Potencials de força mitja i coordenades de reacció en l'enzim Mandelat Racemasa

Reunió de grup

10 de desembre de 2003

Sumari

Introducció:
camins de reacció i un passeig per la bibliografia

Potencials de força mitja
Umbrella Sampling i WHAM

Mandelat Racemasa
La reacció
Els resultats previs
El model teòric

Resultats amb diferents coordenades de reacció

Introducció: camins de reacció

Fase gas (sistemes petits): MEP o IRC sobre PES
 Càlculs de G sobre el MEP (sovint "únic") i
 "al voltant" de punts estacionaris

Fase condensada: molts MEP paral.lels(que no idèntics)
Cal comptar tots els camins accessibles a una T donada.
Com que no hi ha un únic MEP cal trobar un descriptor
que ens serveixi de coordenada de reacció
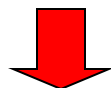
Cal saber *a priori* <u>COM</u> té lloc la reacció

Introducció: camins de reacció

On the calculation of reaction rate constants in the transition path ensemble

Christoph Dellago, Peter G. Bolhuis, and David Chandler
Department of Chemistry, University of California, Berkeley, California 94720

We present improved formulas for the calculation of transition rate constants in the transition path ensemble. In this method transition paths between stable states are generated by sampling the distribution of paths with a Monte Carlo procedure. With the new expressions the computational cost for the calculation of transition rate constants can be reduced considerably compared to our original formulation. We demonstrate the method by studying the isomerization of a diatomic molecule immersed in a Weeks–Chandler–Andersen fluid. The paper is concluded by an efficiency analysis of the path sampling algorithm. © 1999 American Institute of Physics.
[S0021-9606(99)50513-8]

ARTICLES

A concerted variational strategy for investigating rare events

Daniele Passerone, Matteo Ceccarelli, and Michele Parrinello
CSCS-Centro Svizzero di Calcolo Scientifico, via Cantonale, CH-6928 Manno, Switzerland
and Physical Chemistry ETH, Hönggerberg HCI, CH-8093 Zurich, Switzerland

A strategy for finding transition paths connecting two stable basins is presented. The starting poir is the Hamilton principle of stationary action; we show how it can be transformed into a minimur principle through the addition of suitable constraints like energy conservation. Methods fo improving the quality of the paths are presented: for example, the Maupertuis principle can be use for determining the transition time of the trajectory and for coming closer to the desired dynami path. A saddle point algorithm (conjugate residual method) is shown to be efficient for reaching "true" solution of the original variational problem. © 2003 American Institute of Physics.
[DOI: 10.1063/1.1533783]

Exploring reaction paths on potential of mean force surfaces

Guohui Li, Qiang Cui*

Department of Chemistry and Theoretical Chemistry Institute

University of Wisconsin, Madison

Biasing a transition state search to locate multiple reaction pathways

Baron Peters, WanZhen Liang, and Alexis T. Bell
Department of Chemical Engineering, University of California, Berkeley, California 94720

Arup Chakraborty[a]
Department of Chemical Engineering and Department of Chemistry, University of California, Berkeley, California 94720 and Materials Sciences Division and Physical Biosciences Division, Lawrence Berkeley National Laboratory, University of California, Berkeley, California 94720

A temperature-dependent nudged-elastic-band algorithm

Ramon Crehuet[a] and Martin J. Field
Laboratoire de Dynamique Moléculaire, Institut de Biologie Structurale, Jean-Pierre Ebel (CEA-CNRS), 41, rue Jules Horowitz, 38027 Grenoble Cedex 1, France

In this paper we present a method to introduce temperature corrections to a minimum-energy reaction path. The method is based on the maximization of the flux for the Smoluchowski equation and it is implemented using a nudged-elastic-band algorithm. We present the results of applying the algorithm to transitions in three systems—the three-well potential, the alanine dipeptide, and a molecular ratchet—and also remark on some points related to the location of temperature-dependent paths and the nature of the transition state. © 2003 American Institute of Physics.
[DOI: 10.1063/1.1571817]

On the use of the adiabatic molecular dynamics technique in the calculation of free energy profiles

Lula Rosso, Peter Mináry, and Zhongwei Zhu
Department of Chemistry, New York University, New York, New York 10003

Mark E. Tuckerman
Department of Chemistry and Courant Institute of Mathematical Sciences, New York University, New York, New York 10003

Reaction paths based on mean first-passage times

Sanghyun Park
Beckman Institute and Department of Physics, University of Illinois at Urbana–Champaign, Urbana, Illinois 61801

Melih K. Sener
Beckman Institute, University of Illinois at Urbana–Champaign, Urbana, Illinois 61801

Deyu Lu and Klaus Schulten[a]
Beckman Institute and Department of Physics, University of Illinois at Urbana–Champaign, Urbana, Illinois 61801

Potencials de Força Mitja:

És un cas particular d'energia lliure que depèn d'un grau de llibertat

$$W(R_c) = -RT \ln \rho(R_c) + C$$ *Kirkwood 1935*

On Rc pot ser una coordenada geomètrica (o combinació d'elles) o bé una coordenada de solvent (energètica) que descriu el progrés de la reacció.

Si el procés que descriu Rc és un "*rare event*" ($Ea > K_B T$) amb MD o MC lliure no conseguirem convergir la $\rho(Rc)$

L'umbrella sampling i el "free energy perturbation" són dos maneres de calcular el PMF convergint $\rho(Rc)$ "a trossos"

Potencials de Força Mitja: Umbrella Sampling (Valleau & Torrie 1974)

A l'energia QM/MM cal afegir-li un potencial d'esbiaix (bias) per ajudar el mostreig (sampling)
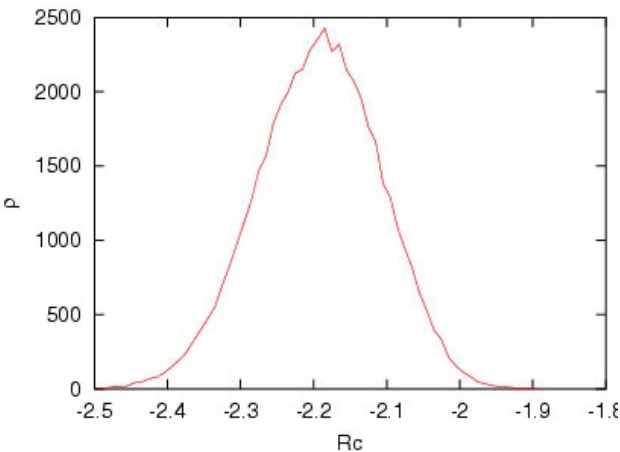
$$V_{tot} = V_{QM/MM} + k(Rc-Rc_0)^2 + P(Rc)$$

La $\rho(Rc)$ "esbiaixada" es calcula segons la següent expressió

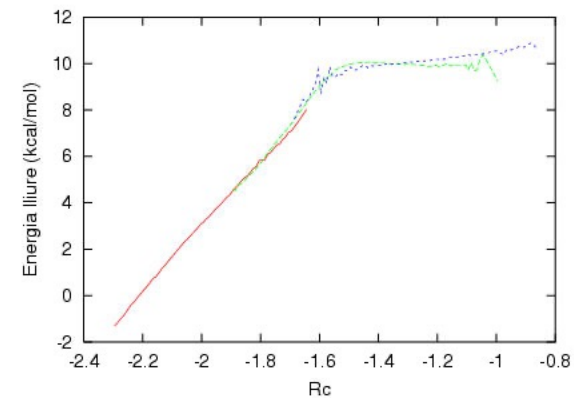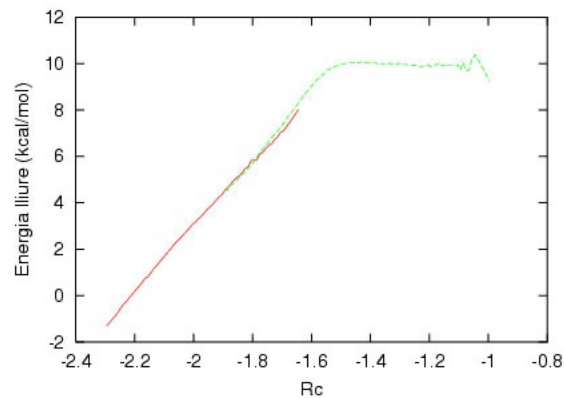$$\langle \rho(Rc_0) \rangle = \frac{\int \delta(Rc(r)-Rc_0)\exp[-V_{tot}(r)/K_BT]dr}{\int \exp[-V_{tot}(r)/K_BT]dr}$$
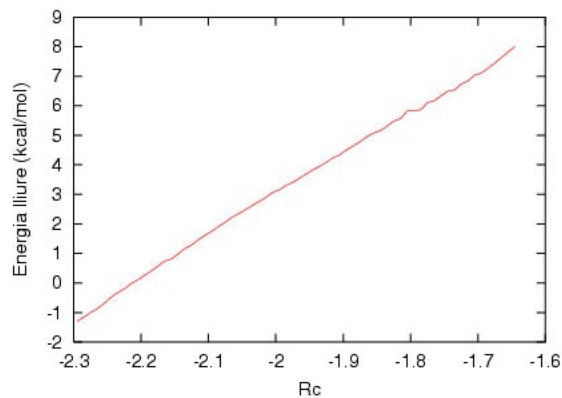
En aquest cas caldrà:

• Escombrar Rc per diferents valors (diferents "finestres" que se solapin)
• Desbiaixar (unbias) la $\rho(Rc)$
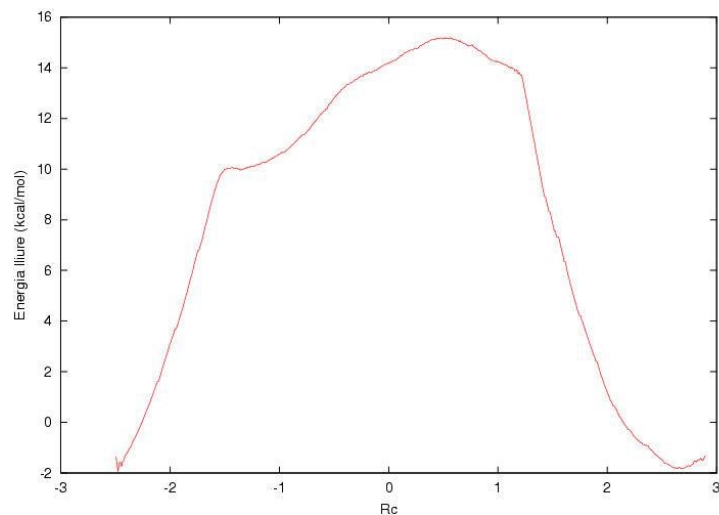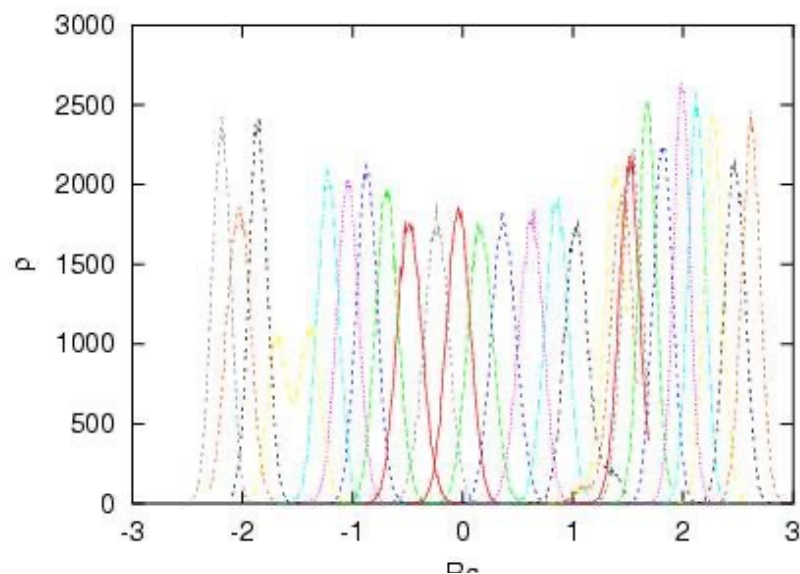• Combinar les diferents "finstres" (opció WHAM (Kumar *et al.* 1992))

Potencials de Força Mitja: Umbrella Sampling (exemple pràctic)
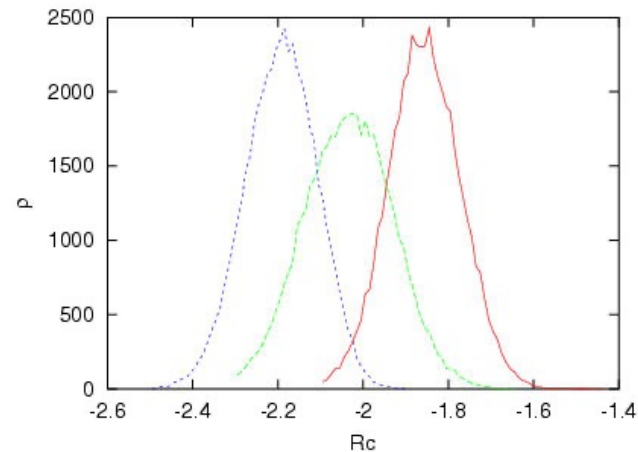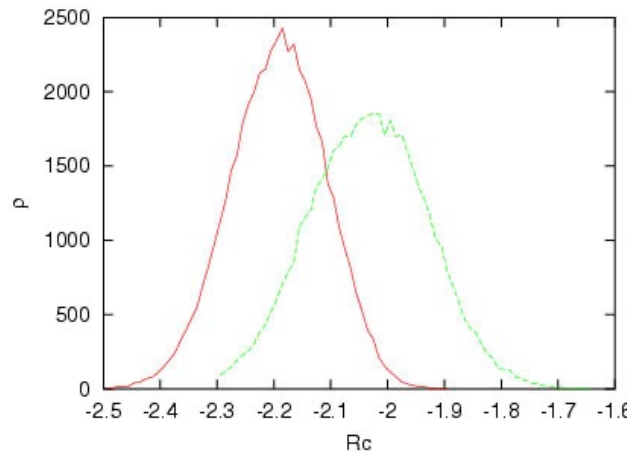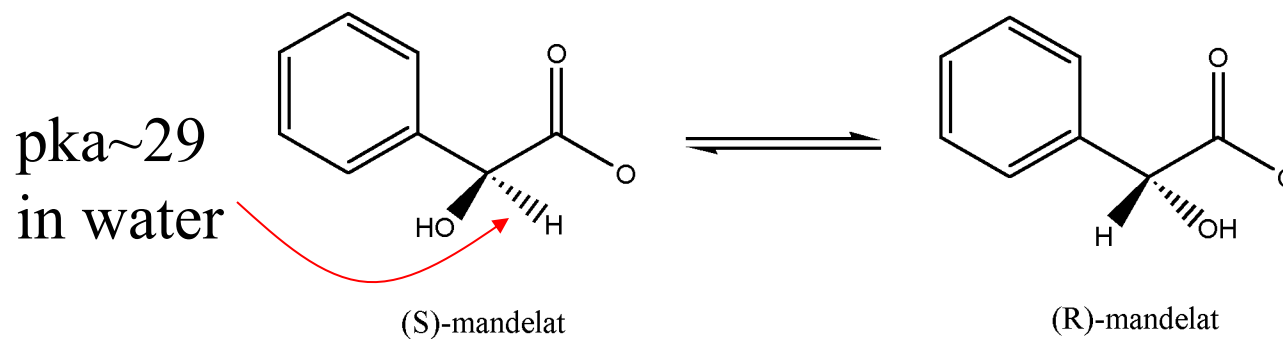

$$W(R_c) = -RT \ln \rho(R_c) + C$$

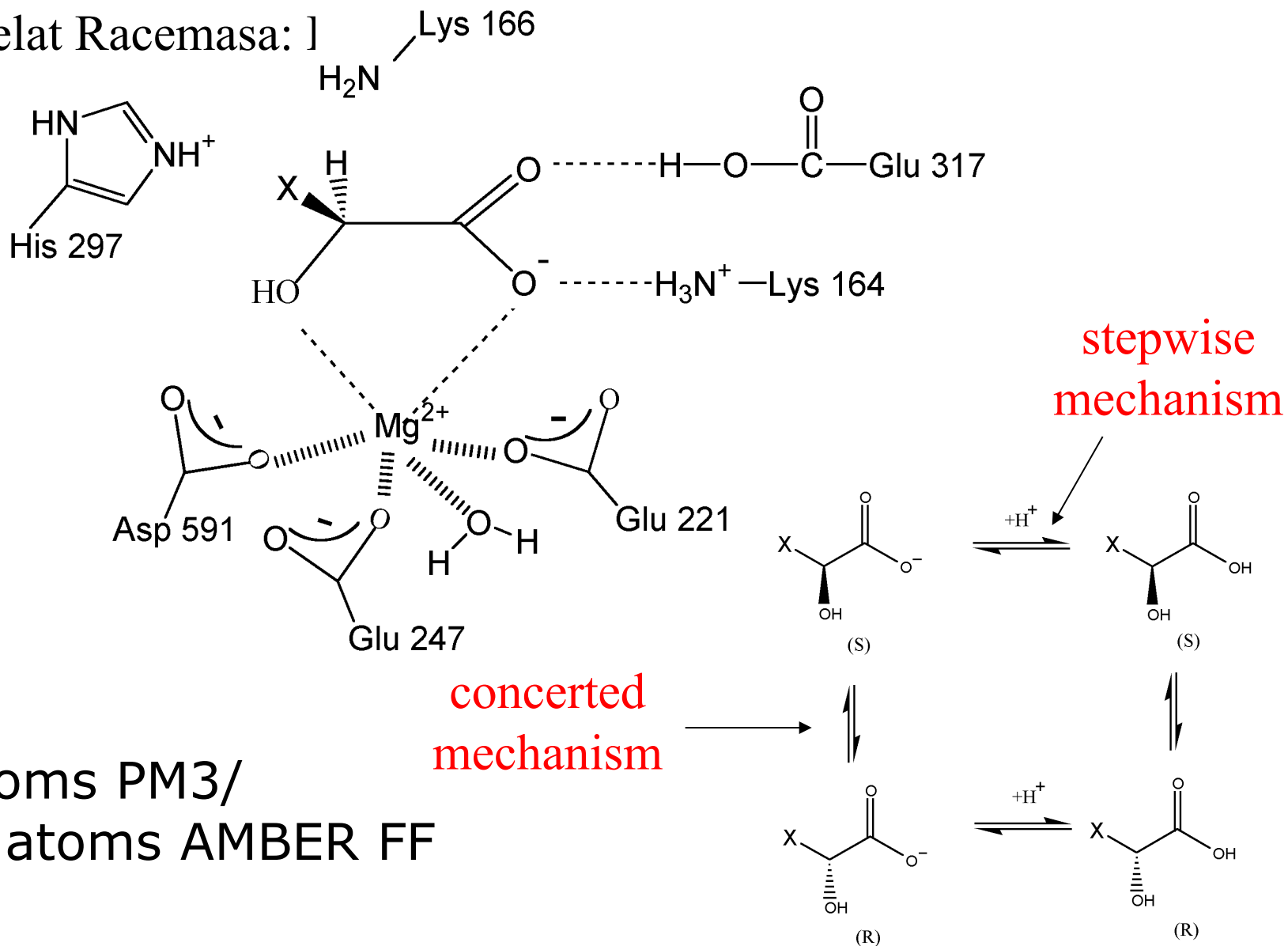Potencials de Força Mitja: Umbrella Sampling (exemple pràctic)

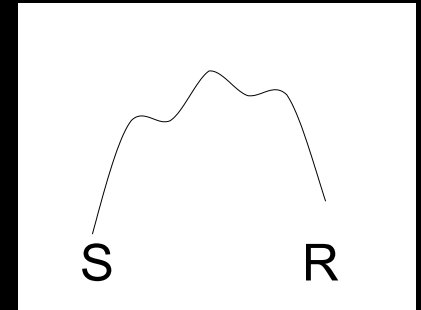$$W(R_c) = -RT \ln \rho(R_c) + C$$

Mandelat Racemasa: La reacció

pka~29
in water

(S)-mandelat   (R)-mandelat

Mandelat Racemasa:]

stepwise mechanism

concerted mechanism

88 atoms PM3/
4000 atoms AMBER FF

Mandelat Racemasa: Resultats Previs

Structure	Stepwise I	Stepwise II	Concerted
S	0.00	0.00	0.00
TS1	17.77 (18.24)	17.69 (17.78)	
TS2	19.52 (19.65)	14.77 (14.46)	
TS3	20.04 (20.06)	14.55 (14.95)	
TS4	22.54 (22.56)		20.19 (19.50)
TS5	25.15 (25.75)	23.57 (23.83)	
TS6	27.22 (27.28)	28.14 (28.18)	
R	6.74	6.74	4.63

Mandelat Racemasa: Model Teòric

His 297 · Lys 166 · H_2N · NH^+ · HN · X · H · HO · O · O · H—O—C—Glu 317 · O^- · H_3N^+—Lys 164
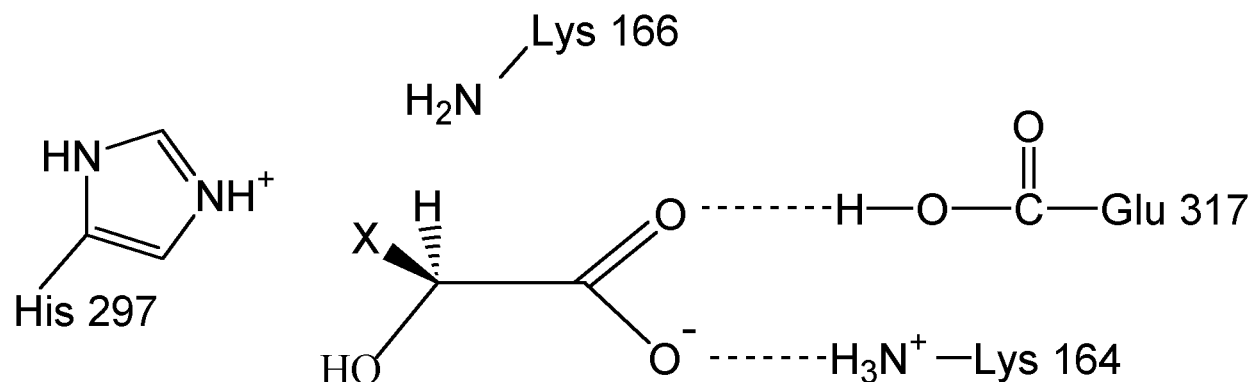
63 àtoms PM3-GHO / 8208 CHARMM
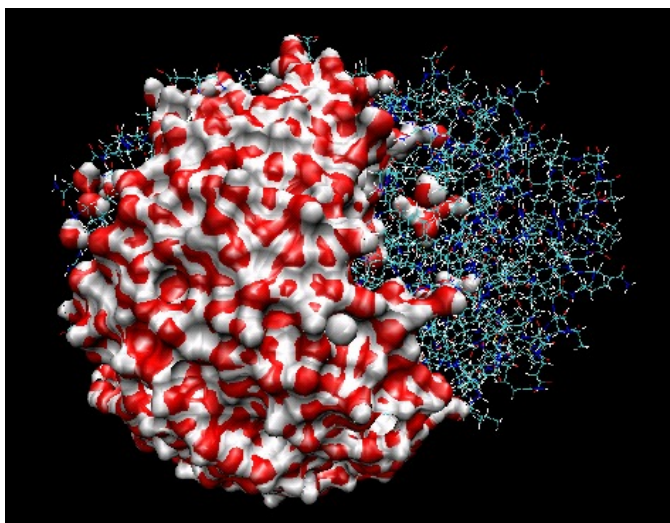
Stochastic Boundary MD
Esfera d'aigües de 24 Å

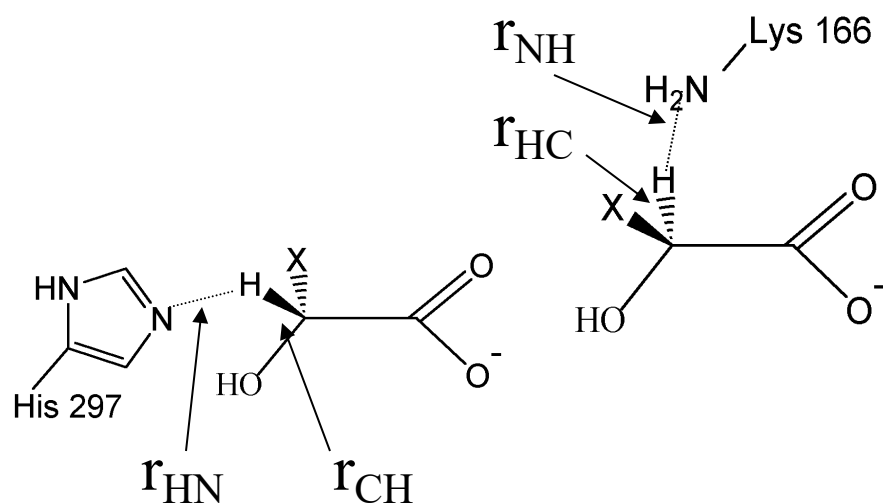0-20: zona de Newton MD

20-24: zona de Langevin MD
   fricció, restricció harmònica + stochastic

24-...: zona fixada

PMF: 15ps eq / 50ps sampling

1ps = 1000 energy & gradient

# Resultats: possibles coordenades de reacció

	N-H	HC	CH	HN
S	1.804	1.158	2.927	.995
Sts	1.194	1.522	2.865	.996
Is	1.151	1.570	2.845	.995
TS	1.011	2.258	2.093	1.013
Ir	1.005	2.612	1.607	1.117
Rts	1.004	2.736	1.509	1.200
R	1.004	2.868	1.165	1.772

	R(NHC)	R(CHN)	R(NHC-CHN)	R(HCH)	dNC	dCN	R(NCN)	Dihedre Θ	ΔE
S	-.646	-1.932	-2.578	-1.769	2.884	2.927	-.043	0.4217	0.0
Sts	.328	-1.869	-1.541	-1.343	2.645	2.865	-.220	0.4127	13.80808
Is	.419	-1.850	-1.431	-1.275	2.644	2.845	-.201	0.3984	13.78808
TS	1.247	-1.080	.167	.165	3.085	2.093	.992	-0.0576	19.46755
Ir	1.607	-.490	1.117	1.005	3.435	1.607	1.828	-0.3064	16.453998
Rts	1.732	-.309	1.423	1.227	3.566	1.509	2.057	-0.3116	16.752551
R	1.864	.607	2.471	1.703	3.708	1.165	2.543	-0.3501	4.611435

Resultats: coordenades simples

S $\longrightarrow$ R

$Rc = r_{HC} - r_{NH}$

R $\longrightarrow$ S
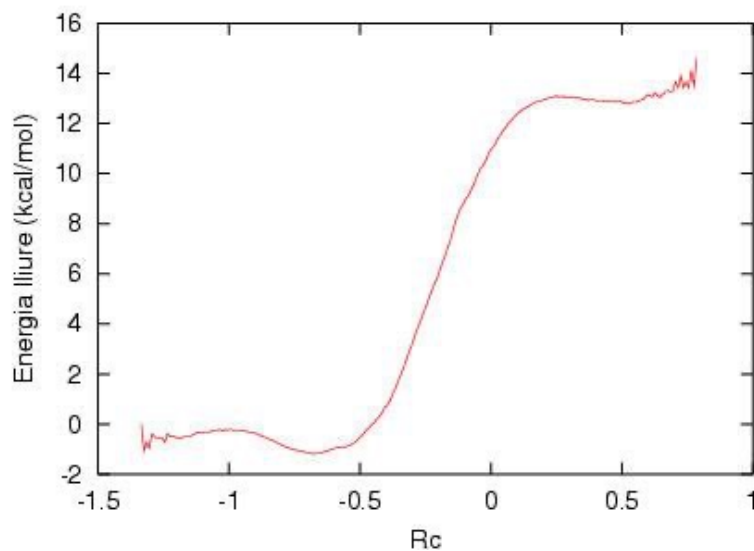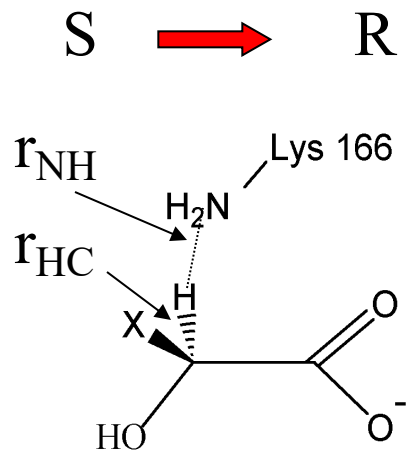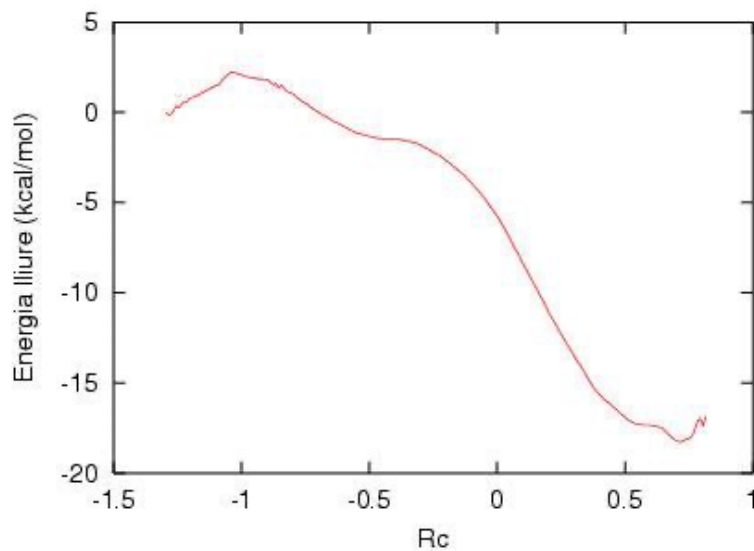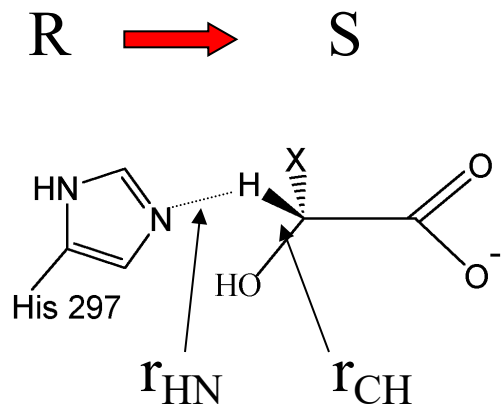
$Rc = r_{CH} - r_{HN}$

Resultats: coordenada doble

$$Rc = r_{HC} - r_{NH} + r_{CH} - r_{HN}$$
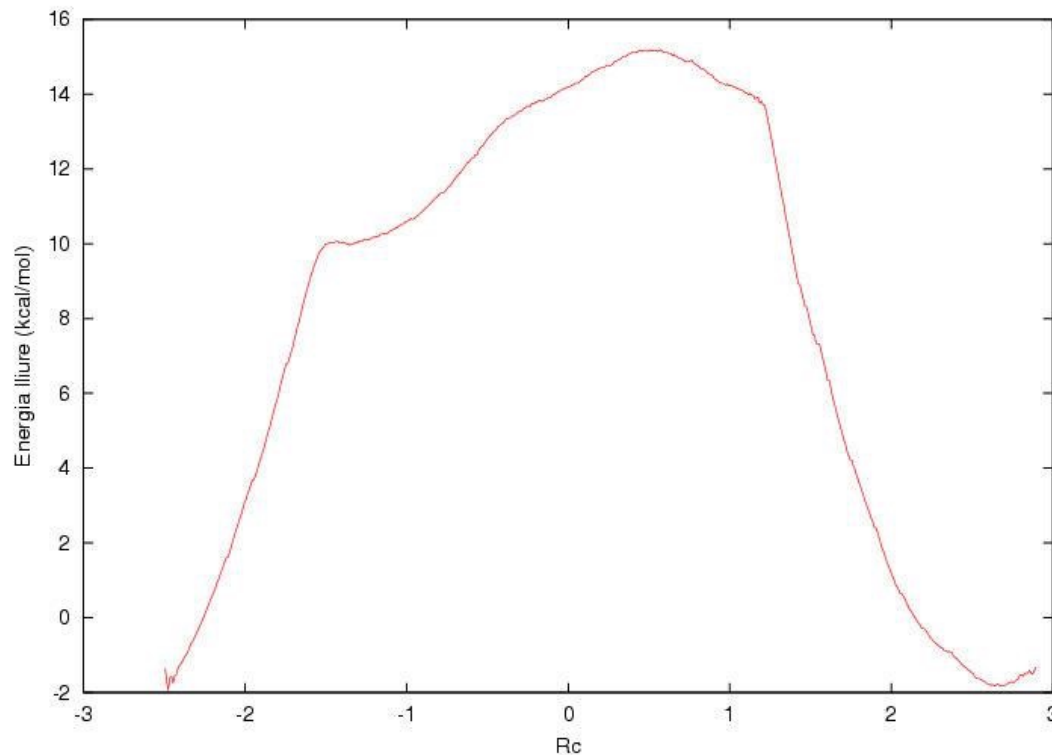
S ⟵ R

zona de His297 lliure   zona de Lys166 lliure

Resultats: conclusions preliminars

ajuda!

És necessari un càlcul de PMF o amb la PES n'hi ha prou?

Són quantitativament diferents els perfils amb diferents coordenades?
És un problema de l'escàs "sàmpling"?

Si estiguéssim en reaccions en dissolució on la coordenada
de reacció és més "col.lectiva" com ens ho fariem?

...de les simulacions de reaccions químiques

This is the notorious time scale gap problem (...)
It is not only a problem in chemical physics. For example
some comets exhibit rapid transitions between heliocentric
orbits inside and outside the orbit of Jupiter.
While the transition, during which the comet transiently
orbits jupiter for a few periods, is swift, many revolutions
of the comet around the sun can occur between transition.

D. Chandler
Transition Path Sampling:
Throwing Ropes Over Rough Mountain Passes,
in the Dark