Electronic Supporting Information

Spontaneous single-crystal to single-crystal transition with self-healing cracks involving solvent exchange

[1] *Department of Chemistry, Zhejiang University, Hangzhou 310028, China*

[2] *Department of Physics and Department of Materials Science and Engineering, City University of Hong Kong, Tat Chee Avenue, Kowloon, Hong Kong, China*

Email: tangguping@zju.edu.cn (G.P. Tang); paul.chu@cityu.edu.hk (P.K. Chu)

1. Crystallization of darunavir ethanolate and dihydrate

Darunavir ethanolate was crystallized from ethyl alcohol by slow evaporation to obtain colorless crystals (Figure 1 a). Darunavir dihydrate was crystallized using two methods. In the first method, the single-crystal to single-crystal transformation from ethanolate was conducted in water vapor (Figure 1c). In the second method, darunavir was directly recrystaled from acetonitrile solution (Figure 1b).

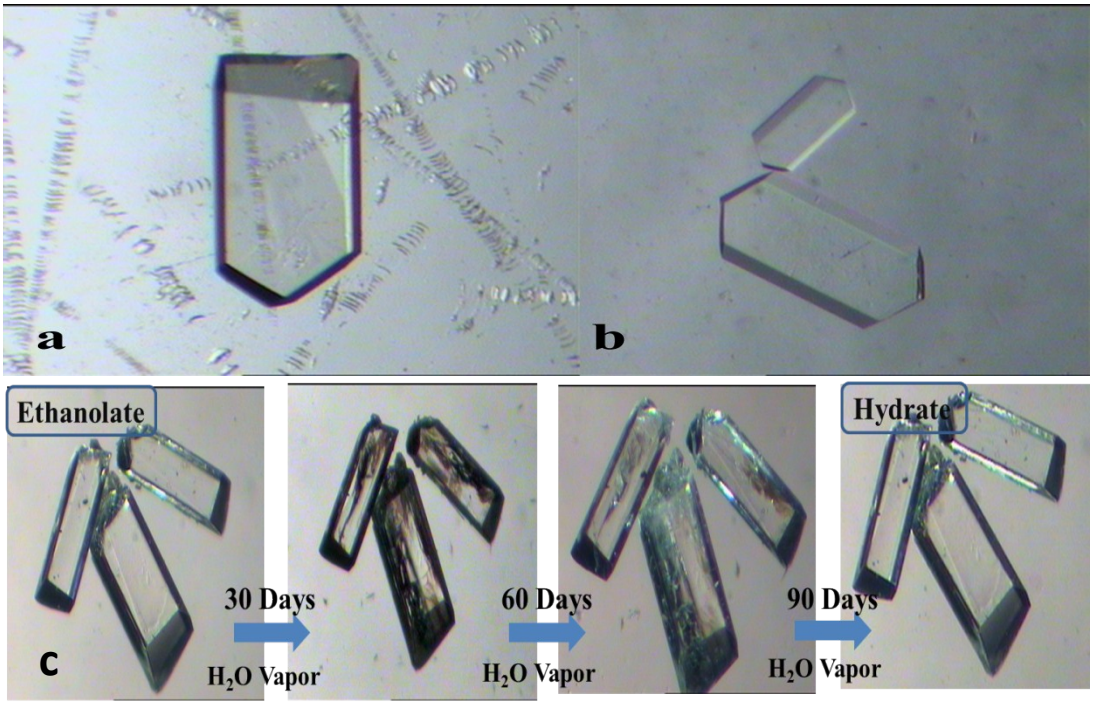

Figure 1. Photographs of the darunavir ethanolate and darunavir dihydrate crystals.

2. FTIR spectra of darunavir ethanolate and dihydrate

Fourier transform infrared (FTIR) spectra were acquired on the Varian Excalibur™ FT-IR spectrometer from the powder form of darunavir ethanolate and dihydrate in KBr discs between 500 and 4,000 cm^{-1}.

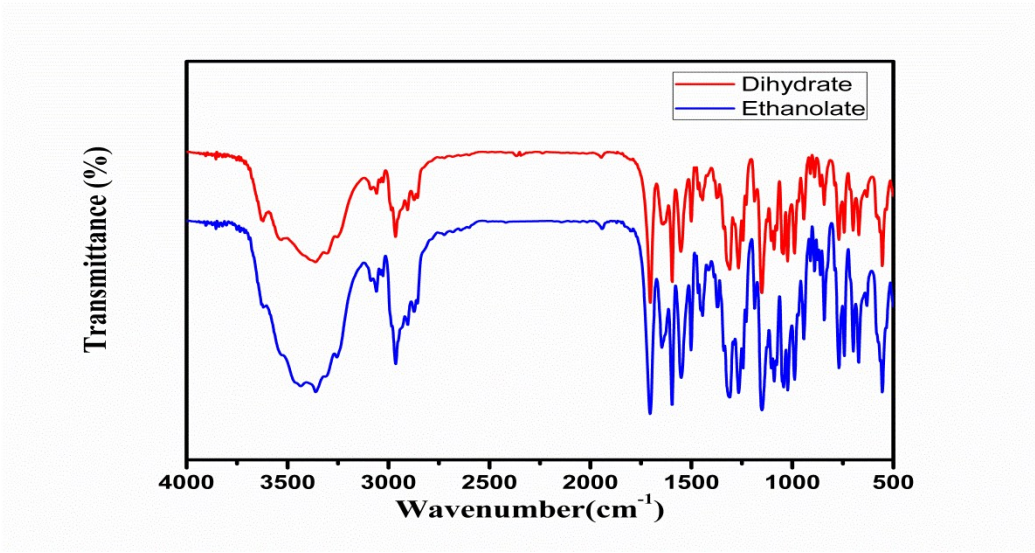

Figure 2. FTIR spectra of darunavir ethanolate and dihydrate showing differernt hydrogen bonding patterns. Darunavir dihydrate shows two distinct OH stretching bands: a broad band from 3,041 to 3,530 cm^{-1} suggesting the presence of hydrogen-bonded OH groups and a sharp peak at 3629 cm−1 indicating non-hydrogen-bonded OH groups. Darunavir ethanolate shows only a broad OH stretching band from 3,264 to 3,619 cm^{-1}, suggesting that only hydrogen-bonded OHs are present. FTIR suggests that in darunavir dihydrate, there are H_2O molecules in which OH doesn't form hydrogen bond with the drug molecule.

3. Single crystal XRD of darunavir ethanolate and dihydrate

Table 1. The hydrogen bond lengths of darunavir ethanolate and dihydrate

	Interaction	**D-H…A**	**D…A (Å)**	**Symmetry code**
Darunavir dihydrate	O-H…O	O3-H3C…O1W	2.923(2)	X,Y,Z
		O1W-H1WB…O2W	2.888(2)	X,Y,Z
		O1W-H1WA…O1	2.950(2)	1-X,1/2+Y,1/2-Z
	N-H…O	N2-H2A…O6	2.948(2)	-1/2+X,1.5-Y,-Z
		N3-H3B…O4	3.065(2)	2-X,-1/2+Y,1/2-Z
Darunavir ethanolate	O-H…O	O3-H3C…O8	2.963(2)	1-X,-1/2+Y,1/2-Z
		O8-H8…O1	2.846(2)	X,Y,Z
	N-H…O	N2-H2A…O6	2.970(2)	1/2+X,1/2-Y,-Z

Table 2. Crystal data of ethanolate and dihydrate.

	Darunavir ethanolate	**Darunavir dihydrate**
CCDC number	1863702	1854201
Temperature(K)	296(2)	296(2)
Crystal system	orthorhombic	orthorhombic
Space group	P 21 21 21	P 21 21 21
Z	4	4
Formula weight	593.72	583.69

***a* (Å)**	9.9846(5)	9.9965(5)
***b* (Å)**	16.6017(10)	16.5620(10)
***c* (Å)**	19.0274(10)	18.7532(11)
***α* (degree)**	90	90
***β* (degree)**	90	90
***γ* (degree)**	90	90
Cell volume (Å^3)	3154.0(3)	3104.8(3)
ρ_{calcd} (g/cm^3)	1.250	1.249
λ (MoKα) (Å)	0.71073	0.71073
μ/mm^{-1}	0.154	0.157
F(000)	1272.0	1248.0
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.382 to 51.992	6.446 to 58.814
Index ranges	-11 ≤ h ≤ 12, -20 ≤ k ≤ 20, -23 ≤ l ≤ 23	-9 ≤ h ≤ 12, -21 ≤ k ≤ 16, -23 ≤ l ≤ 23
Reflections collected	26982	22461
Independent reflections	6191 [R_{int} = 0.1089, R_{sigma} = 0.0931]	7509 [R_{int} = 0.0369, R_{sigma} = 0.0410]
Data/restraints/parameters	6191/13/375	7509/61/395
Goodness-of-fit on F^2	1.103	0.971
Final R indexes [I>=2σ (I)]	R_1 = 0.0923, wR_2 = 0.1391	R_1 = 0.0455, wR_2 = 0.1003
Final R indexes [all data]	R_1 = 0.1451, wR_2 = 0.1592	R_1 = 0.0725, wR_2 = 0.1175

Largest diff. peak/hole / e Å^{-3}	0.29/-0.31	0.18/-0.27
Flack parameter	0.01(5)	0.01(3)

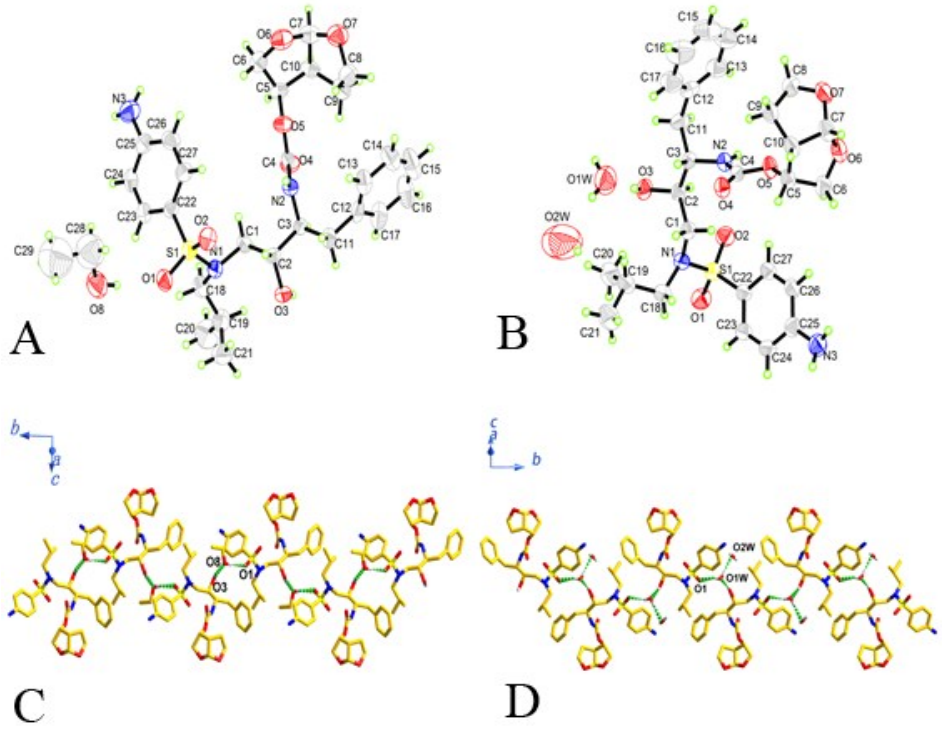

Figure 3. The molecular structure of the darunavir ethanolate (A) and dihydrate (B) , showing the atom labelling scheme and displacement ellipsoids at the 50% probability level. H atoms are shown as small circles of arbitrary radii. And (C, D) Packing diagram of darunavir ethanolate and dihydrate.

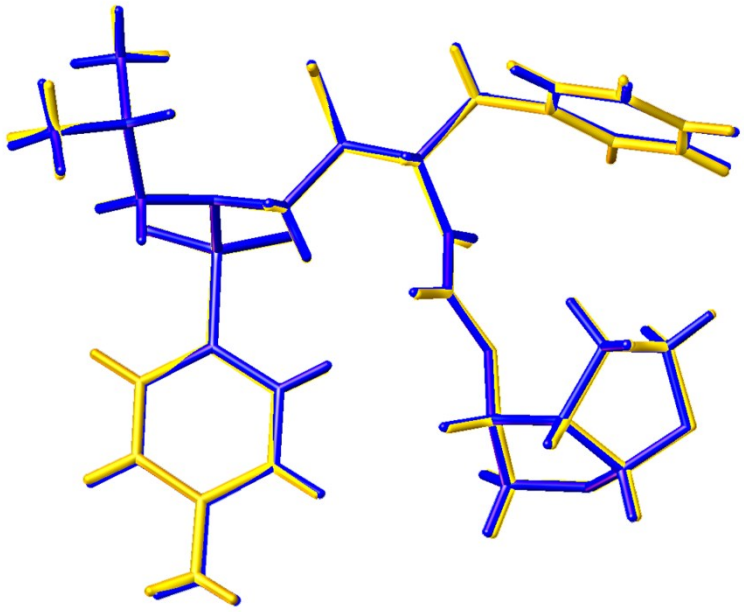

Figure 4. Overlay of conformers of darunavir ethanolate and dihydrate (overlaid using Olex2 softeware)

4. Hirshfeld surface analysis and 2D finger print plot

Hirshfeld surface analysis was carried out to distinguish polymorphs with the software CrystalExplorer 3.0 . The Hirshfeld surface on the molecule in a crystal is constructed by calculating the spherical atom electron densities. On the surface, when intermolecular contacts are shorter than the sum of van der Waals radii, they are highlighted in red, whereas longer contacts are shown in blue and contacts around the sum of van der Waals radii are in white.

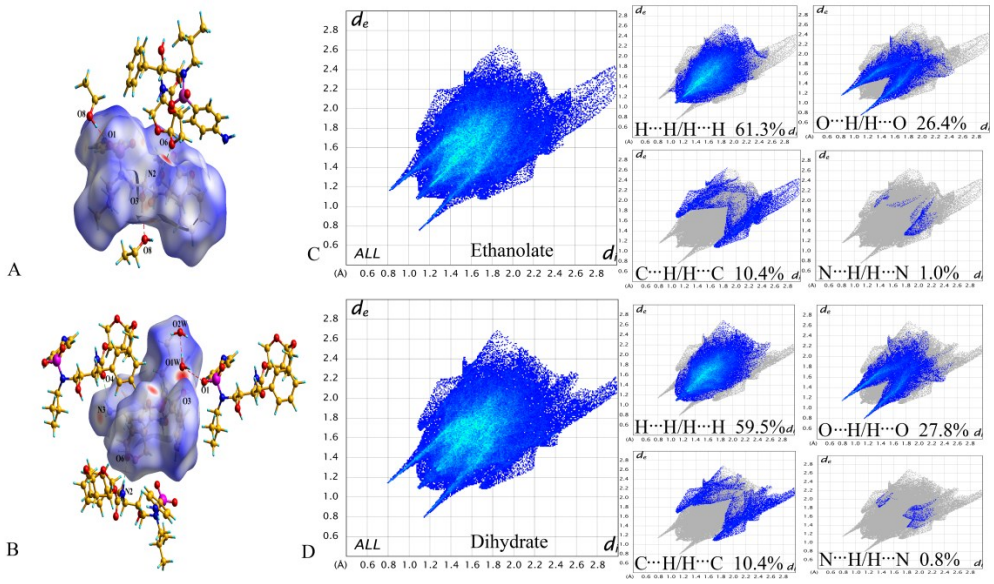

Figure 5. Hirshfeld surfaces and 2D finger print plot of darunavir ethanolate and dihydrate.

5. Material Studio data of darunavir ethanolate and dihydrate

Table 3. Crystal surface data of ethanolate and dihydrate.

	hkl	Surface area
Darunavir ethanolate	{ 0 1 1 }	252.1301089
	{ 0 0 2 }	165.7613338
	{ 1 0 1 }	356.7373466
	{ 1 1 0 }	368.6156354
	{ 0 2 0 }	189.980978
Darunavir dihydrate	{ 0 1 1 }	250.108825
	{ 0 0 2 }	165.562033
	{ 1 0 1 }	351.9619929
	{ 1 1 0 }	362.7810569
	{ 0 2 0 }	187.4663638

6. DSC and TGA profiles of darunavir ethanolate and dihydrate

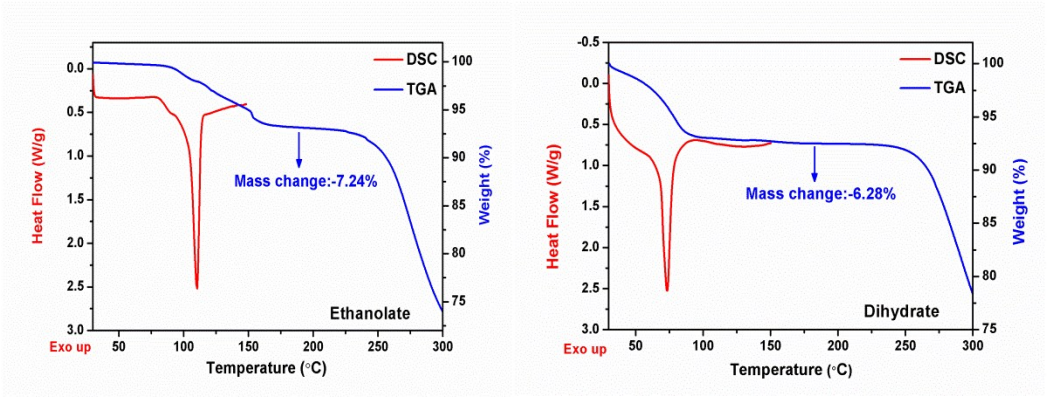

Figure 6. TGA and DSC of darunavir ethanolate and dihydrate

7.TGA profiles of SCSC transformation from DLNW-EA to DLNW-2H

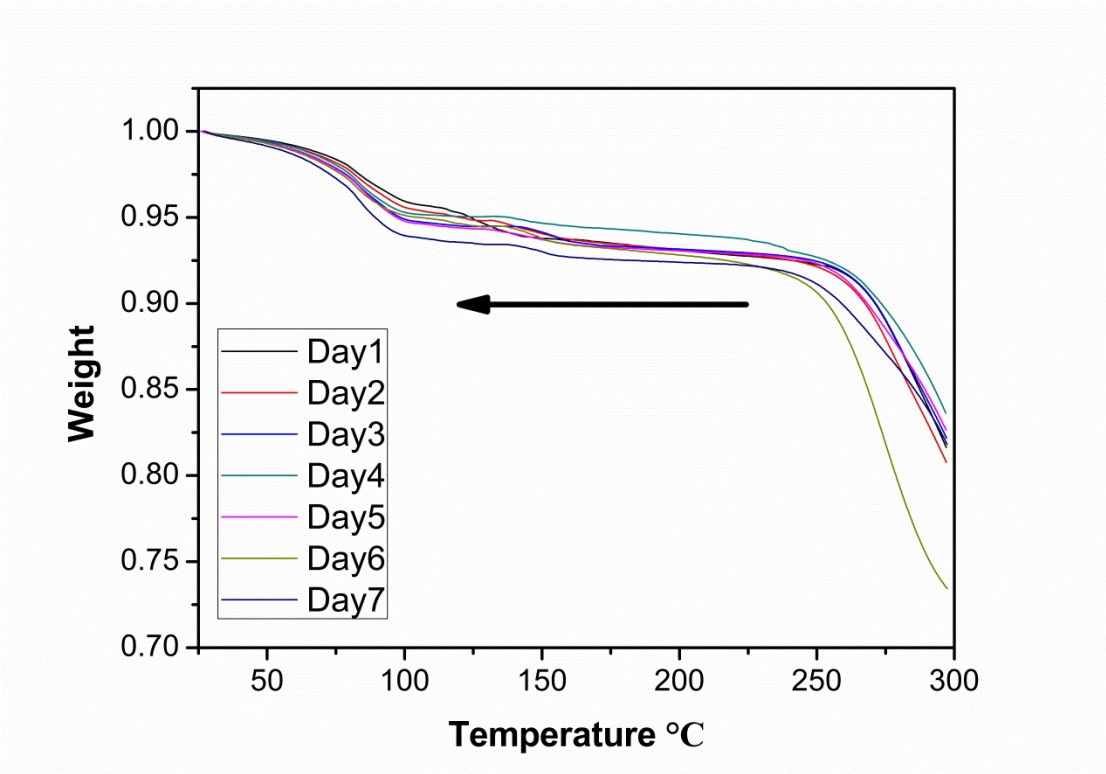

Figure 7. TGA of SCSCT process through 7days

8. Charge distribution and electrostatic potential

The experimentally determined single crystals structures with X−H bond lengths constrained to standard neutron diffraction values were used in the intermolecular interaction energy calculation. The energies were calculated between all unique nearest neighbor molecular pairs in the darunavir structure using Multifwn[1] and Gaussian09[2]. The model used the B3LYP/6-31G(d,p) molecular wave functions calculated by applying the molecular geometries extracted from the crystal structures. Each energy term was scaled independently to fit a large training set of B3LYP/6-31G(d,p) counterpoise.

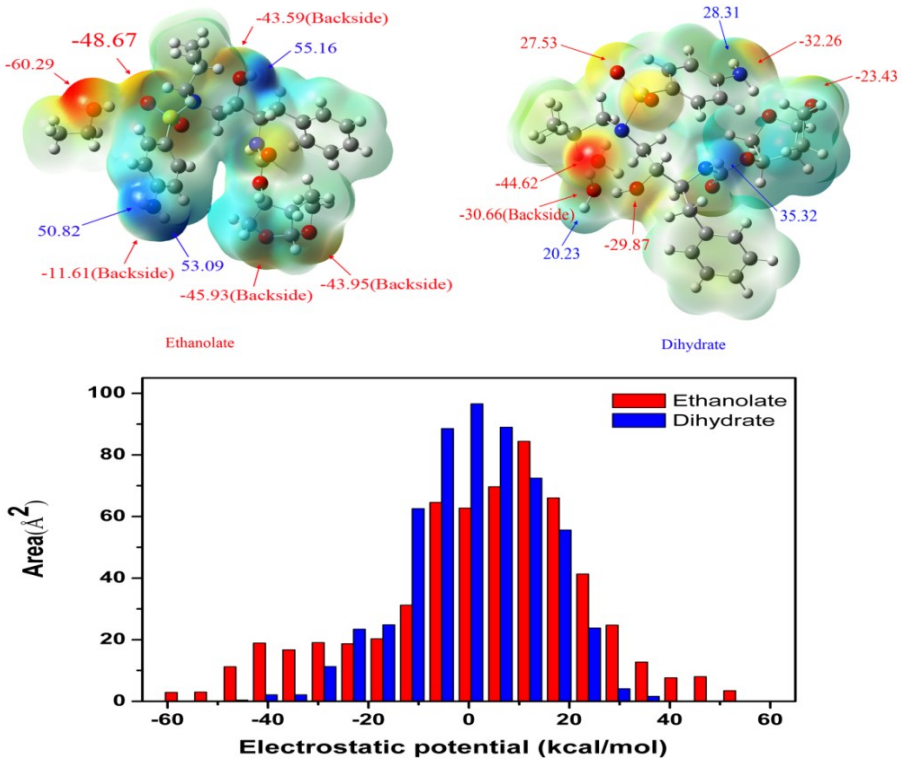

Figure 8. ESP-mapped molecular vdw surface of darunavir ethanolate and darunavir dehydrate (unit of kcal/mol). The surface local minima and maxima of ESP are represented by red and blue arrows.

References

1. Tian Lu, Feiwu Chen, Quantitative analysis of molecular surface based on improved Marching Tetrahedra algorithm, J. Mol. Graph. Model., 38, 314-32

2. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2010.