[MS25-P03] Melting of Organic Salt Crystals Simulated by Molecular Dynamics.

Carl H. Schwalbe[1,2] Dan L. Rathbone[1],

[1]*School of Life and Health Sciences, Aston University, Birmingham B4 7ET, U.K.*
[2]*Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ.*
E-mail: c.h.schwalbe@aston.ac.uk

Nucleation at the start of crystal growth is of great importance to the pharmaceutical industry since it will profoundly influence the properties of the final product. We have used molecular dynamics to simulate the reverse process, namely the disintegration of a crystal confined in a cage of water molecules at 600K, above its melting point. A fragment of the crystal salt containing 150 units each of the anion and cation was planted in a box of TIP3P water extending 12Å from the surface of the crystal. Water molecules within 6Å of the crystal were deleted. The remaining water molecules were restrained and the ensemble was subjected to 2000 steps of energy minimisation and subsequent MD simulation using the Sander module with the ff99SB Amber force field within the Amber 11 package [1]. The ensemble was heated from 0 to 600K over 20ps with the non-bonded cut-off distance set to 12Å. Thereafter, the dynamics were conducted at 600K for a period of 50ns with the SHAKE algorithm implemented and a time step of 2fs. By the principle of microscopic reversibility, conclusions can be drawn from this about the early stages of crystal formation. The t-butylammonium salt of the anti-inflammatory drug flurbiprofen [2] was chosen as the test compound because its NH_3^+ and COO^- groups form hydrogen-bonded ladders of successive $R_4^3(10)$ rings, the motif that occurs most frequently in ammonium carboxylate salts [3]. In accord with expectations that such a common motif should be durable, the initial response to the application of heat is for lines of ionically-linked molecules to start moving independently. Eventually the lines do break, mostly into small aggregates, frequently composed of 4 cations and 4 anions with their hydrophobic portions pointing outwards. These aggregates are persistent and may be of significance in the liquid state.

[1] D.A. Case, T.A. Darden, T.E. Cheatham, III, C.L. Simmerling, J. Wang, R.E. Duke, R.Luo, R.C. Walker, W. Zhang, K.M. Merz, B. Roberts, B. Wang, S. Hayik, A. Roitberg, G. Seabra, I. Kolossváry, K.F. Wong, F. Paesani, J. Vanicek, J. Liu, X. Wu, S.R. Brozell, T. Steinbrecher, H. Gohlke, Q. Cai, X. Ye, J. Wang, M.-J. Hsieh, G. Cui, D.R. Roe, D.H.Mathews, M.G. Seetin, C. Sagui, V. Babin, T. Luchko, S. Gusarov, A. Kovalenko, and P.A. Kollman (2010), AMBER 11, University of California, San Francisco.
[2] Schwalbe, C.H., Ramirez, M., Conway, B.R., Bache, C.J., Coles, S.J. & Timmins, P. (2010) *ACA Transactions.*
[3] Lemmerer, A., Bourne, S.A. & Fernandes, M.A. (2008) *CrystEngComm*, **10**, 1605-1612.

Keywords: molecular dynamics simulations, melting, pharmaceutical compounds