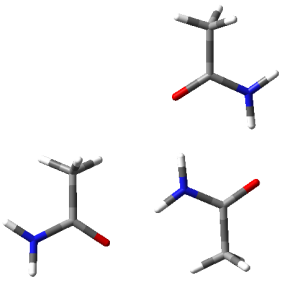
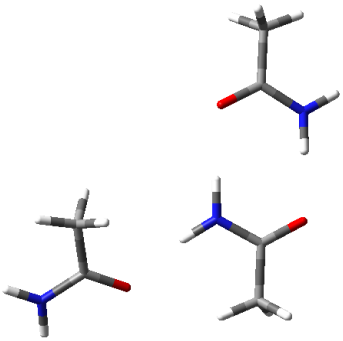
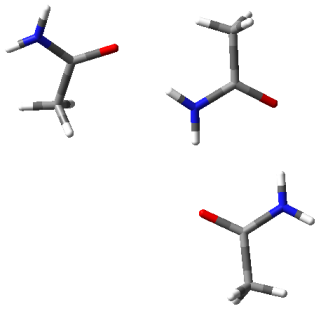
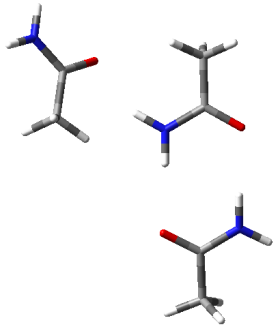
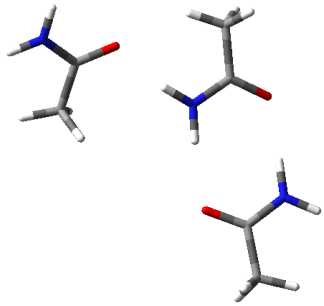
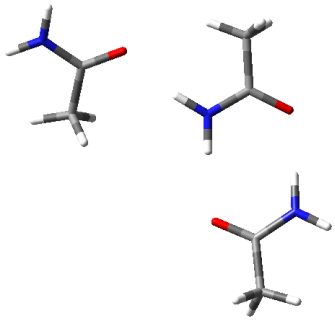
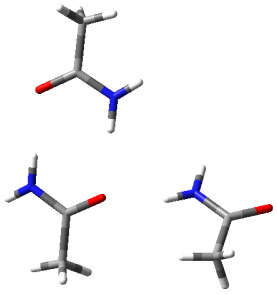
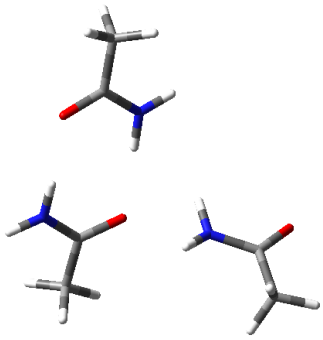
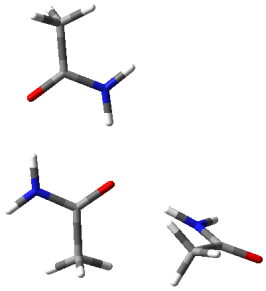
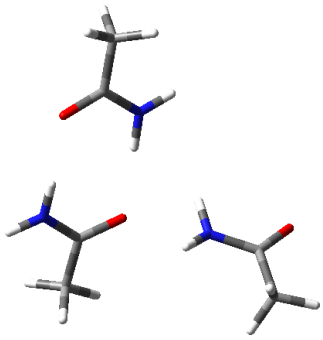
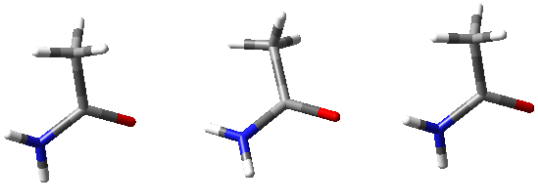
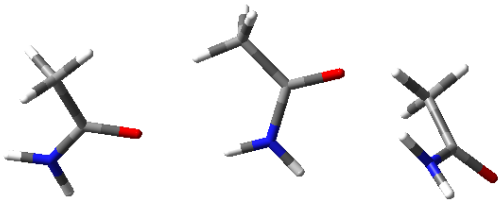
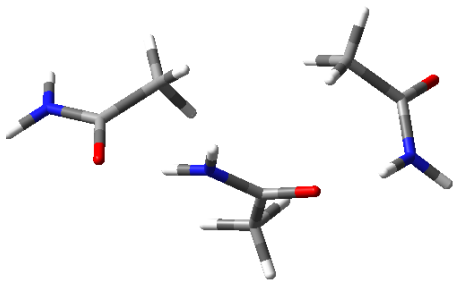
MMH-2/ AM1				
MP2/6-311G**				
MP2/aug´ -cc-pVTZ				

Table S2. Different orientations of acetamide trimers after the full optimization

Configuration	Orientation results from different methods	
t_1	EXP	
	MMH-2/AM1	

	MP2-aug´-cc-pVTZ	
	CP2K(HCTH120/TZPV)	
t_2	EXP	
	MMH-2/AM1	
	MP2-aug´-cc-pVTZ	
	CP2K(HCTH120/TZPV)	

t_3	EXP	
	MMH-2/AM1	
	MP2-aug´-cc-pVTZ	
	CP2K(HCTH120/TZPV)	
t_4	EXP	

	MMH-2/AM1	
	MP2-aug´-cc-pVTZ	
	CP2K(HCTH120/ TZPV)	
t_5	EXP	
	MMH-2/AM1	
	MP2/aug´-cc-pVTZ	

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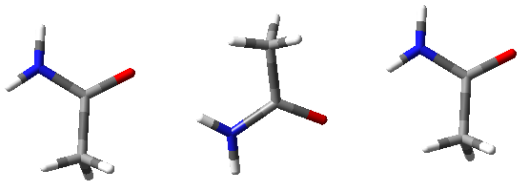
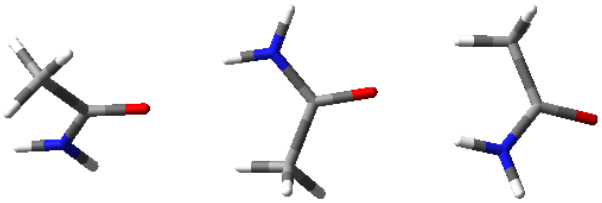
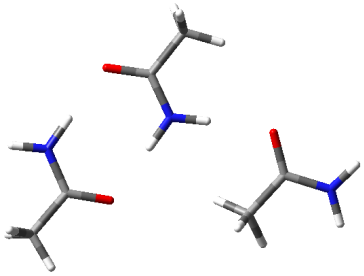
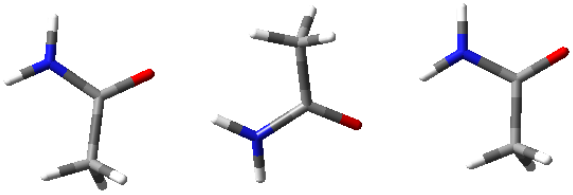
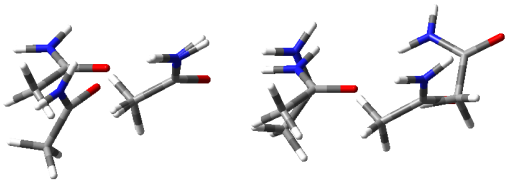
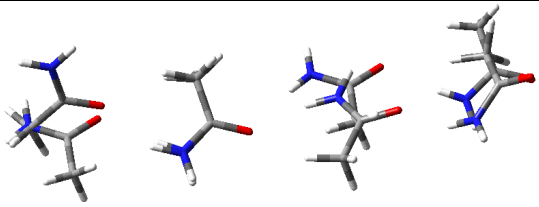
t_6	EXP	
	MMH-2/AM1	
	MP2-aug´-cc-pVTZ	
	CP2K(HCTH120/ TZPV)	

 q_1
 q_2

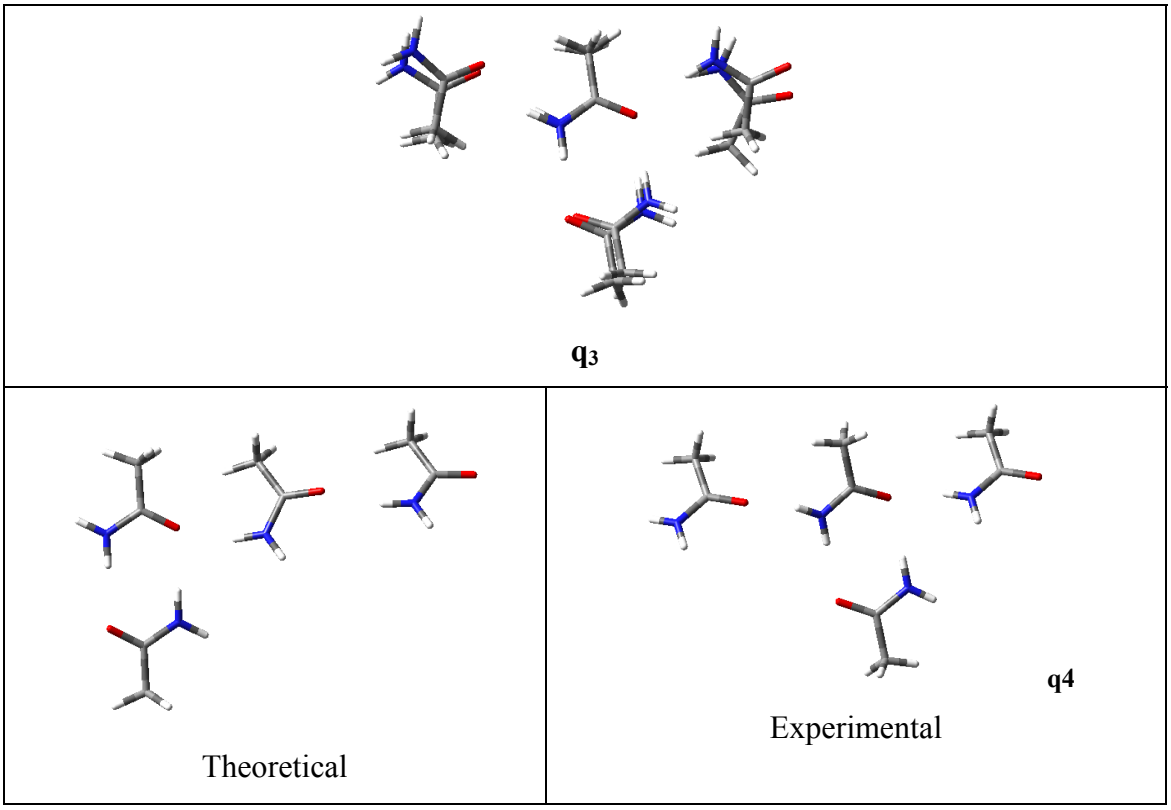
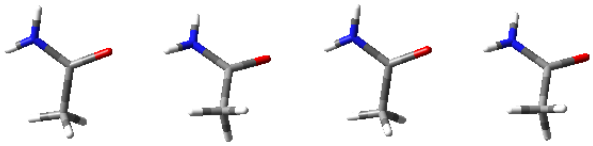
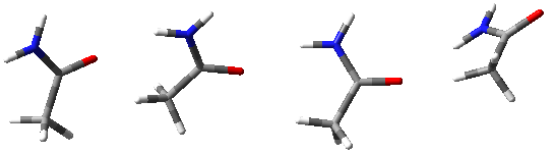
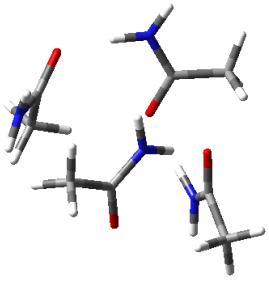
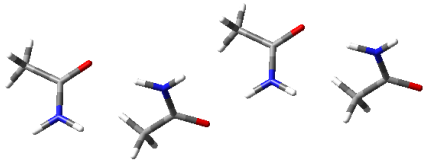
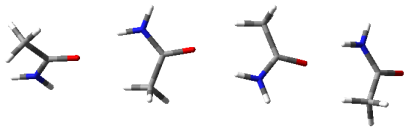
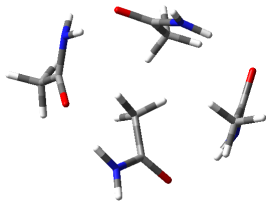
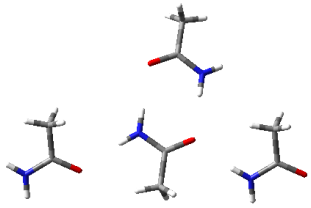
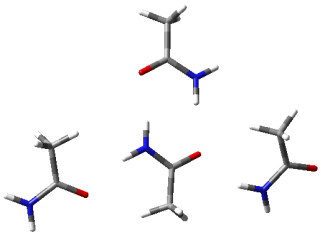
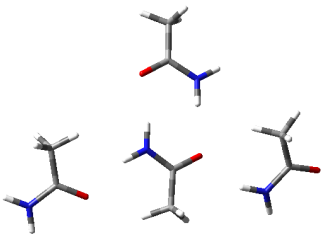
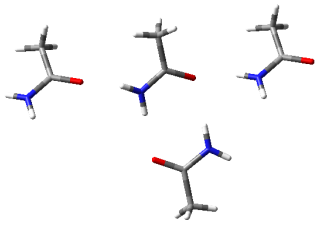


Figure S5. Superimposed experimental and predicted structures (**MMH-2/AM1**) of acetamide tetramers

Table S3. Orientations of acetamide tetramers related with ACEMID06 by different methods

q_1	Exp	
	MMH-2/AM1	
	MP2/aug´-cc-pVTZ	

q_2	Exp	
	MMH-2/AM1	
	MP2/aug´-cc-pVTZ	
q_3	Exp	
	MMH-2/AM1	
	MP2/aug´-cc-pVTZ	
q_4	EXP	

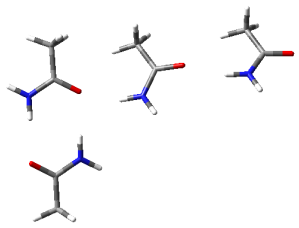
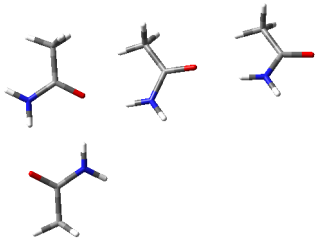
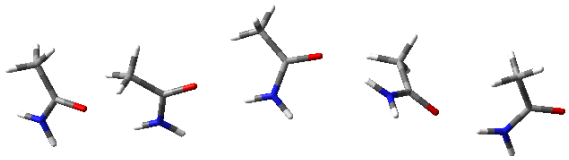
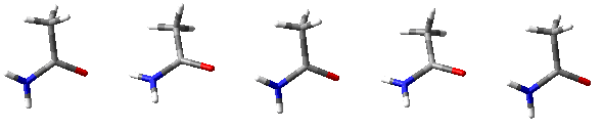
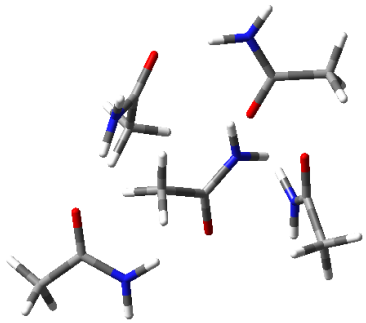
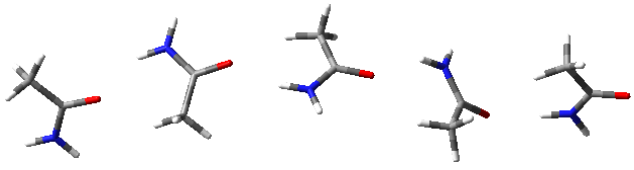
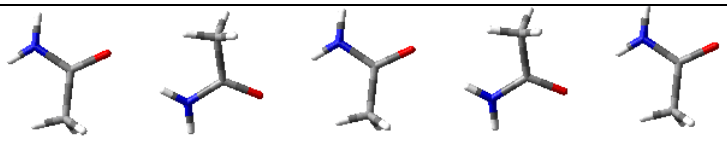
	AM1	
	MP2-aug´-cc-pVTZ	

Table S4. Orientations of acetamide pentamers related with ACEMID06 by different methods

p_1	MMH-2/AM1	
	EXP	
	MP2-aug´-cc-pVDZ	
p_2	MMH-2/AM1	
	EXP	

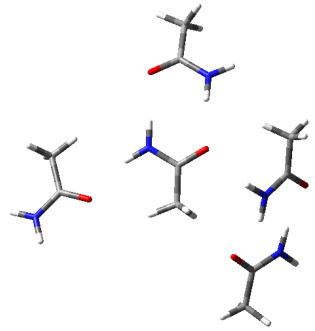
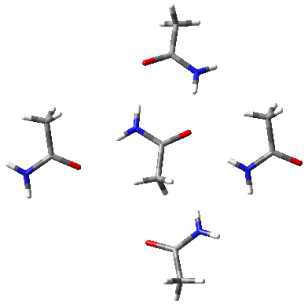
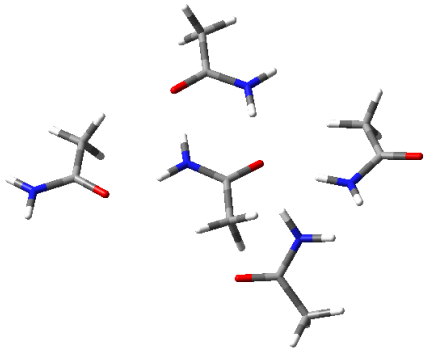
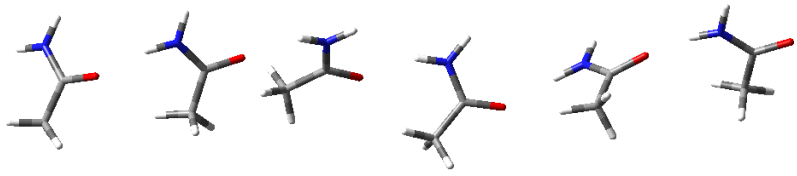
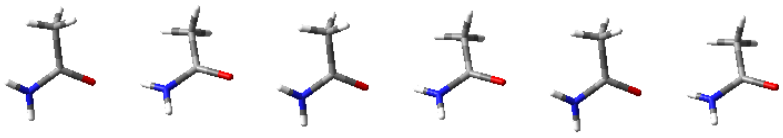
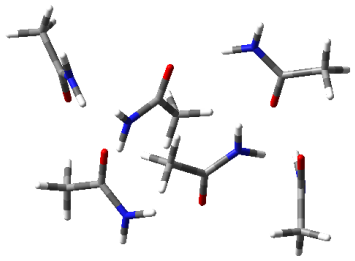
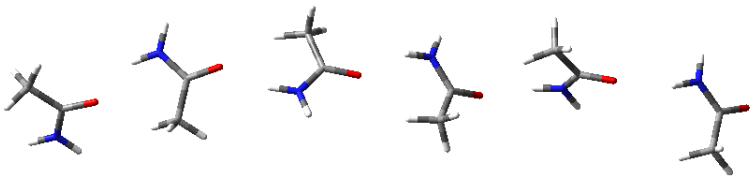
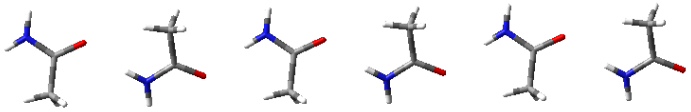
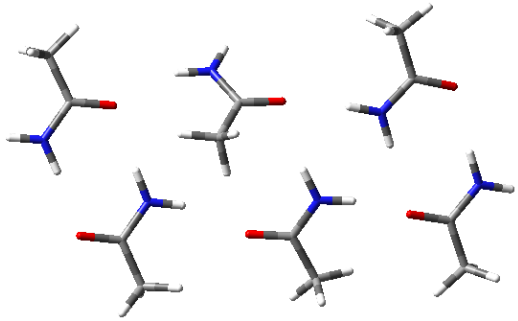
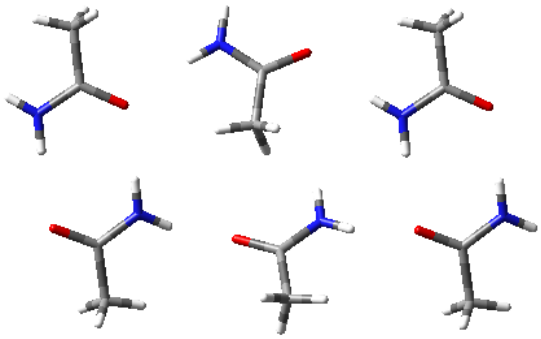
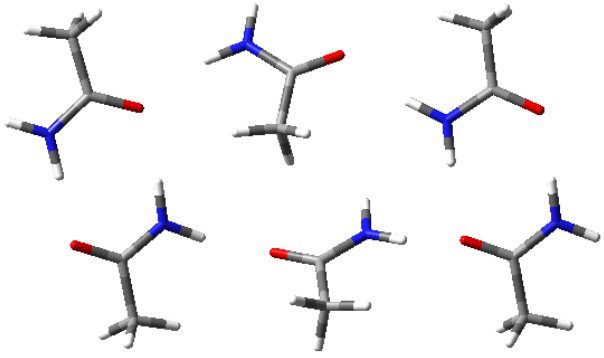
p_3	MMH-2/AM1	
	EXP	
	MP2/aug´-cc-pVDZ	

Table S5. Orientations of acetamide hexamers related with ACEMID06 by different methods

h_1	MMH-2/AM1	
	EXP	

	MP2/aug'-cc-pVDZ	
h_2	MMH-2/AM1	
	EXP	
h_3	MMH-2/AM1	
	EXP	
	MP2/aug'-cc-pVDZ	

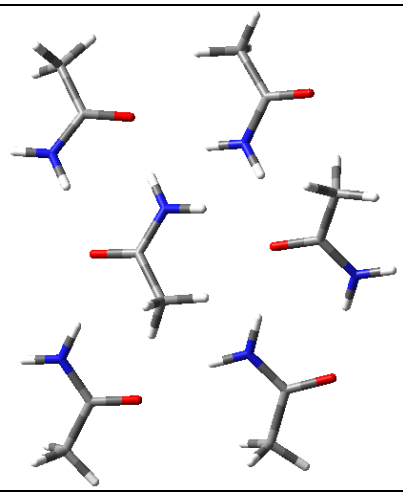
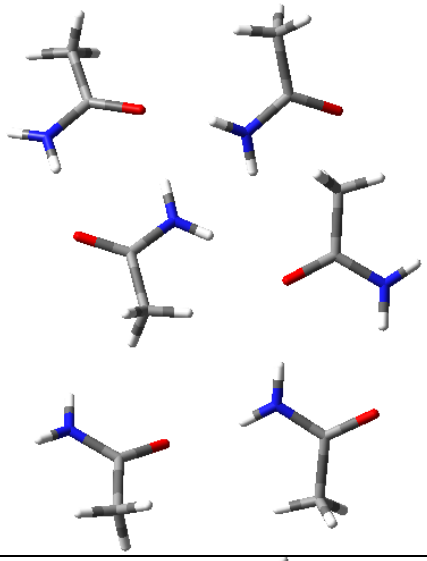
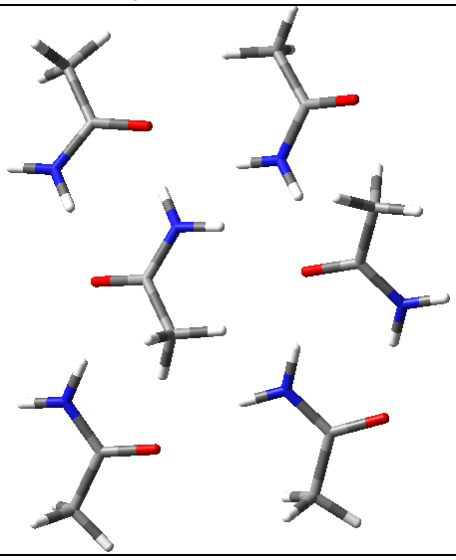
h4	MMH-2/AM1	
	EXP	
	MP2/aug'-cc-pVDZ	

Table S6. Geometrical parameters experimental and theoretical acetamide pentamers

Conf	**$d_{(H\text{-}bond)}$ (Å)**	**Exp.**	**MMH-2/AM1**	**MP2/aug-cc-pVTZ**

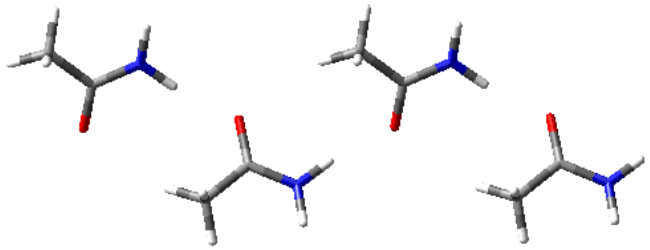
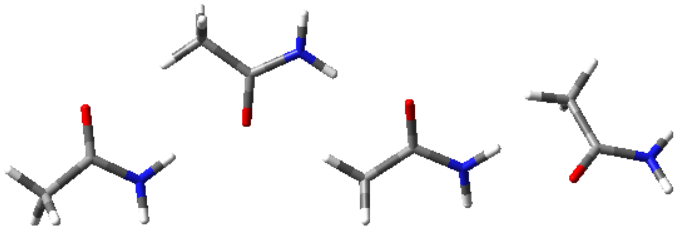
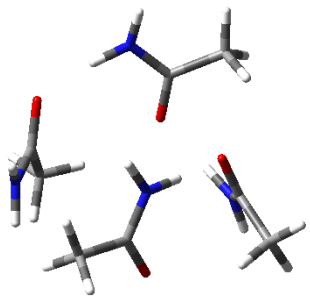
p_1	CO--NH_2	2.01	2.17	N/A
	CO--NH_2	2.01	2.14	
	CO--NH_2	2.01	2.14	
	CO--NH_2	2.01	2.14	
	CO--CH_3	3.02	2.38	
p_2	CO--NH_2	1.87	2.17	N/A
	CO--NH_2	1.87	2.14	
	CO--NH_2	1.87	2.14	
	CO--NH_2	1.87	2.15	
	CO—CH_3	2.92	2.38	
p_3	CO--NH_2	2.05	2.04	1.85
	CO--NH_2	2.02	2.13	1.90
	CO--CH_3	3.93	2.29	2.63
	CO--NH_2	4.12	2.15	2.04
	CO--NH_2	2.05	2.14	1.87
	CO--NH_2	2.02	2.04	1.94

Table S7. Geometrical parameters experimental and theoretical acetamide hexamers

Conf	**$d_{(H\text{-}bond)}$ (Å)**	**Exp.**	**MMH-2/AM1**	**MP2/aug-cc-pVTZ**
h_1	CO--NH_2	2.01	2.17	N/A
	CO--NH_2	2.01	2.14	
	CO--NH_2	2.01	2.14	
	CO--NH_2	2.01	2.14	
	CO--NH_2	2.01	2.13	
	CO--CH_3	3.02	2.38	
h_2	CO--NH_2	1.87	2.17	N/A
	CO--NH_2	1.87	2.14	
	CO--NH_2	1.87	2.14	
	CO--NH_2	1.87	2.15	
	CO--NH_2	1.87	2.16	
	CO—CH_3	2.92	2.38	
h_3	CO--NH_2	2.09	2.15	2.06
	CO--NH_2	2.09	2.14	2.05
	CO--NH_2	2.05	2.04	1.73
	CO--NH_2	2.02	2.12	1.90
	CO--NH_2	2.05	2.13	1.93
	CO--NH_2	2.02	2.14	1.75
	CO--NH_2	2.01	2.19	1.84

	CO--NH_2	2.01	2.17	1.93
h_4	CO--NH_2	2.02	2.22	1.87
	CO--NH_2	2.01	2.06	1.90
	CO--NH_2	2.09	2.19	1.92
	CO--NH_2	2.02	2.09	1.87
	CO--NH_2	2.01	2.17	1.90
	CO--CH_3	-	2.29	2.60
	NH_2--NH_2	2.76	2.37	1.96

Table S8. Orientations of tetramers related with ACEMID 03 by different methods

q_5	EXP	
	MMH-2/AM1	
	MP2-aug´-cc-pVTZ	

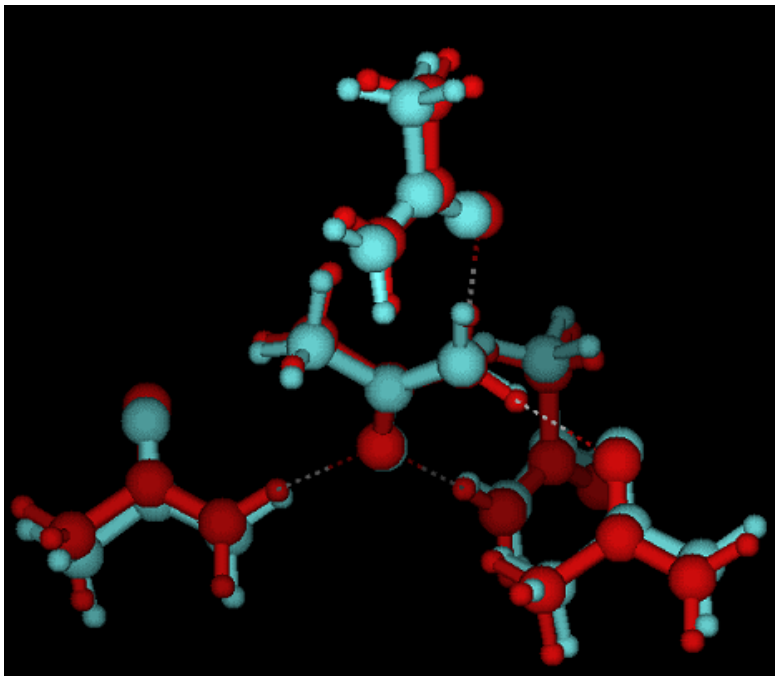
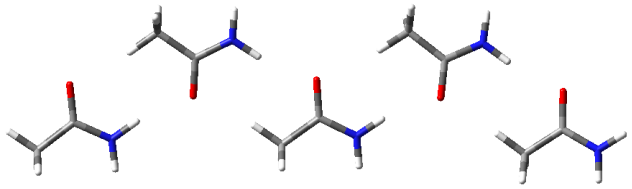
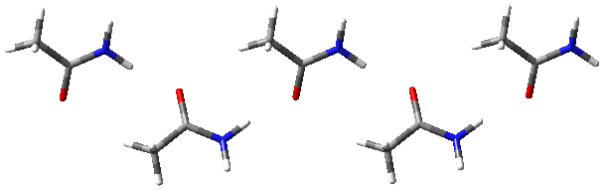
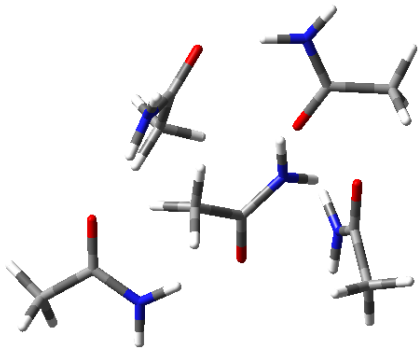


Figure S6. Superimposed experimental ($C_{2,2}(8)$) and predicted structure of one calculated pentamer

Table S9. Orientations of pentamers related with ACEMID 03 by different methods

p_4	MMH-2/AM1	
	EXP	
	MP2/aug´-cc-pVDZ	

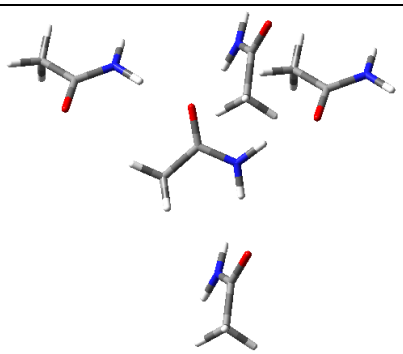
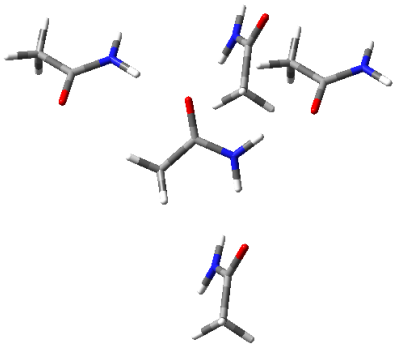
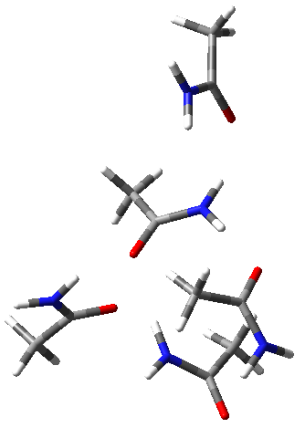
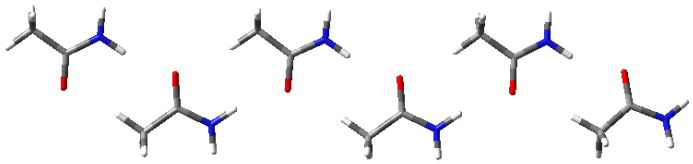
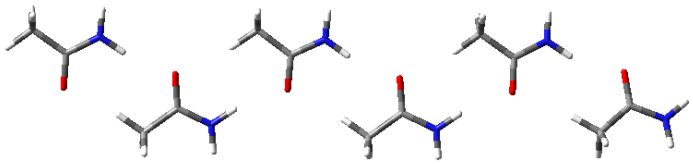
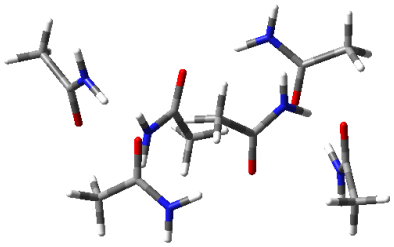
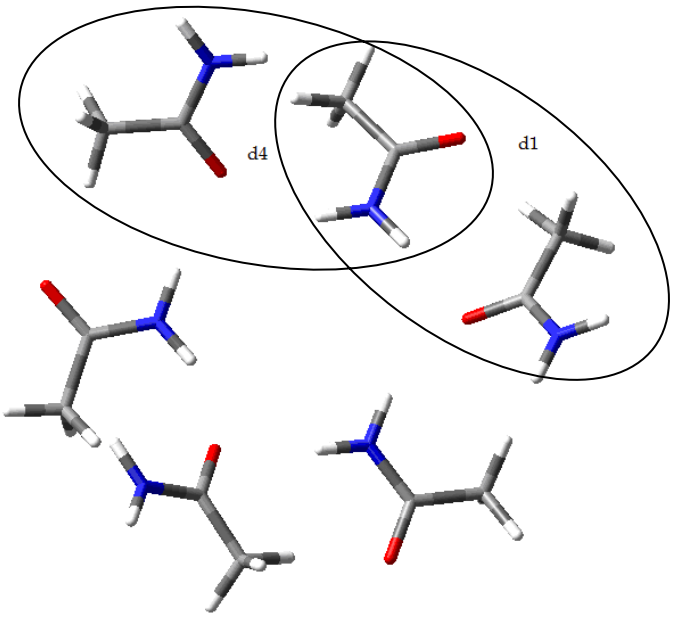
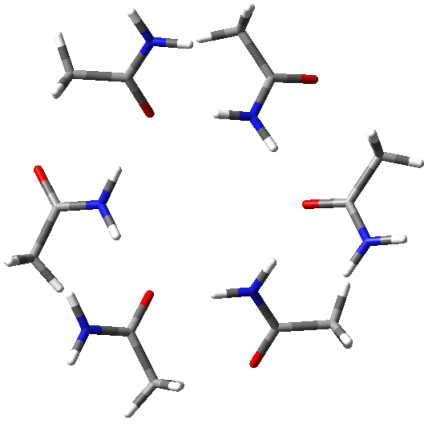
p_5	MMH-2/AM1	
	EXP	
	MP2/aug´-cc-pVDZ	

Table S10. Geometries of pentamers by different methodologies

Config	**$d_{(H\text{-}bond)}$ (Å)**	**Exp.**	**MMH-2/AM1**	**MP2/aug´-cc-pVDZ**
p_4	CO--$CH_{3\ all}$	3.02	2.35	1.89
	CO--$NH_{2\ (1)}$	2.01	2.17	2.27
	CO--$NH_{2\ (2)}$	2.01	2.14	2.26
	CO--$NH_{2\ (3)}$	2.01	2.14	2.27
p_5	CO--$NH_{2\ (1)}$	1.86	2.14	---
	CO--$NH_{2\ (2)}$	1.89	2.17	
	CO--$NH_{2\ (3)}$	1.86	2.14	
	CO--$NH_{2\ (3)}$	1.89	2.17	

Table S11. Orientations of hexamers related with ACEMID 03 by different methods

$\mathbf{h_5}$	MMH-2/AM1	
	EXP	
	MP2/aug´-cc-pVDZ	
$\mathbf{h_6}$	MMH-2/AM1	
	EXP	

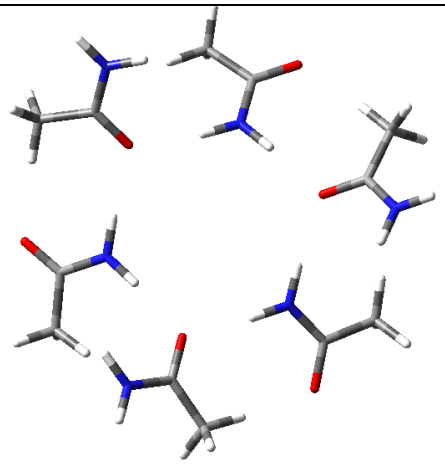
	MP2/aug´-cc-pVDZ	

Table S12. Geometries of hexamers by different methodologies

Config	**$d_{(H\text{-}bond)}$ (Å)**	**Exp.**	**MMH-2/AM1**	**MP2/aug´-cc-pVTZ**
h_5	CO--$CH_{3\ all}$	3.02	2.35	1.89
	CO--$NH_{2\ (1)}$	2.01	2.17	2.27
	CO--$NH_{2\ (2)}$	2.01	2.14	2.26
	CO--$NH_{2\ (3)}$	2.01	2.14	2.27
h_6	CO--$NH_{2\ (1)}$	1.87	2.16	2.01
	CO--$NH_{2\ (2)}$	1.89	2.22	1.95
	CO--$NH_{2\ (3)}$	1.86	2.16	2.01
	CO--$NH_{2\ (4)}$	1.89	2.22	1.95
	CO--$NH_{2\ (5)}$	1.86	2.16	2.01
	CO--$NH_{2\ (6)}$	1.89	2.22	1.95