

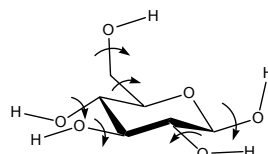
Carbohydrates

- polar
- anomeric (stereoelectronic) effect
- flexible
- hypervalent
- biomolecular recognition



Computational Challenge I

- floppy conformations (especially in solution)
 - adequate sampling difficult *eg.* one glucose anomer has $3^6 = 729$ conformations



Computational Challenge II

- carbohydrate force fields

- CHARMM

- Rasmussen (1979), Brady (1988)

- MMx (x=2,3,4)

- Allinger (1976), Jeffrey (1980), Allinger (2003)

- AMBER

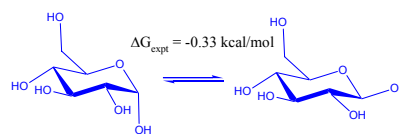
- Homans (1990), Merz (1992), Woods (1995), Kollman (1998), Woods (2000)

- OPLS-AA

- Jorgensen (1997), van Gunsteren (2000)



Anomeric Equilibrium



- glucose

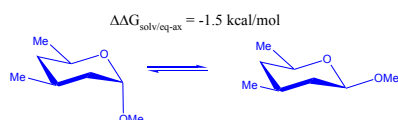
- Karplus JACS 1991 (+0.31 kcal/mol)

- xylose

- Karplus JACS 1996 (+0.15 kcal/mol)

Effect of Solvent Model

- anomeric equilibrium of model solute (tetrahydropyran derivative)



- reference interaction site model (RISM)

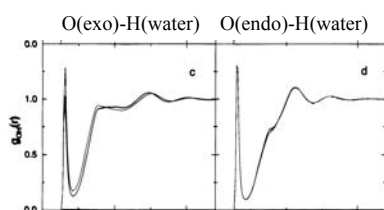
$$h_{\alpha\beta} = \sum_{\alpha'\gamma'} \omega_{\alpha'\alpha} c_{\alpha'\gamma'} \omega_{\gamma'\beta} + \rho \sum_{\alpha'\gamma'} \omega_{\alpha\alpha} c_{\alpha'\gamma'} h_{\gamma'\beta}$$

Differential Solvation Energies

Model	Method	$\Delta\Delta G_{\text{eq-ax}}$
DMT	calorimetry	-1.5
DMT	AM1/SM5.4	-0.6
DMT	PCM	-0.7
MTP	OPLS/FEP	-2.1
DMT	RISM/HNC	-1.7
DMT	RISM/GF	-1.7

Differential Solvation Energies (kcal/mol)

Differential Solvation Energies



- differential solvation mainly at exocyclic O

Biomolecular Interactions
- a conference dedicated to Peter A. Kollman

MGMS Annual International Meeting 2002
Wills Hall, Bristol, UK, April 3rd-5th 2002

Thursday April 4th

Chairman: Tom Simonson

9:00-9:35 Gernady Verkhivser L10 Computer simulations of biomolecular interactions: structure, energetics, dynamics and design of ligand-protein and protein-protein interfaces

9:35-10:10 Jonathan Essex L11 Small molecule docking to flexible proteins

10:10-10:35 Alexandra Villa L12 Applications of free-energy calculations in the investigation of biomolecular interactions

10:35-11:00 Coffee

Chairman: Kristin Eilbeck

11:00-11:35 Mike Gilson L13 Molecular recognition, modeling and informatics

11:35-12:10 John Mitchell L14 Predicting protein-ligand interactions

12:10-12:35 Paul Labute L15 High throughput conformational search

12:35-2:00 Lunch

Chairman: Peter Grodzinski

2:00-2:30 Alan Cooper L16 Microcalorimetry and modeling of the thermodynamics of biomolecular interactions

2:35-3:10 Richard Pezzitt L17 The temptations of inactivity

3:10-3:35 Chris Murray L18 Structural screening for the identification of enzyme inhibitors

3:35-4:00 Tea

Chairman: Guy Grant

4:00-4:35 Steve Homans L19 Structure, dynamics and thermodynamics of biomolecular interactions probed by high resolution NMR

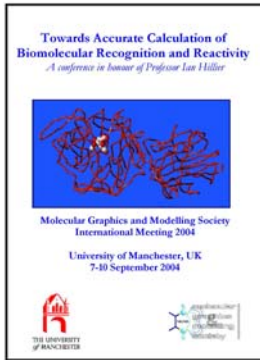
4:35-5:00 David J. Chipchase L20 A physics-based potential model for ab initio protein folding: lessons from CASP4

5:00-5:25 Ray Luo L21 Accelerated protein folding simulation by combining Poisson-Boltzmann continuum solvent and self-guided forces: application to folding of small protein domains

5:25-7:00 MGMS AGM

7:00-7:15 Transport to ss Great Britain (coaches leave at 7:00 pm and 7:15 pm)

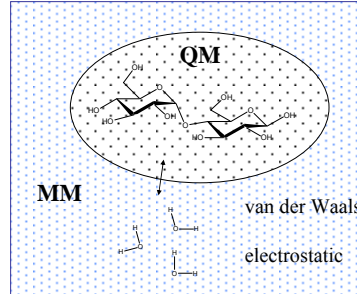
Evening Conference Dinner on board the ss Great Britain, sponsored by Chemical Computing Group, Inc. Preceded by Reception on board sponsored by Accelrys, Inc. (Coaches leave ss Great Britain at 11:00 pm and 11:15 pm.)



PROGRAMME

Tuesday 7th September
 12:00-2:00 Registration
 12:45-2:00 Lunch
 3:00-4:30 *Biomolecular Reactivity I*
 Chair: MB Hill
 3:00-3:15 RA Brown "Opening remarks"
 3:15-3:30 MJ Field "QM/MM studies of enzyme reactions"
 3:30-3:45 IH Hillier "Challenges in modelling enzyme catalysis"
 3:45-3:55 JH Williams "Computational mechanistic enzymology: modelled O-methyltransferase"
 3:55-4:10 Coffee
 4:10-4:40 Q Gu "Theoretical analysis of mechanochemical coupling in enzymes"
 4:45-5:20 CA Reynolds "Including polarization in QM/MM"
 5:25-5:45 IH Gould "Rigger: a hybrid exploration of the photosynthetic process in light harvesting centres of purple bacteria"
 7:00 Evening meal
 Wednesday 8th September
 9:20-9:35 *Biomolecular Reactivity II*
 Chair: IH Hillier
 9:20-9:35 MB Hill "Modelling metalloenzymes: nickel-iron and iron-only hydrogenases"
 9:35-10:10 J Gu "Dynamics, pathways and tunnelling: a computational perspective of enzyme catalysis"
 10:10-10:25 U Ryde "Active geometries and energies for metalloproteins estimated by QM/MM methods"
 10:25-10:40 Coffee
 10:40-11:15 KT Douglas "Rational, structure-based design of molecular diagnostics based on enzymes assembled in three dimensions by a biological virus"
 11:15-12:00 JD Hirst "Quantum biochemistry"
 12:00-12:15 MP Gagan "Infrared spectroscopy with ab initio molecular dynamics simulation"
 12:45-2:00 Lunch
 3:00-4:30 *Biomolecular Recognition I*
 Chair: WJ Porymon
 3:00-3:15 BC Wade "Predicting protein binding specificity"

Hybrid QM/MM Methods



$$E_{tot} = E_{QM} + E_{QM/MM} + E_{MM}$$

$$= \langle \Psi_0 | \hat{H}_{QM}^{elec} - \sum_{I_i} \frac{Q_i}{r_{I_i}} | \Psi_0 \rangle + E_{QM}^{vac}$$

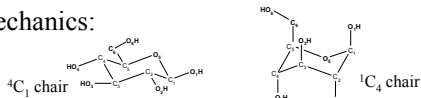
$$+ E_{QM/MM} + E_{QM/MM}^{vac} + E_{QM/MM}^{ind} + E_{MM}$$

$$V_{\mu\nu}^{chg} = -\sum_i Q_i \langle \mu | r_i^{-1} | \nu \rangle$$

$$E_{QM/MM}^{elec} = 2 \sum_{\mu\nu} D_{\mu\nu} V_{\mu\nu}^{chg}$$

Subtle Conformational Energetics

- Quantum mechanics:



Conf	comp	MP2/ 6-31G*	MP2/cc- pVDZ	MP2/cc- pVTZ ^b	B3LYP/ 6-31G*	B3LYP/ 6-31+G*	HF/ 6-31G*
⁴ C ₁	0.00	0.00	0.00	0.00	0.00	0.00	0.00
⁴ C ₁	0.27	-0.45	-0.50	0.07	-0.70	-0.12	-0.15
¹ C ₄	6.41	0.66	-0.11	4.13	1.65	6.92	6.73
¹ C ₄	6.99	-0.60	-0.81	3.65	-0.60	4.93	6.76

Barrows et al. *Carbohydr. Res.* **1995**, 276, 219

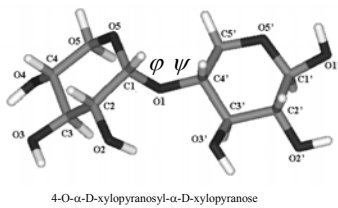
Semi-empirical methods

- PM3 applied to carbohydrates:
 - Woods et al., *Chem. Comm.* 1991
 - Cramer & Truhlar, *JACS* 1993, 1994
 - PM3 also overstabilises ¹C₄
- cf. condensed phase calculations using QM/MM approach:
 - treat carbohydrate solute *via* PM3 Hamiltonian
 - treat solvent using TIP3P force field

Conf	comp	PM3
⁴ C ₁	0.00	0.00
⁴ C ₁	0.27	-1.50
¹ C ₄	6.41	-0.90
¹ C ₄	6.99	2.30

Molecular Dynamics

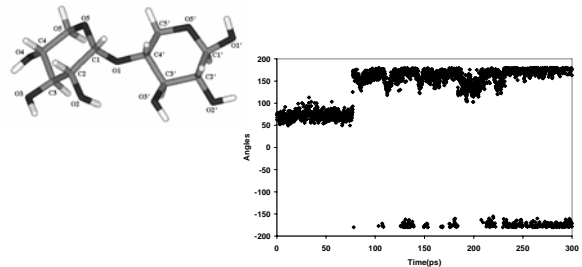
- PM3/TIP3P dynamics of dixylose



4-O- α -D-xylopyranosyl- α -D-xylopyranose

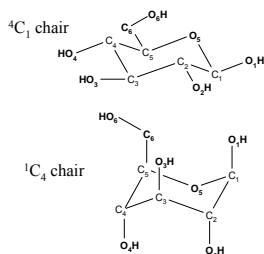
Molecular Dynamics

- PM3/TIP3P dynamics of dixylose



1C_4 Global Minimum

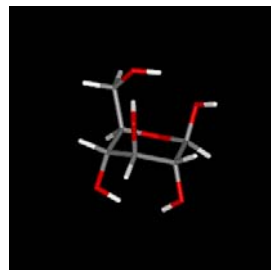
- pyranose ring conformation (Barrows et al., 1995)



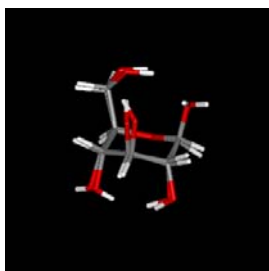
Conf	B3LYP	PM3
${}^4C_1/cc/tg$	0.00	0.00
${}^1C_4/cc/gg$	9.48	1.44
${}^1C_4/cc/g^-g^-$	8.77	0.82
${}^1C_4/cl/g^-g$	8.69	-2.43

${}^1C_4/\beta/cl/g^-g$

- underestimation of H-H repulsion



cf B3LYP Structure



Semi-empirical Theory

- minimal basis in field of nuclear cores
- neglect/parametrize integrals of Hamiltonian
 - Neglect of Diatomic Differential Overlap (NDDO) approximation

$$(\mu\nu | \lambda\sigma) = (\mu^A \nu^A | \lambda^B \sigma^B)$$

$= 0$ if μ, ν not both on A
 $= 0$ if λ, σ not both on B
 no 3 or 4 centre integrals

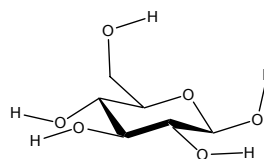
- used in MNDO, AM1, PM3
- developed to handle "large" systems
- limited use, as difficult to identify systematic errors
- poor treatment of weak interactions (H-bonds and dispersion)

Semi-empirical Methods

- Specific Reaction Parameters (SRP)
 - Rossi & Truhlar, *Chem. Phys. Lett.* 1995
 - fitted parameters for H, C, Cl to structure and energetics of *ab initio* QM calculations
- fit to *ab initio* energies/geometries cf. a force field
 - fit H and O parameters
 - require training set

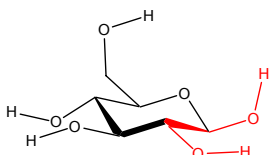
SRP for Carbohydrates

- base on fitting to small representative molecules

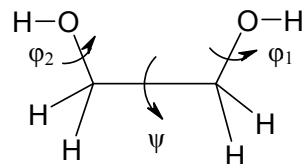


SRP for Carbohydrates

- base on fitting to small representative molecules



Ethanediol Conformations

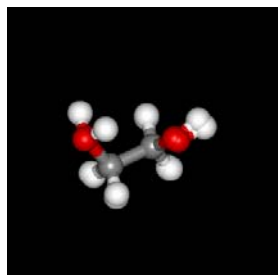


10 unique conformers

Ethanediol Energetics

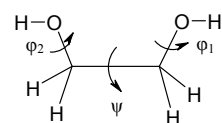
• intramolecular hydrogen bond (Cramer & Truhlar, 1994)

Conf	MP2	AM1	PM3
g^-Gg^-	1.19	-0.98	-0.78
gGg	3.15	-0.98	-0.82
gGg^-	0.30	-0.88	-1.39
gTg	3.00	0.39	-0.43
gTg^-	2.81	0.20	-0.67
tGg	3.81	2.56	1.76
tGg^-	0.00	0.00	0.00
tGt	3.48	3.19	-0.78
tTg	2.92	1.55	1.07
tTt	2.87	2.98	2.56



1,2-Ethanediol Conformers

Conf	MP2	AM1	PM3	PM3CARB-1
g^-Gg^-	1.19	-0.98	-0.78	1.45
gGg	3.15	-0.98	-0.82	1.75
gGg^-	0.30	-0.88	-1.39	1.10
gTg	3.00	0.39	-0.43	2.87
gTg^-	2.81	0.20	-0.67	2.50
tGg	3.81	2.56	1.76	3.63
tGg^-	0.00	0.00	0.00	0.00
tGt	3.48	3.19	-0.78	2.56
tTg	2.92	1.55	1.07	2.40
tTt	2.87	2.98	2.56	2.23



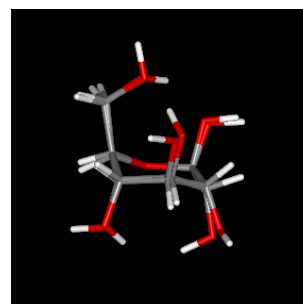
•RMS error in energy = 0.57 kcal/mol (PM3 = 2.56 kcal/mol)
•RMS error in structure = 6.5 deg (PM3 = 11.6 deg)

β -glucopyranose

• improved ranking of ring conformers

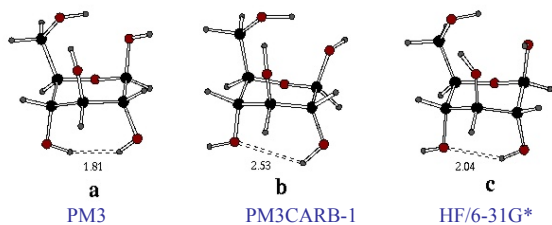
Conf	B3LYP	PM3	PM3CARB-1
${}^4C_1/cc/tg$	0.00	0.00	0.00
${}^1C_4/cc/gg$	9.48	1.44	6.52
${}^1C_4/cc/g^-g^-$	8.77	0.82	6.31
${}^1C_4/cl/g^-g^-$	8.69	-2.43	4.73

β -glucopyranose



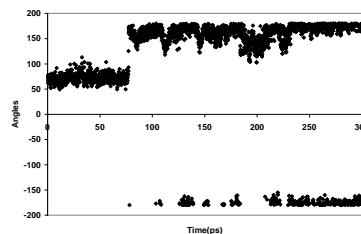
β -glucopyranose

- improvement in structure



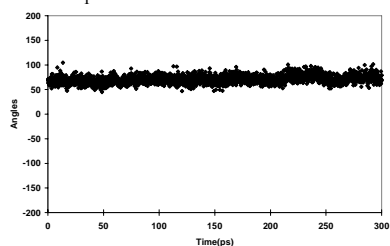
QM/MM Molecular Dynamics

- PM3/TIP3P dynamics of dixylose



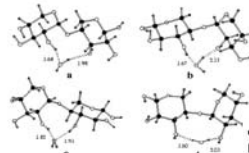
QM/MM Molecular Dynamics

- PM3CARB-1/TIP3P dynamics of dixylose
- stable 4C_1



Modelling carbohydrate dynamics

- oligosaccharides can adopt different conformations
- large conformational space
 - complex conformational transitions
 - sufficient to describe by a single TS, pathway?

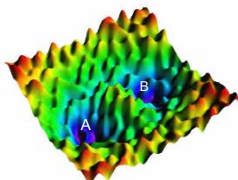


molecular graphics & modelling society 18th international meeting
modelling biomolecular mechanism

from states to processes, at the atomic level
a meeting focused on biomolecular processes, showcasing advances in modelling and experimental methods that address mechanisms in structure-function relationships

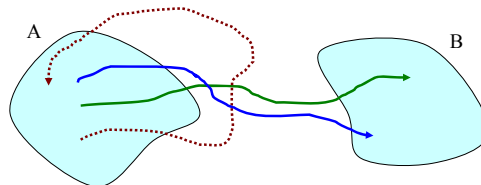
Transition Path Sampling

- generates *ensemble* of transition pathways and transition states
 - developed by Chandler to study transition events in complex systems
 - models conformational or reactive transitions without assumption of specific reaction coordinates



Generation of the TP Ensemble

- apply Metropolis importance sampling to bias towards transitional trajectories



TPS Moves

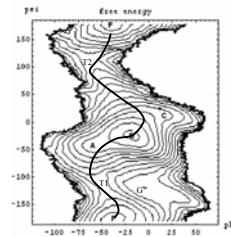
- Shooting

- perform small modification of velocities of transitional configuration
- then shoot forwards/backwards in time



- Shifting

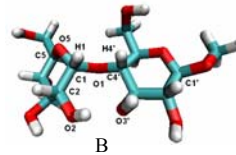
- perform small translation of existing transitional trajectory in time
- then complete trajectory by integrating forwards or backwards as necessary
- in both move types, accept move if it connects desired minima



Model Disaccharide: Methyl β -Maltoside

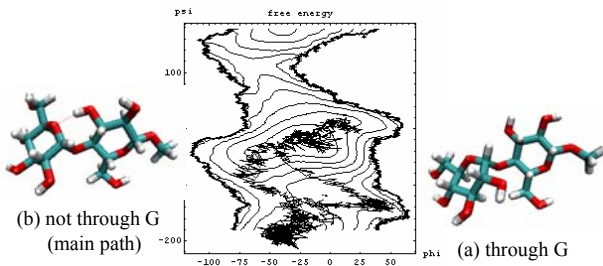
in vacuo $\phi\psi$ potential of mean force

- consider transition between conformations B (-20°, -20°) and F (-40°, -180°)
- “G” plateau
- two MEPs for B→F
- ΔG barriers are 7 and 11 kcal/mol



TPS of Negative ψ Route

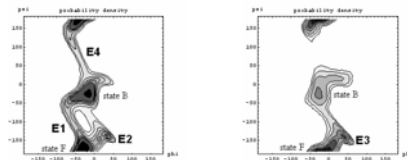
- two types of transition path detected



Importance of the O5...H-O3' Hydrogen Bond for Pathway

- computer experiments:

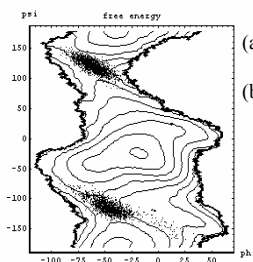
- E2: constrain paths to travel through G
- E3: switch off electrostatics of O5/H-O3' interaction



- none of E2 had the hydrogen bond; all E3 passed through G

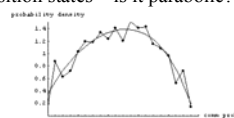
Transition State Ensembles

- committor probability = 0.5



Two ways to check $\phi\psi$ as coordinates for main path:

- compare location of TS ensemble to PMF transition states on $\phi\psi$ map
- calculate committor probability profile in locality around PMF transition states - is it parabolic?



Rate of B to F transition

- From transition state theory and PMF
 - $k = 4 \times 10^7 \text{ s}^{-1}$
- From TPS
 - $k = 6 \times 10^6 \text{ s}^{-1}$
 - *ie.* one transition every 160 ns
 - rate calculation takes 25x effort of PMF
 - generation of a TP ensemble is 2.5x PMF

Conclusions

- TPS detected an extra B to F route
- TPS and PMF confirms $\phi\psi$ are reasonable coordinates for the B to F transition *in vacuo*
- Challenges
 - aqueous phase more difficult – diffusive
 - methods rely upon good potential energy functions for carbohydrates
- Future
 - potential to combine TPS and umbrella sampling for studying large-scale changes (*cf.* protein-DNA interactions, Schlick 2004)



The image shows a poster for the MGMS International Meeting 2005, held at Trinity College Dublin. The poster features a central illustration of a classical building with a dome, surrounded by greenery. Logos for the principal sponsor (SFI), poster sponsors (OCF, CHEMICAL COMPUTING GROUP, and THE ILLIUMINATE), and the meeting title "Biomolecular Simulations - From Prediction to Practice" are visible. To the right of the poster is a detailed program for Wednesday 14th September, listing sessions, chairs, speakers, and topics.

Time	Activity	Speaker/Chair	Topic
14:45	COFFEE & TEA, Posters and Exhibitors	Osman Güner (Accelrys, USA)	"Use and evolution of pharmacophore tools in drug discovery"
15:30	Session 10	Chair: Amir Khan	
15:45		Tony Watts (University of Oxford, UK)	"Simulation of drug target interactions and activation for membrane receptors to validate solid state NMR"
16:30		Mike Hana (Glaxo-Smithkline, UK)	"What we can not do in computational chemistry in support of drug discovery"
17:15-18:00	Posters open for final viewing / judging		
19:00	Conference Banquet	College Dining Hall, Front Square	
Wednesday 14th September			
09:30	Session 11	Chair: Paul Lyne	
09:30		Brian Sholet (UCSF, USA)	"Model systems for docking and virtual screening"
10:15		Vladimir Sobolev (Weizmann Institute, Israel)	"Surface complementarity in molecular recognition"
11:00	TEA & COFFEE and Exhibitors		
11:15	Session 12	Chair: Paul Lyne	
11:15		Mike Thorpe (Arizona State University, USA)	"Flexibility and mobility in biomolecules"
12:00		Diane Joseph-McCarthy (Wyeth, USA)	"Virtual screening for lead discovery and optimization"
12:45	End of Conference, Award of Poster Prizes		

Acknowledgements

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