## Role of Entropy in Polymorphism David A. Kofke, Dept of Chemical & Biological Engineering University at Buffalo, The State University of New York



- Polymorphism: Ability of molecule to form more than one crystalline phase
  - Example: Paracetamol (acetaminophen)



• Importance:

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- Polymorph determines physical behavior



Orthorhombic



Monoclinic

- Shape, solubility, stability, mechanical and optical properties, bioavailability, dissolution rate
- Impacts manufacture and processing, usability, pharmaceutical efficacy
- Emergence of new structure during manufacture can be very costly to eliminate
- Problem: Very difficult to predict which polymorph will be formed
  - Prediction requires ability to calculate thermodynamic energy and entropy of candidate crystals
  - Two key sources of error: (1) model of intermolecular energy; (2) how entropy is estimated
- Focus of this work is on the entropy
  - Historically entropy has been neglected because it is hard to calculate accurately
  - We are developing molecular simulation techniques that are both accurate and efficient
  - With methods in hand, we apply them to assess importance of entropy to polymorphic behavior