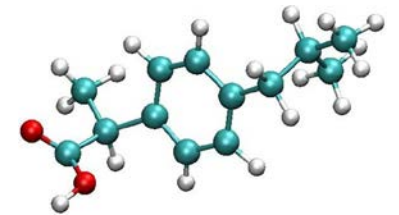
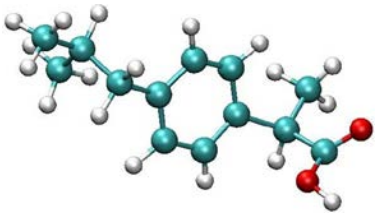


Journées VERRE 23-24 Novembre 2017 LILLE

Transition vitreuse et état vitreux dans les matériaux moléculaires: les "autres" verres !



F. Affouard

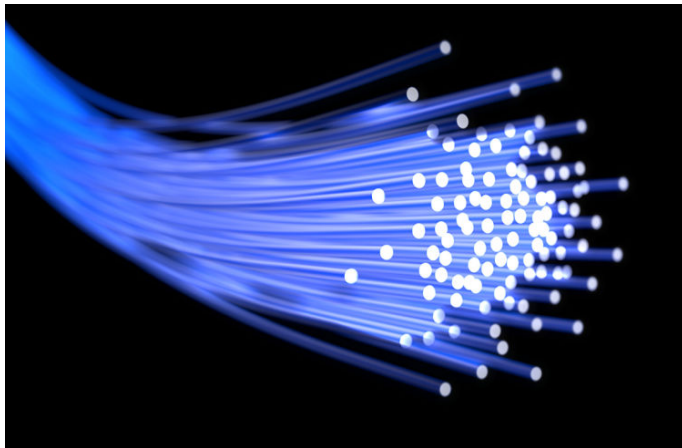
Unité Matériaux et Transformations (UMET)

Université Lille 1, Villeneuve d'Ascq

UMET
Unité Matériaux Et Transformations

 **Université
de Lille**
1 SCIENCES
ET TECHNOLOGIES

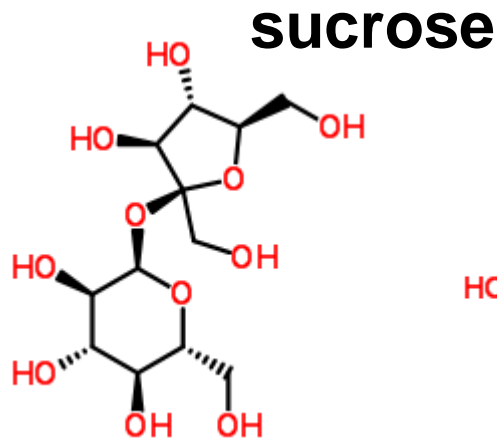
« des verres... »



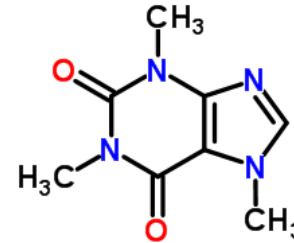
« et d'autres verres... »



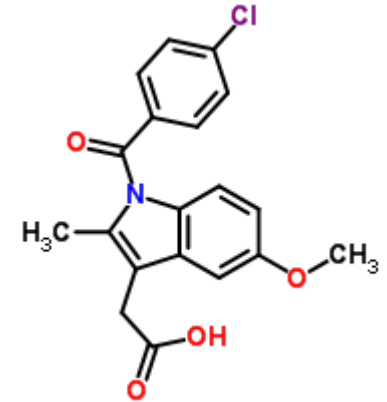
Petites molécules organiques (C, H, O, N):



caffeine



indomethacin



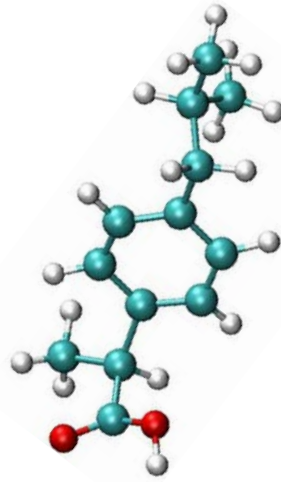
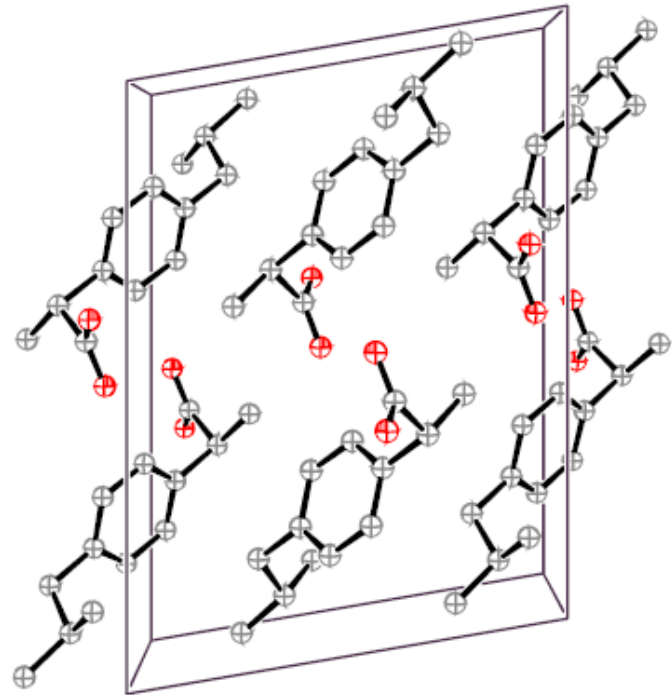
**Interactions intra- + inter-moléculaire
(covalente) (van der Waals +
liaison hydrogène)**

Degrés de liberté:

- translationnels
- orientationnels
- internes

Basse symétrie moléculaire

Basse symétrie cristalline

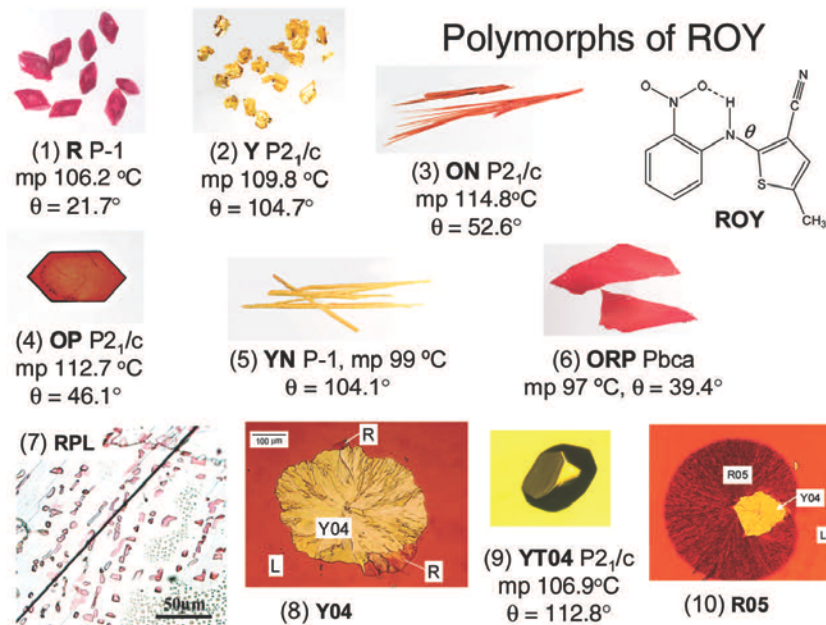


Ibuprofène $P2_1/c$

Symétrie	%
Triclinique	25.6
Monoclinique	52.0
Orthorhombique	17.3
Tetragonal	2.2
Trigonale	1.8
Hexagonale	0.5
Cubique	0.6

Cambridge Structural Database (CSD)
Janvier 2017
865,342 structures

POLYMORPHISME RICHE



Polymorphism in Molecular Solids: An Extraordinary System of Red, Orange, and Yellow Crystals

LIAN YU*

School of Pharmacy and Department of Chemistry, University of Wisconsin—Madison, 777 Highland Avenue, Madison, Wisconsin 53705

RECEIVED ON MARCH 4, 2010

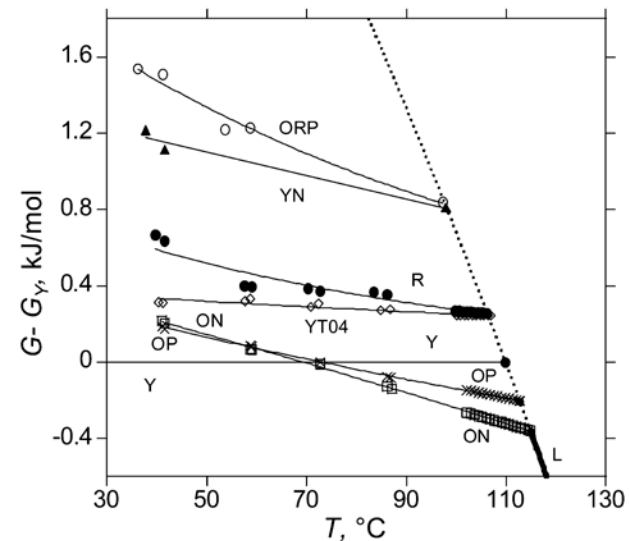


FIGURE 1. Polymorphs of ROY. The number 1–10 indicates the order of discovery. The polymorphs have different colors, *n* and molecular conformations (most pronounced in the torsional angle θ).

TABLE 1. Crystal Structures and Selected Properties of ROY Polymorphs^a

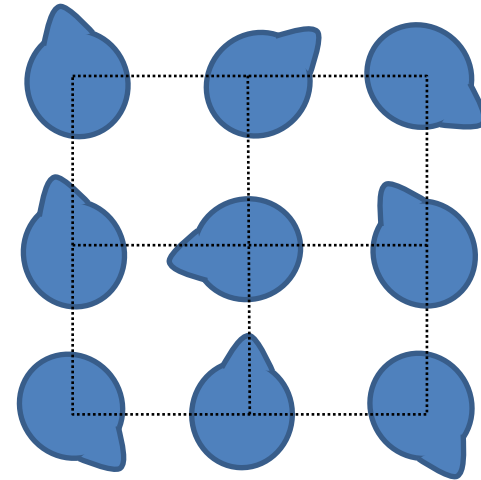
form	Y	YT04	R	OP	ON	YN	ORP
crystal system	monoclinic	monoclinic	triclinic	monoclinic	monoclinic	triclinic	orthorhombic
space group [No.]	<i>P</i> ₂ / <i>1</i> / <i>n</i> [14]	<i>P</i> ₂ / <i>1</i> / <i>n</i> [14]	<i>P</i> ₁ [2]	<i>P</i> ₂ / <i>1</i> / <i>n</i> [14]	<i>P</i> ₂ / <i>c</i> [14]	<i>P</i> ₁ [2]	<i>Pbca</i> [61]
description	yellow prism	yellow prism	red prism	orange plate	orange needle	yellow needle	orange-red plate
<i>a</i> , Å	8.5001	8.2324	7.4918	7.9760	3.9453	4.5918	13.177
<i>b</i> , Å	16.413	11.8173	7.7902	13.319	18.685	11.249	8.0209
<i>c</i> , Å	8.5371	12.3121	11.9110	11.676	16.3948	12.315	22.801
α , deg	90	90	75.494	90	90	71.194	90
β , deg	91.767	102.505	77.806	104.683	93.830	89.852	90
γ , deg	90	90	63.617	90	90	88.174	90
<i>Z</i>	4	4	2	4	4	2	8
<i>D</i> _{calc} , g cm ⁻³	1.447	1.473	1.438	1.435	1.428	1.431	1.429
θ (deg)	104.7	112.8	21.7	46.1	52.6	104.1	39.4
ν_{CN} , cm ⁻¹	2231	2224	2212	2226	2224	2222	2217
mp, °C	109.8	106.9	106.2	112.7	114.8	99	97
ΔH_m , kJ/mol	27.2	26.6	26.0	25.5	25.1	24.2	24.2
<i>H</i> – <i>H</i> _Y , kJ/mol ^b	0	0.9	1.4	1.9	2.6	3.0	4.1

MESOPHASES

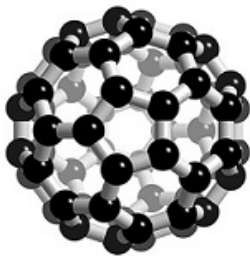
Degrés de liberté: {

- translationnels
- orientationnels

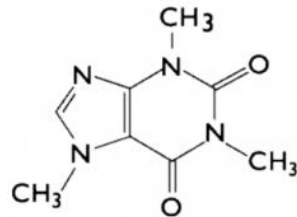
Cristaux plastiques ou à désordre d'orientation : ordre positions & désordre (dynamique) orientations



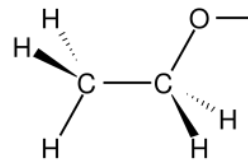
= C_{60} ,



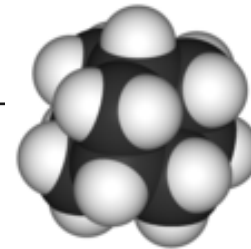
caféine,



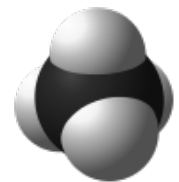
éthanol,



adamantane,

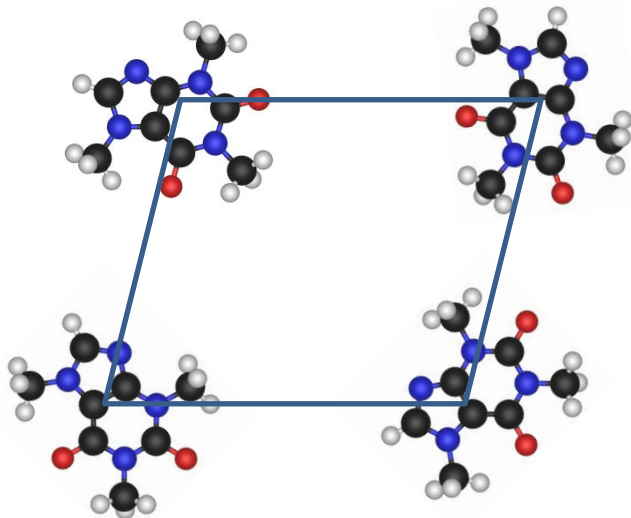
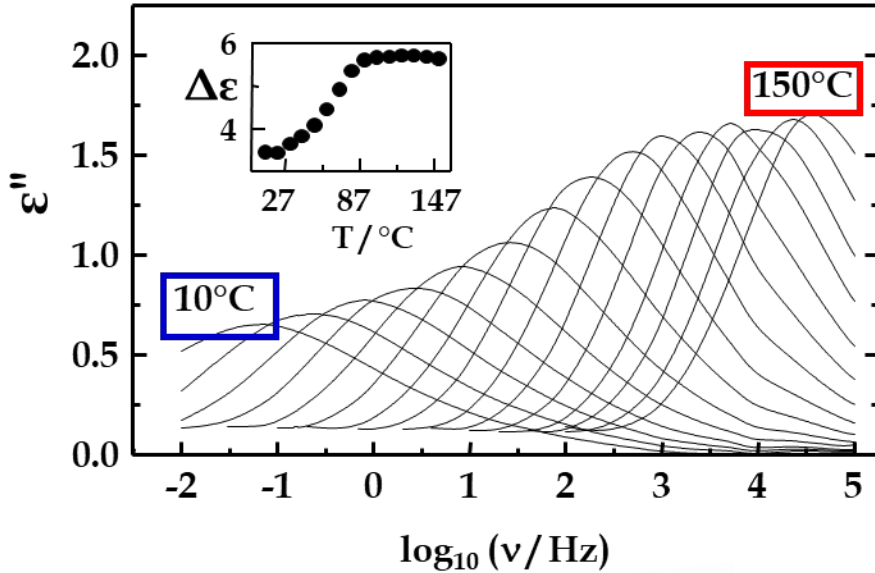


CH_4 , ...

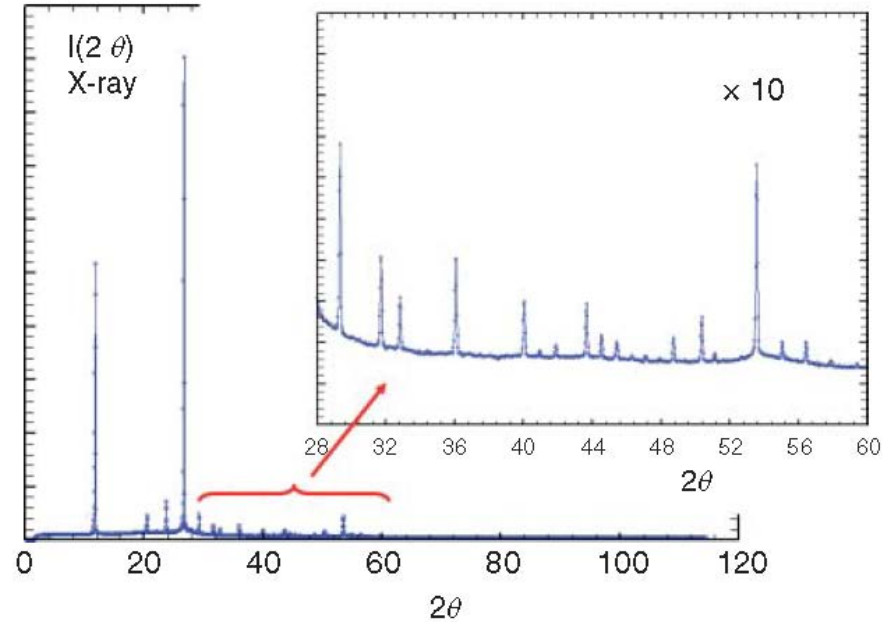


VITRIFICATION DES DEGRES DE LIBERTE ROTATIONNELS SEULEMENT : CAFEINE

Dynamique



Structure $\langle u^2 \rangle$ important

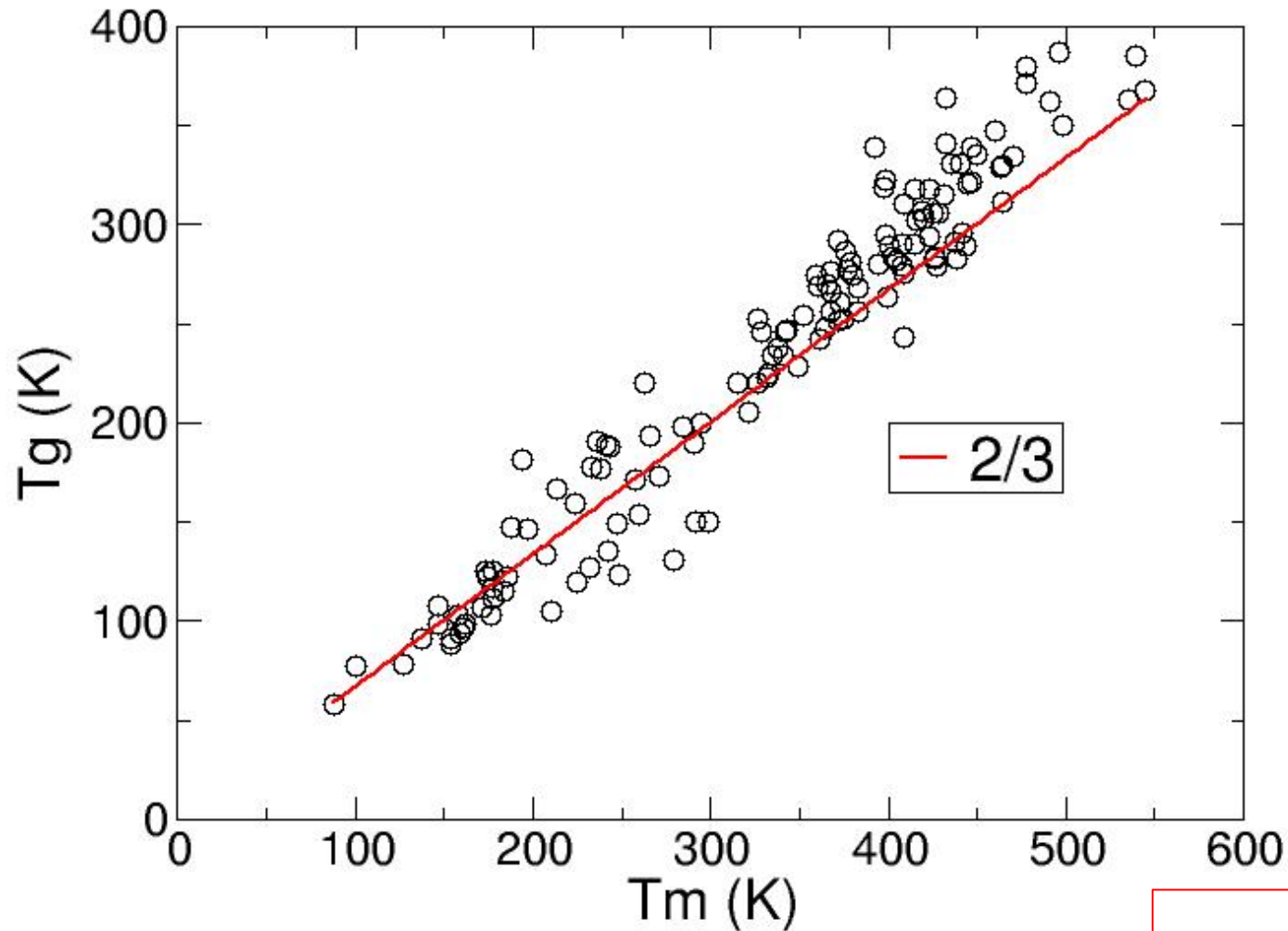


Transition vitreuse dans un cristal !

$$T_g(\tau \text{ rotation} = 100\text{s}) = -13^\circ\text{C}$$

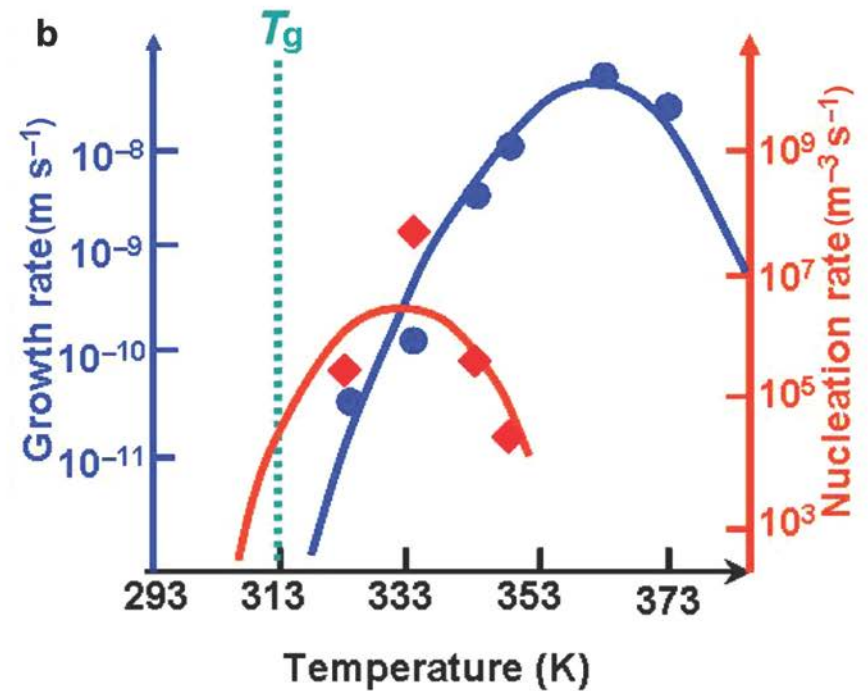
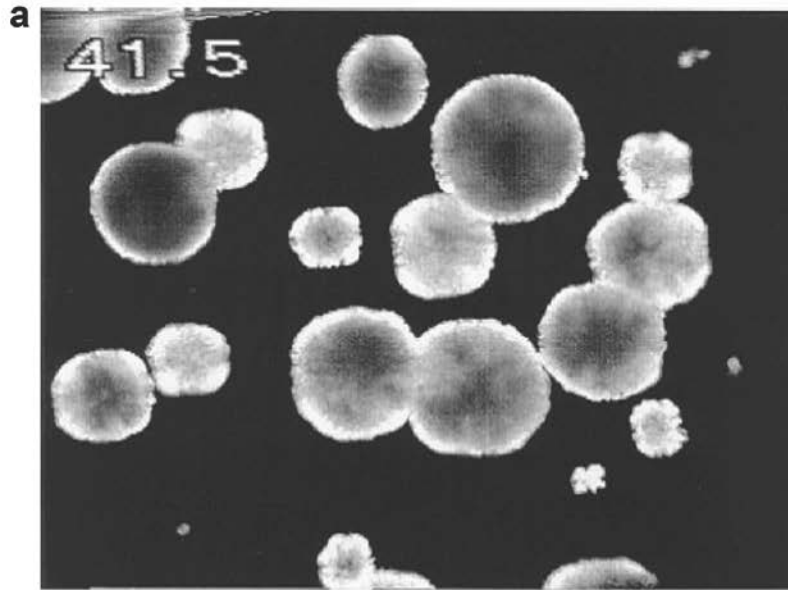
Descamps, Correia, Derollez, Danede, Capet
J. Phys. Chem. B, 109, 16092-16098 (2005)

T_g « bas », T_m « bas »

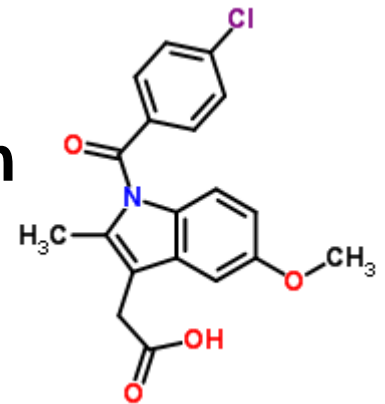


$$T_g \approx \frac{2}{3} T_m$$

NUCLEATION-CROISSANCE



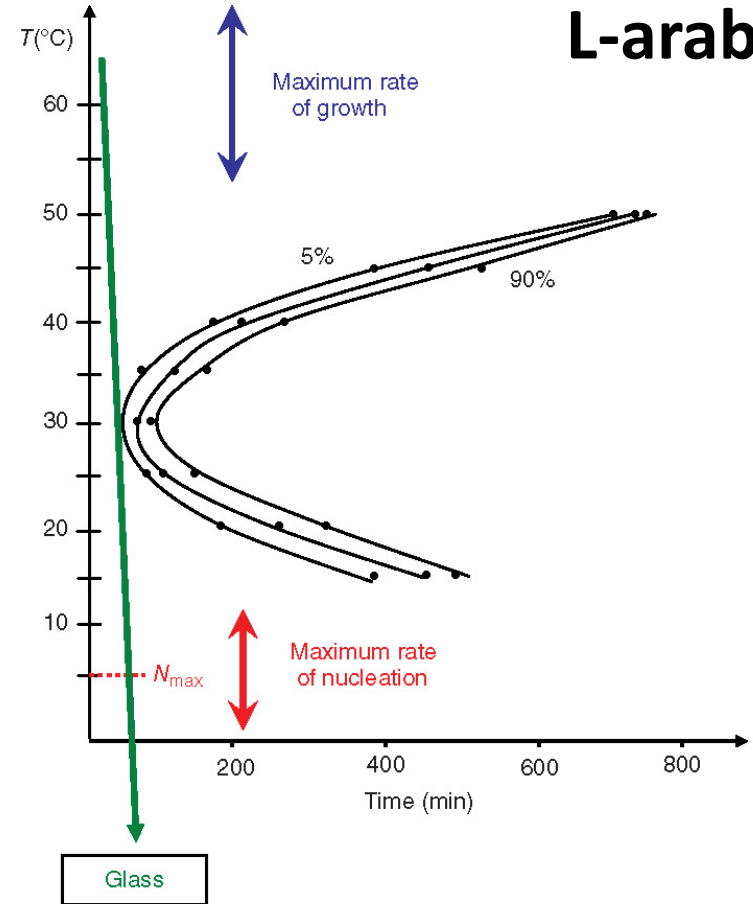
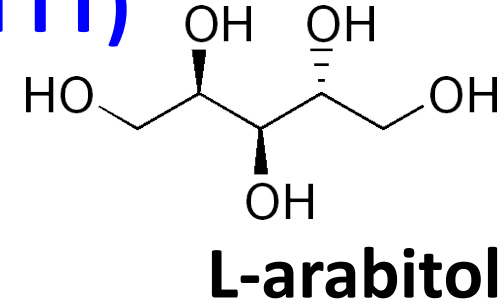
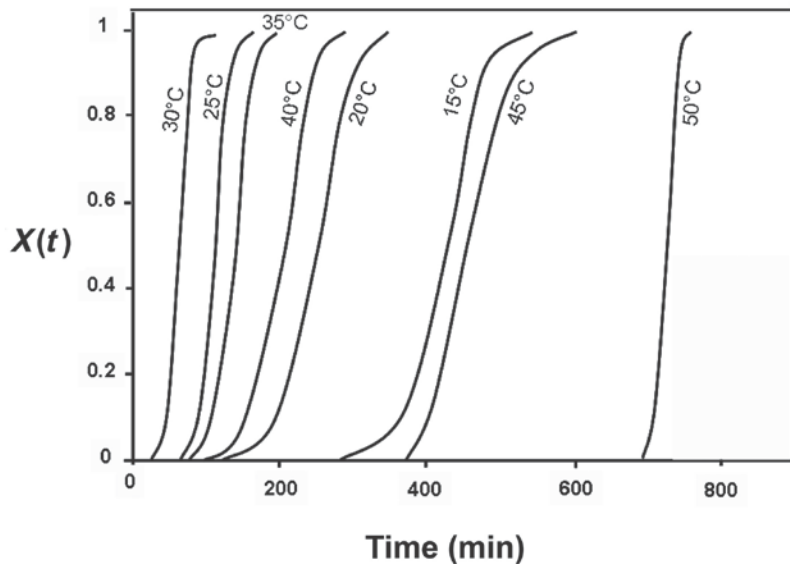
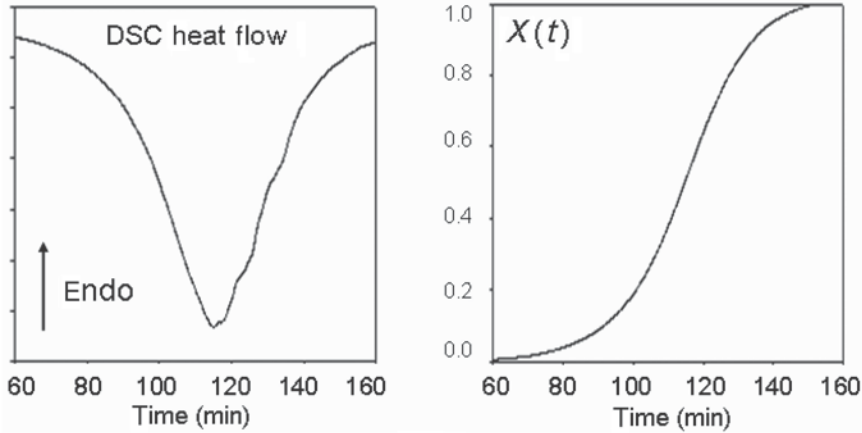
indomethacin



Andronis V, Zografi G. Crystal nucleation and growth of indomethacin polymorphs from the amorphous state. *J Non-Cryst Solids* 271 (2000) 236

Temps-Température-Transformation (TTT)

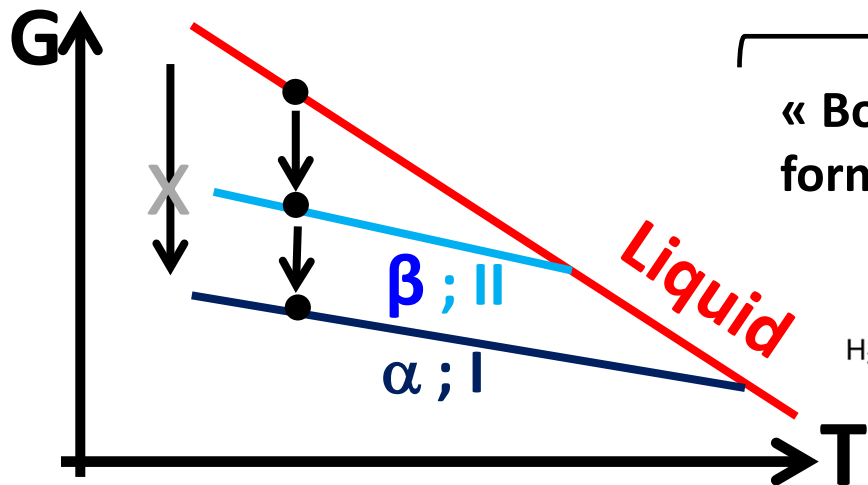
Calorimétrie isotherme



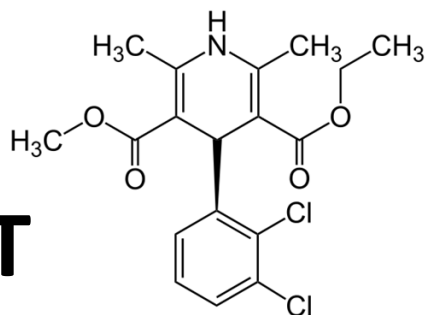
[M. Descamps, E. Dudognon, JOURNAL OF PHARMACEUTICAL SCIENCES 103 (2014) 2615]

Tendance/résistance à cristallisation/vitrification

Même $T_g \approx 318$ K ; Même fragilité $m \approx 80$

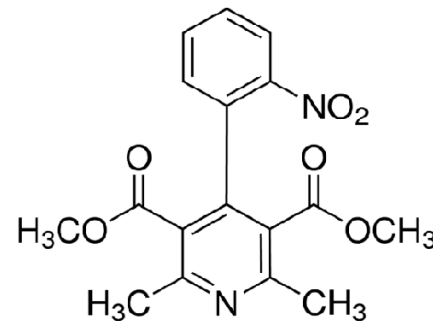


« Bon »
formateur de verre



Felodipine forms: I and II

« Mauvais »
formateur de verre



Nifedipine forms: α and β

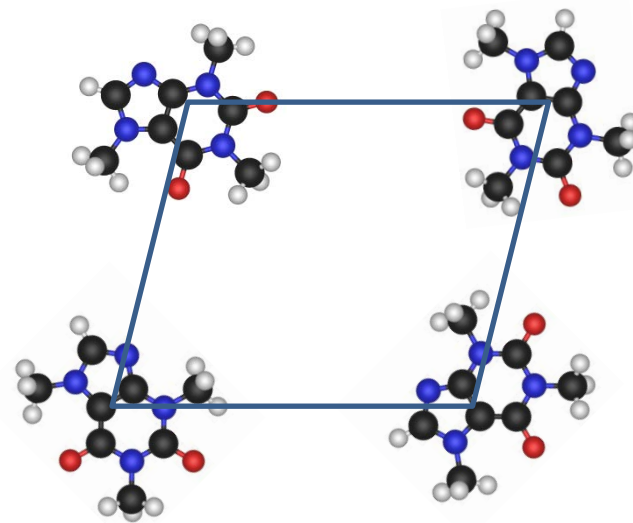
**Cristallisation de Nifédipine ?
Quel polymorphe cristallise ?
SIMULATIONS MD**

Polymorphe	FI	FII	N α	N β
γ (mJ/m ²)	28.7	15.5	21.5	14.4

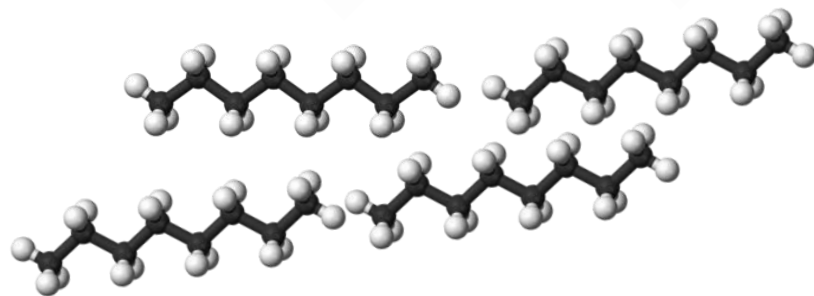
**Barrière Nucleation : COMPROMIS ENTRE γ and ΔG
Règle phases d'Ostwald**

**Nombreuses validations modèle neg-entropique
(Spaepen): γ faible ($\sim \text{mJ}/\text{m}^2$) \rightarrow cristallisation aisée**

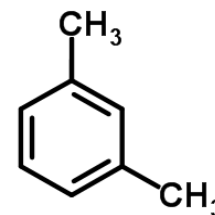
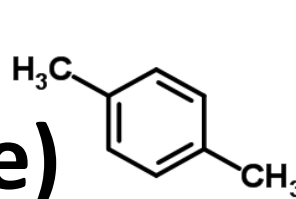
**Cristaux désordonnés
(ex: caffeine, succinonitrile)**



**Liquides « ordonnées »
(ex : alcanes)**



**Symétrie moléculaire
(ex: p-xylene vs m-xylene)**



Formateurs de verres « fragiles »

Dynamique cooperative marquée → Interactions VDW + LH !!!

Fragilités intermédiaires à élevées

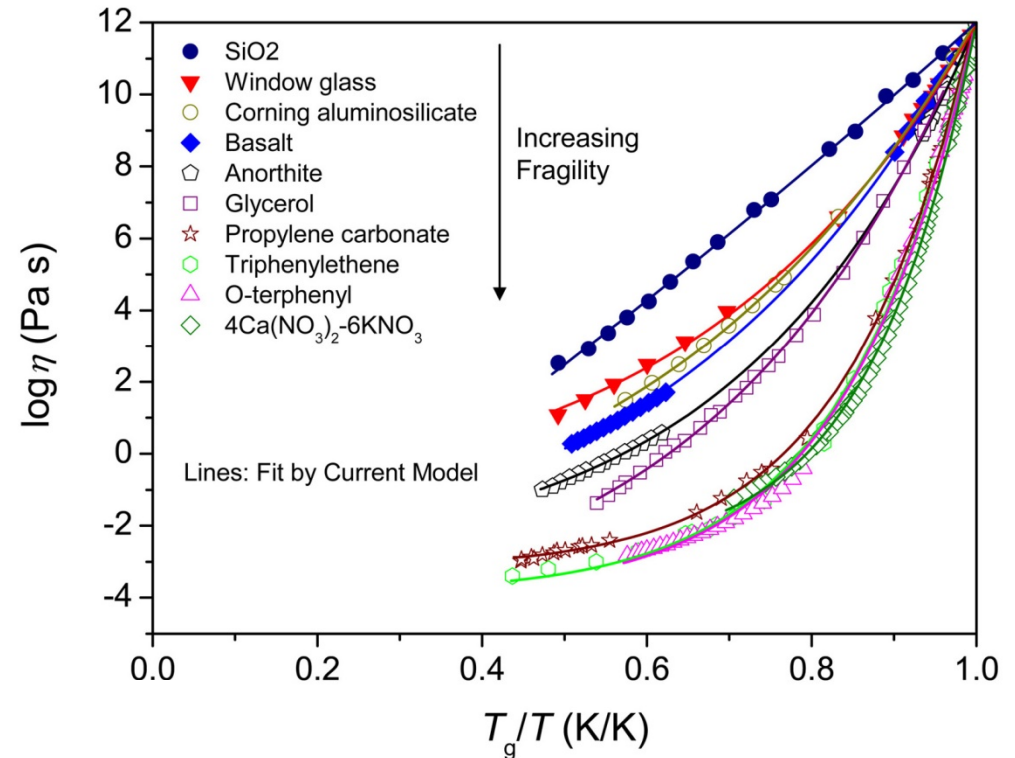
Organic small molecules

2-methylpentane	2-MP	58
Dibutylphthalate	DBP	69
Triphenylchloromethane	TPCM	93
Tri-2-naphthylbenzene	T-2-NB	66
<i>o</i> -terphenyl	OTP	76
di-2-ethylhexylphthalate	D-2-EHP	67
<i>m</i> -xylene	MX	56
<i>o</i> -xylene	OX	55
Toluene	T	59
3-bromopentane	3-BP	53
α -phenyl- <i>o</i> -cresol	APOC	83
<i>m</i> -fluorotulene	MFT	45
5-phenyl-4-ether	5P4E	85

Hydrogen bonding liquids

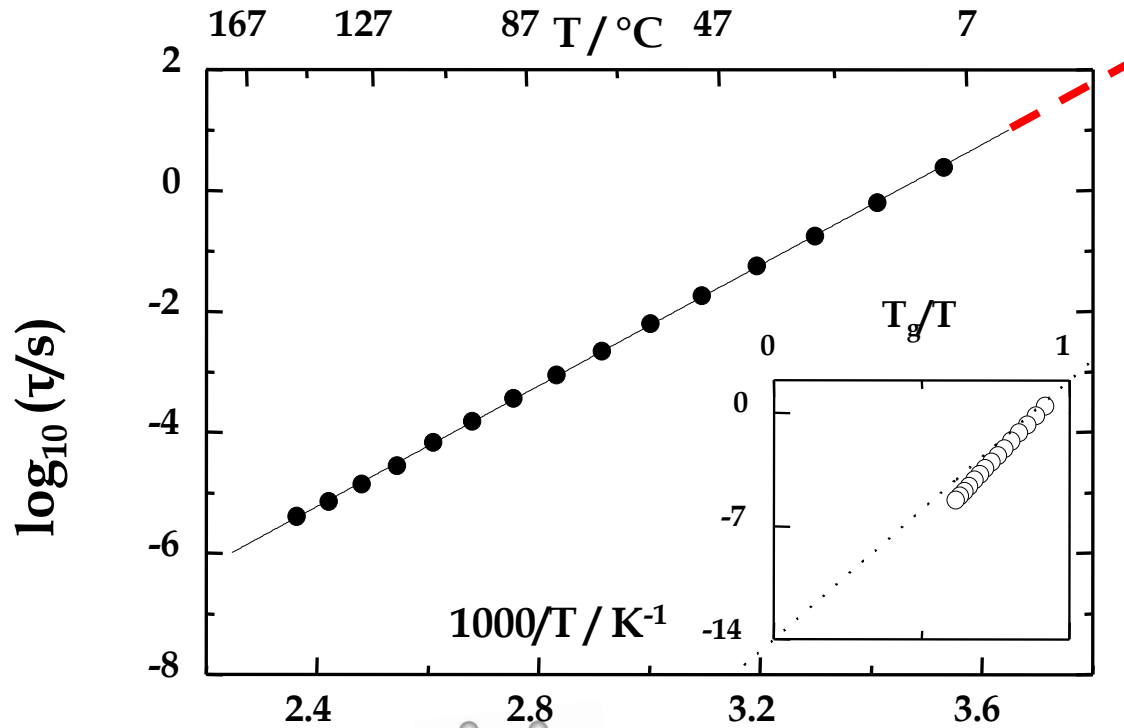
Ethyl alcohol	Ethanol	55
Glycerol		53
<i>n</i> -propanol		35
Propylene glycol		52
Sorbitol		93
Salol		63
<i>m</i> -cresol		57
<i>m</i> -fluoroaniline		70
<i>m</i> -toluidine		79

[J. C. Mauro et al., PNAS 106 (2009)]



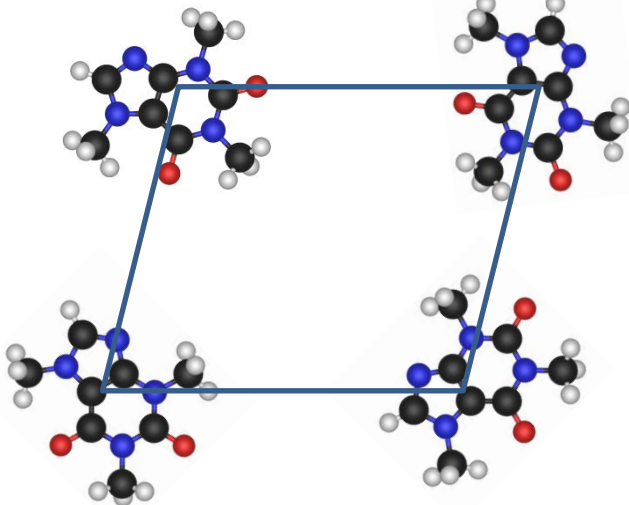
[Huang & McKenna, JCP **114** (2001) 5621]

Il existe quelques verres moléculaires « forts » : cafeine



$$m = \left. \frac{d \log_{10}(\tau)}{d(T_g/T)} \right|_{T=T_g}$$

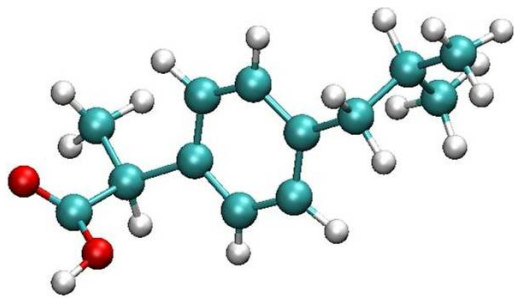
$$m = 19$$



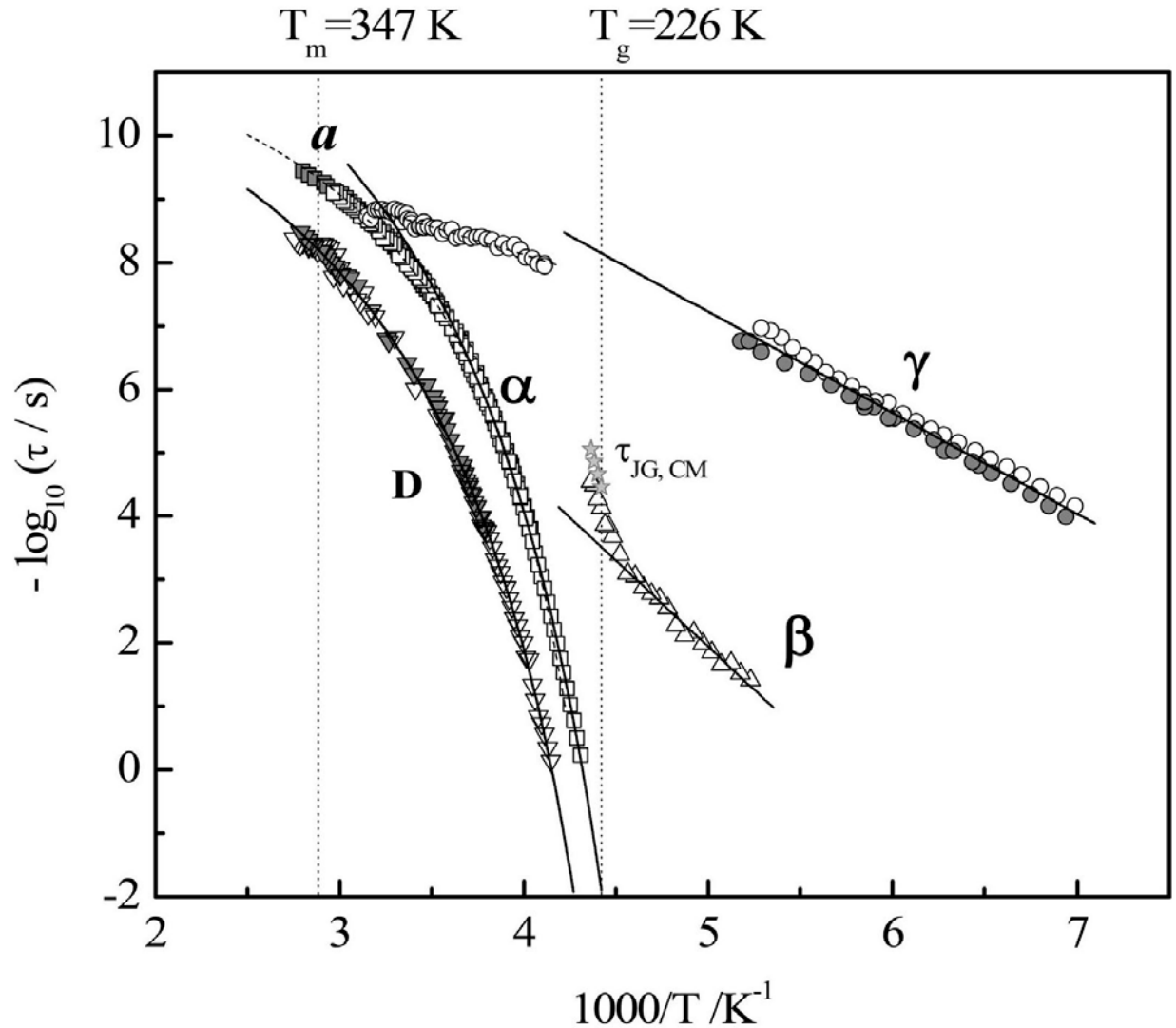
Mobilité : réorientation entre orientations les plus probables de la molécule dans la maille

Dynamiques complexes

Plusieurs processus pour $T > T_g$ et pour $T < T_g$

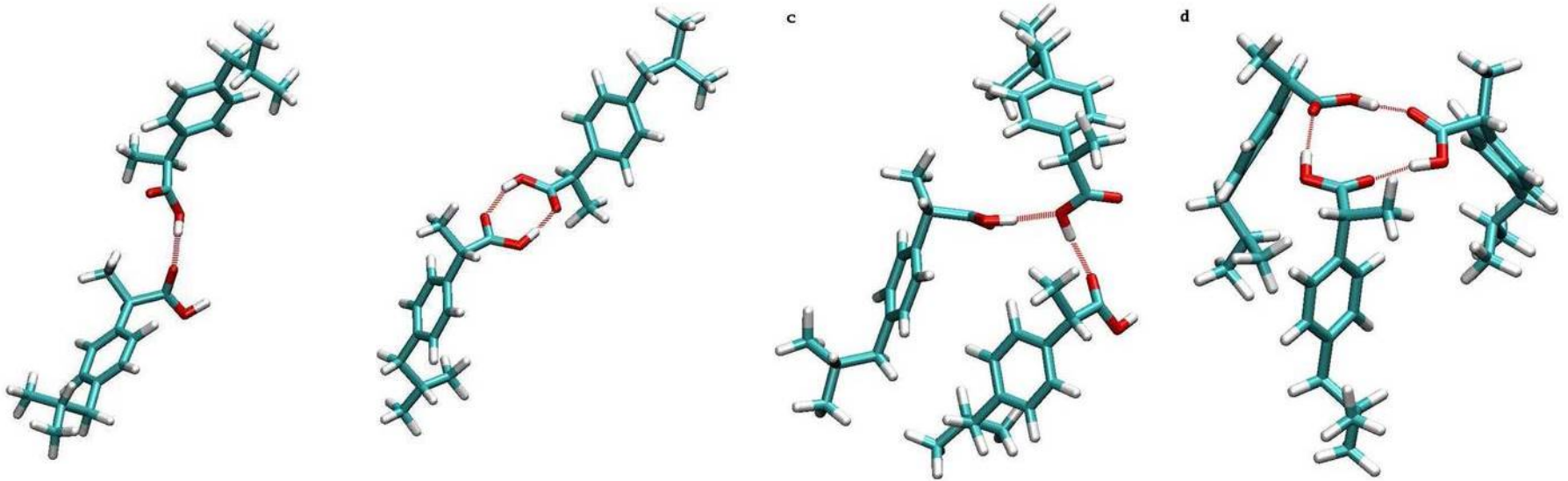


Ibuprofène

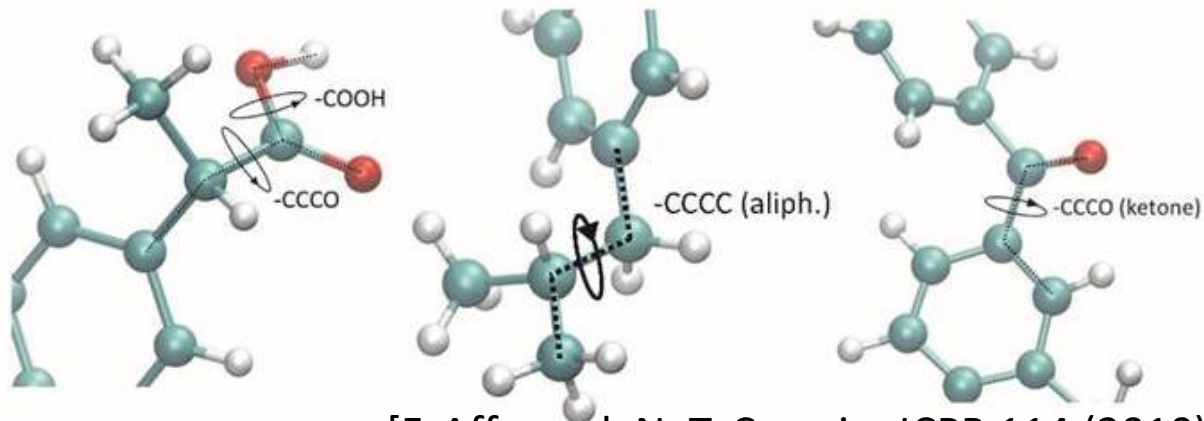


ASSOCIATION INTER-MOLECULAIRE PAR LIAISON H.

→ dynamiques collectives spécifiques ($T > T_g$)



DYNAMIQUES INTRA-MOLECULAIRES ($T < T_g$)



[F. Affouard, N. T. Correia, JCPB 114 (2010) 11397]

**VERRES : beaucoup
d'applications pour
les matériaux de la
pharmacie**

PROBLEME SOLUBILITE DS L'EAU DES PRINCIPES ACTIFS DE LA PHARMACIE



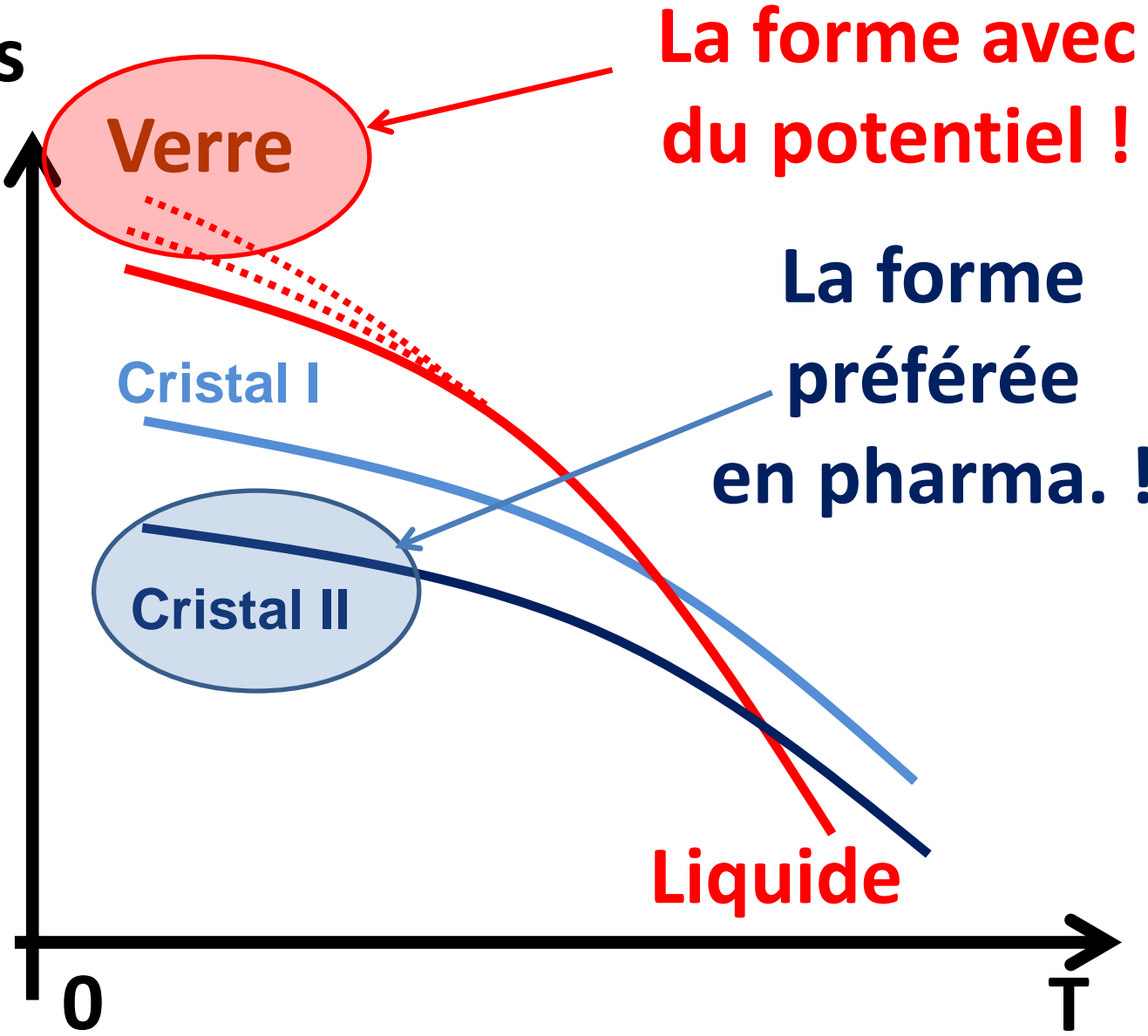
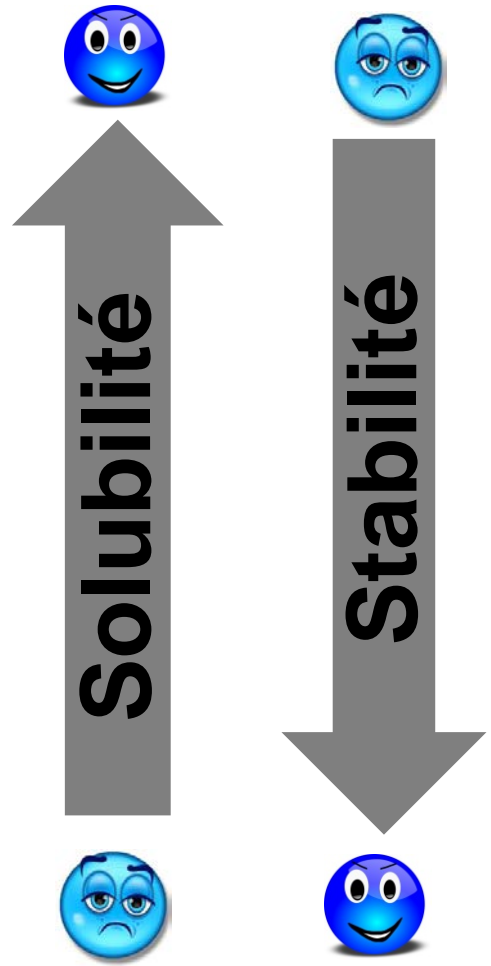
Solubilité sel (NaCl) $\approx 365000 \mu\text{g/mL}$

Solubilité marbre (CaCO_3) $\approx 10 \mu\text{g/mL}$

Principe actif	Solubilité ($\mu\text{g/mL}$)
Ibuprofène	21
Griséofulvine	15
Indométacine	4
Itraconazole	0.001

Amorphe vs Cristal

Energie Gibbs

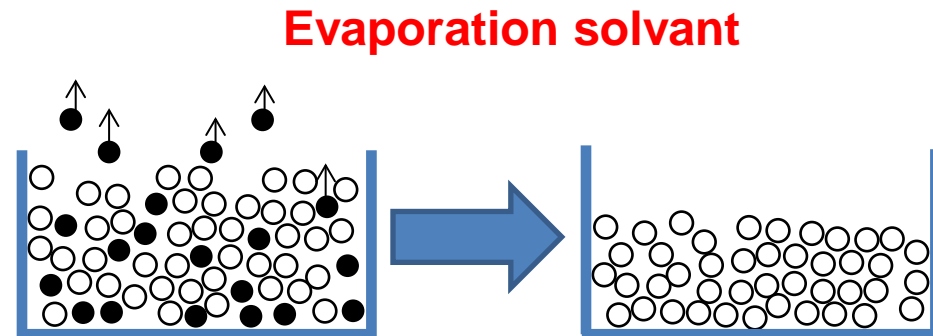
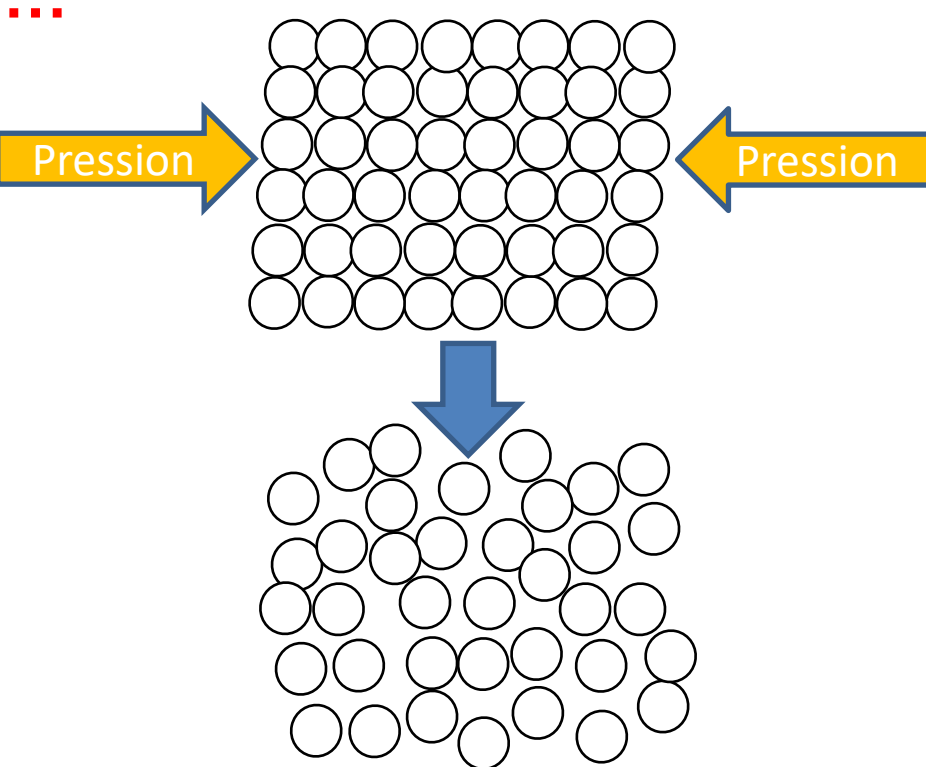


Nombreuses voies d'amorphisation...

- **Broyage**
- **Compression**
- **Evaporation solvant**
- **Lyophilisation**
- **Atomisation (spray-drying)**
- **Déposition en phase vapeur**

**Même Amorphe ?
PolyAmorphisme ?**

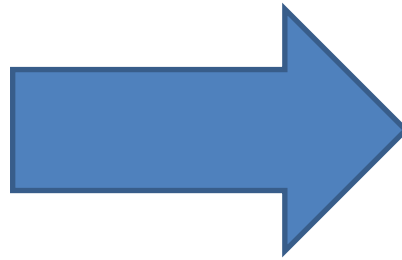
QUESTION OUVERTE !



Amorphisation par fusion-trempe



Sucre (cristal)

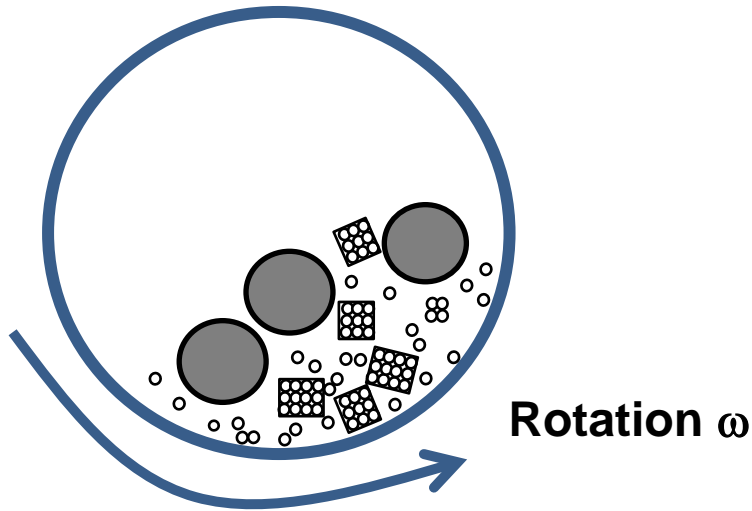


**Caramel (amorphe)
"verre de sucre"**

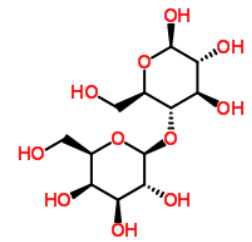
CHANGEMENT DE COULEUR : DEGRADATION

Amorphisation par broyage

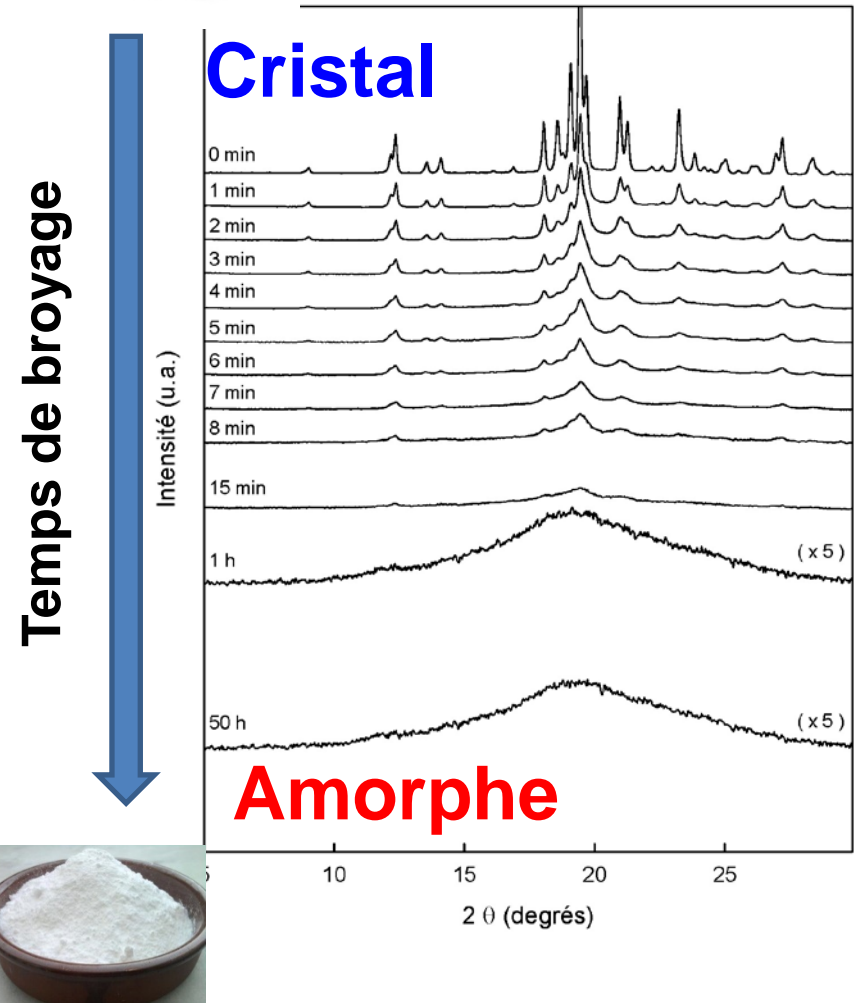
- : Bille métallique
- ⊙ : Poudre cx a amorphiser



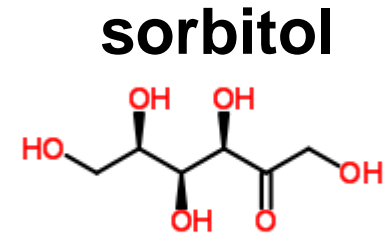
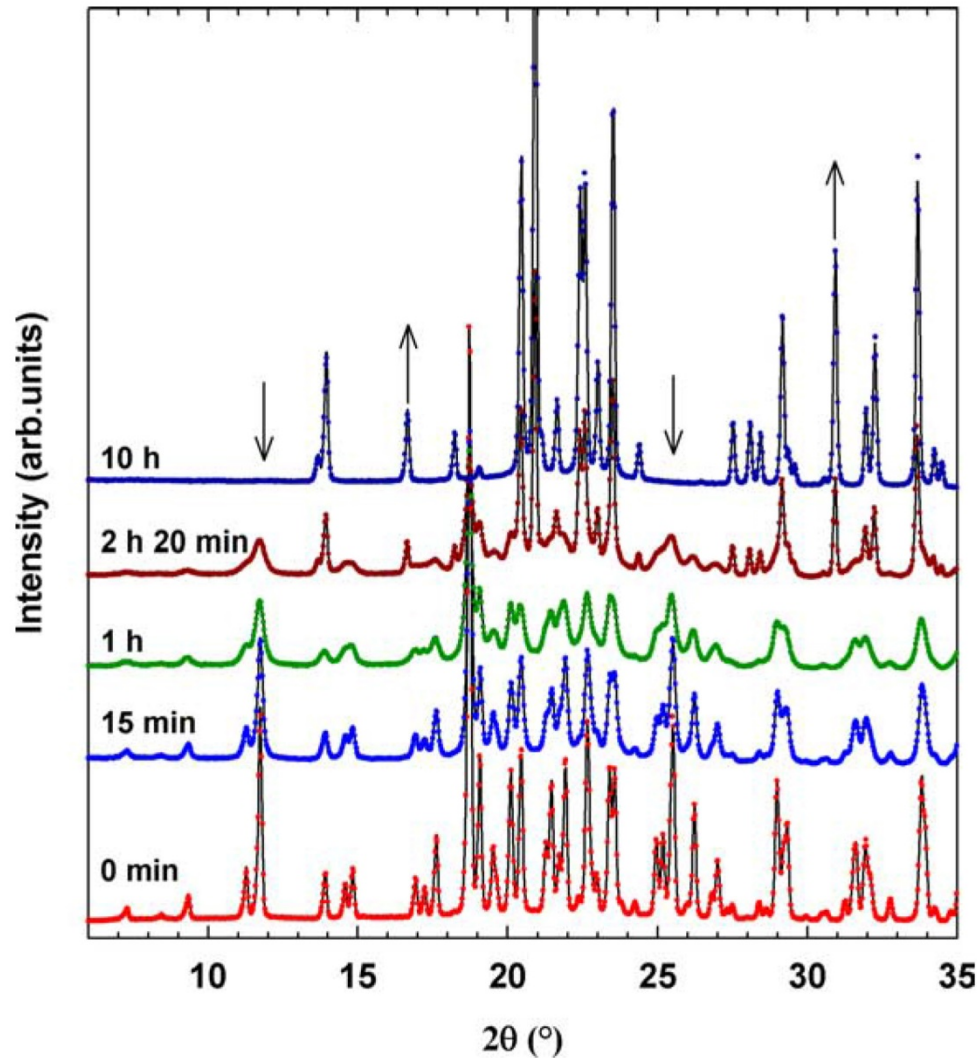
Sucre amorphe « blanc »
→ Pas de caramélisation
→ Pas d'élévation réelle de
Température



Lactose



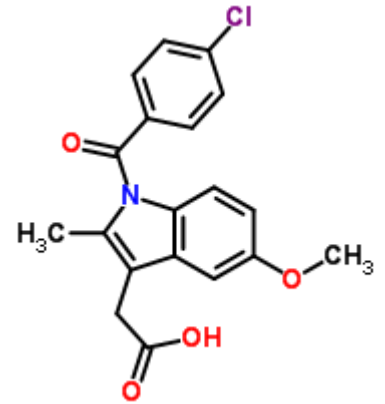
Transformation cristal-cristal par broyage



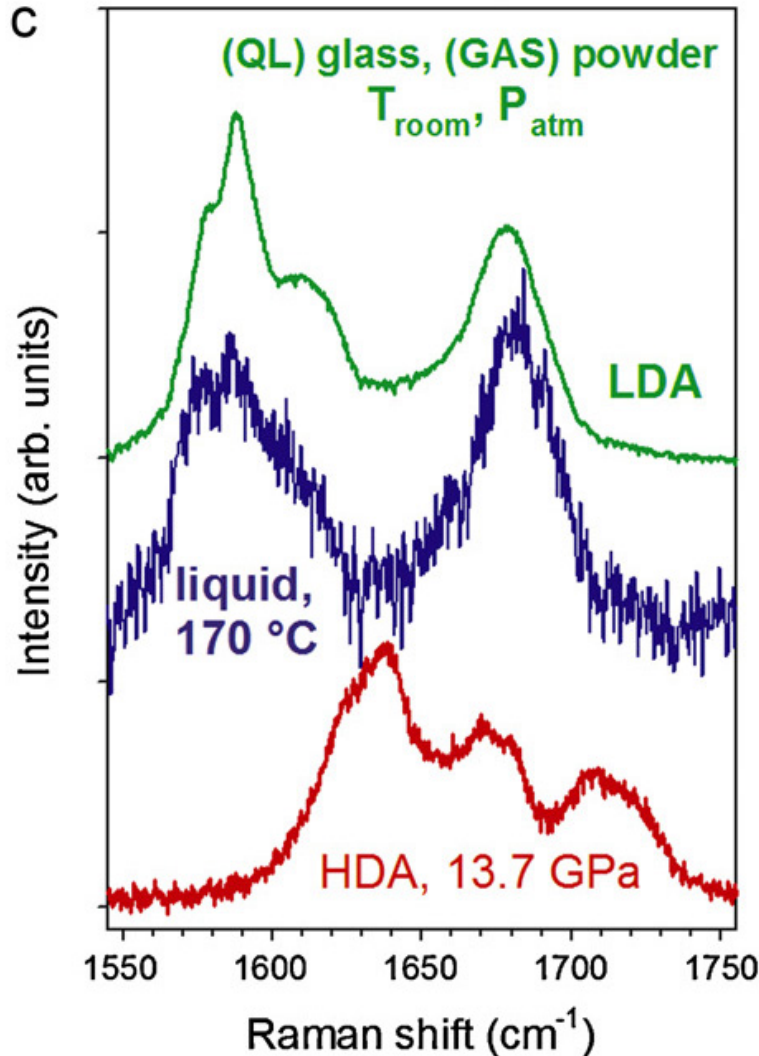
A polymorph

Γ polymorph

Compression vs Broyage PolyAmorphisme



indomethacin



**Verre basse densité
(Broyage) ~ verre liquide**

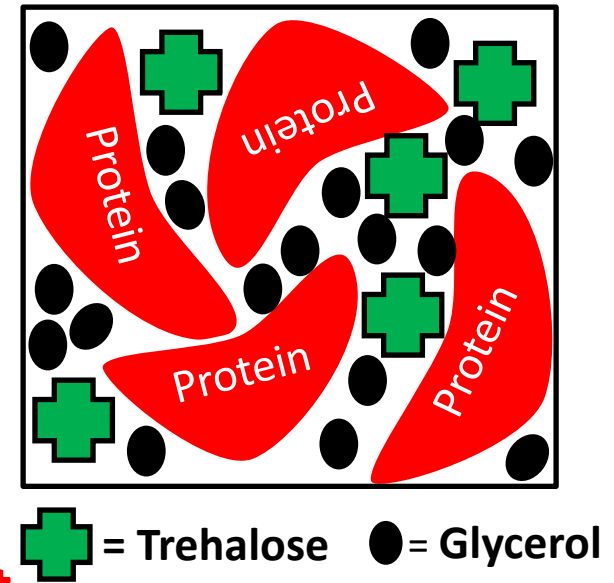
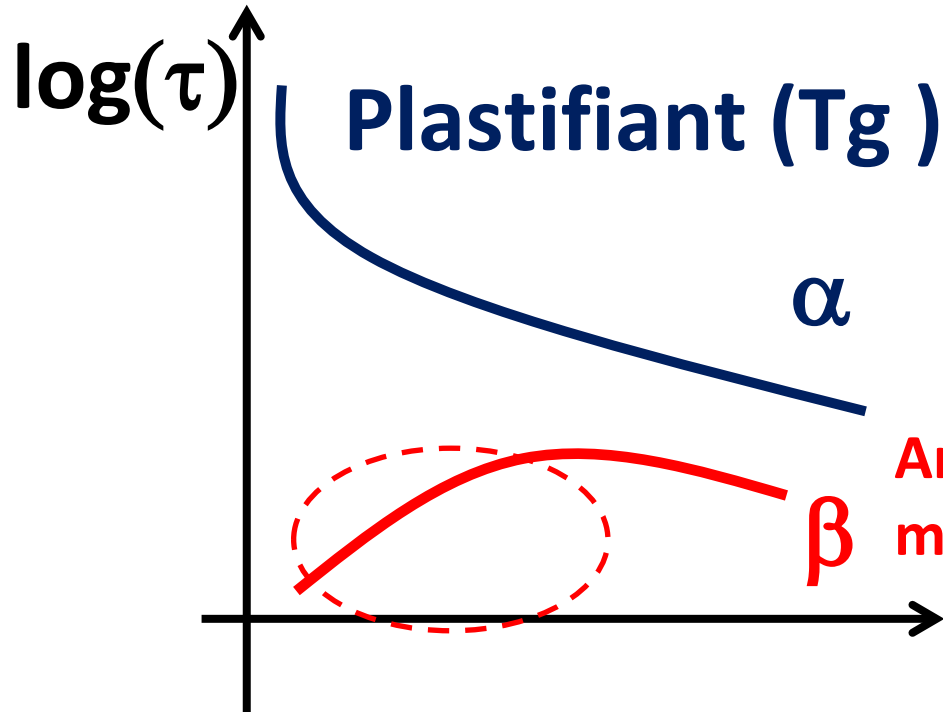
**≠ réseau de liaisons
hydrogènes**

**Verre haute densité
(Compression)**

Bioprotecteurs vitreux pour lyophilisation des protéines



BIOPROTECTEUR	Tg (° C)
PEG	- 106
Glycerol	- 83
Sucrose	60
Trehalose/5%Glycerol	97
Trehalose	120

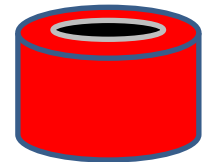
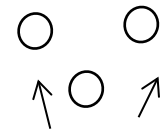
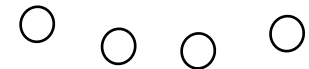
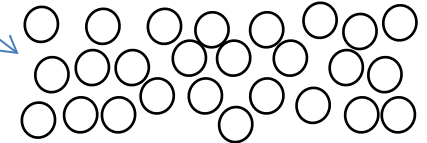


[A. Lerbret, F. Affouard, JPCB 121 (2017) 9437]

[T. Starciuc, Y. Guinet, L. Paccou, A. Hedoux,,J. Pharm. Sciences 106 (2017) 2988]

VERRE ULTRASTABLE par déposition en phase vapeur

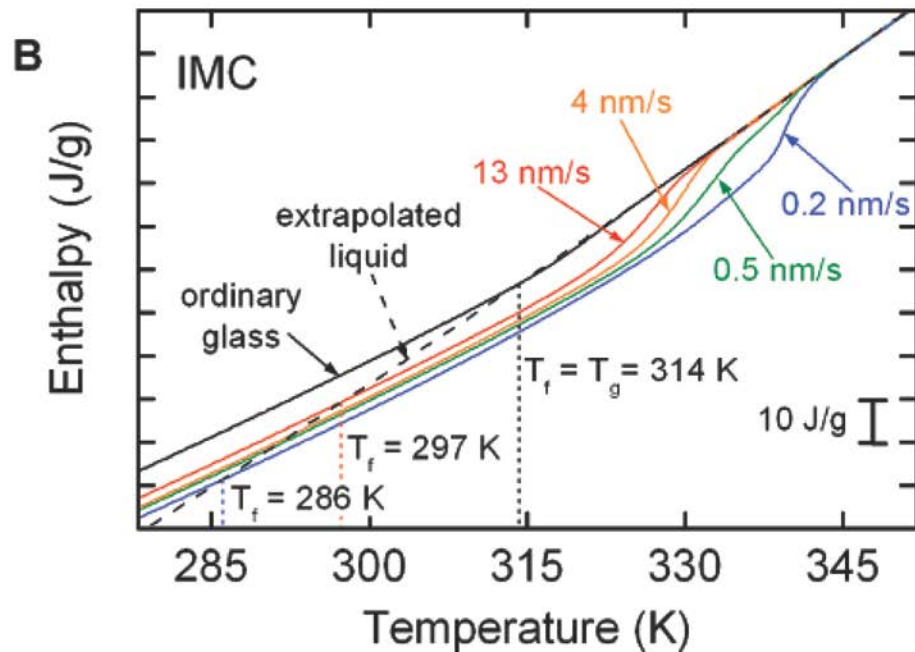
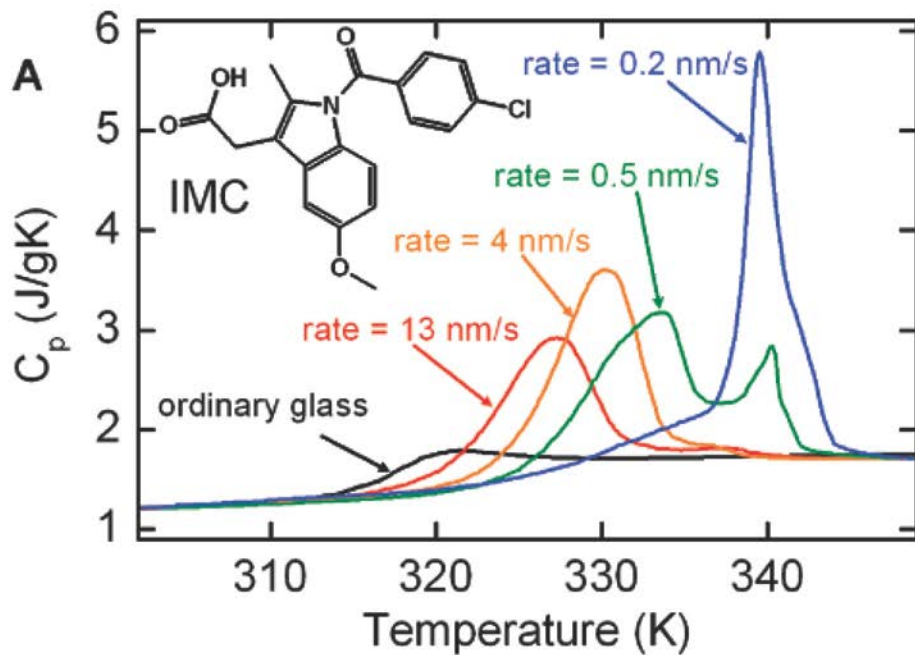
Substrat Basse
température



Organic Glasses with Exceptional Thermodynamic and Kinetic Stability

Stephen F. Swallen,¹ Kenneth L. Kearns,¹ Marie K. Mapes,¹ Yong Seol Kim,¹
Robert J. McMahon,¹ M. D. Ediger,^{1*} Tian Wu,² Lian Yu,² Sushil Satija³

University of Wisconsin-Madison (USA)
[Science 315 (2007) 353]



VERRES ULTRASTABLES:

- Basse enthalpie
- Haute densité
- Vieillissements: 10^n ans

PARAMETRES IMPORTANTS:

Faible vitesse déposition
température substrat:

$$T \approx 0.85T_g$$

*≠ déposition classique
(vitesses élevées, $T \ll T_g$)*

MECANISME : MOBILITE DE SURFACE

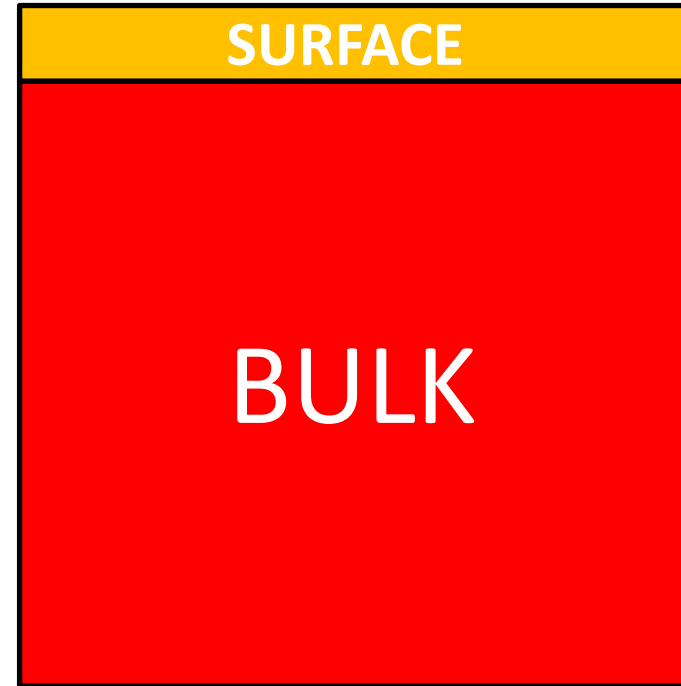
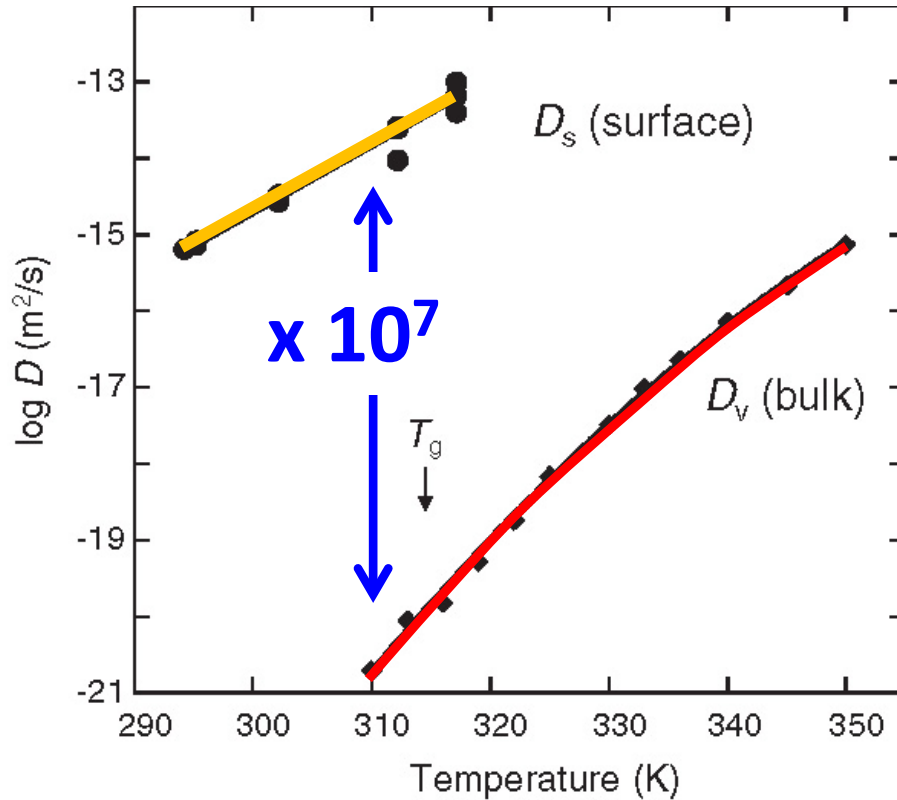
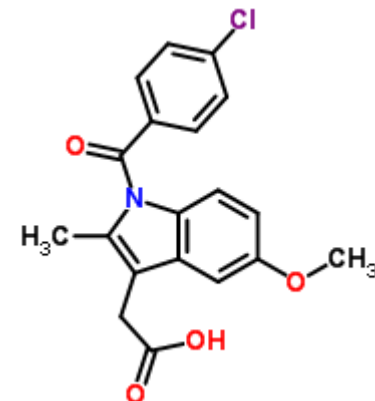


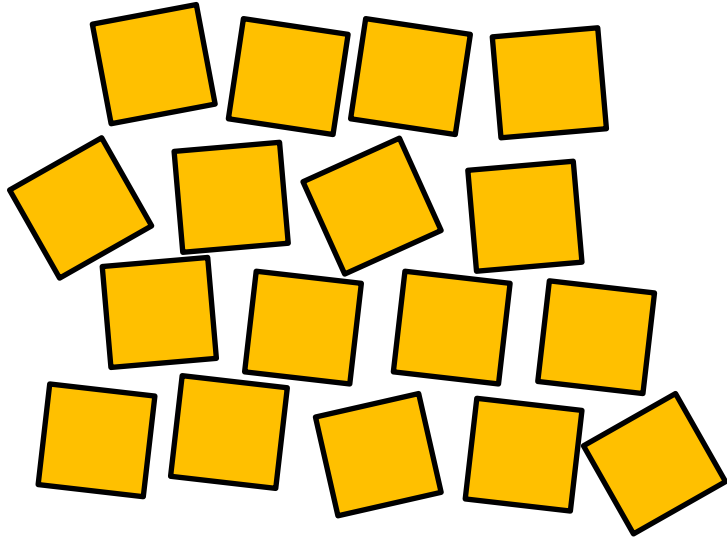
FIG. 3. Surface and bulk diffusion coefficients of IMC liquid and glasses.

indomethacin

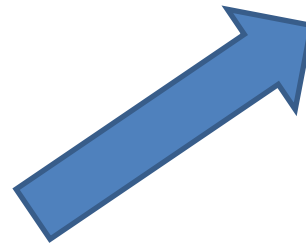
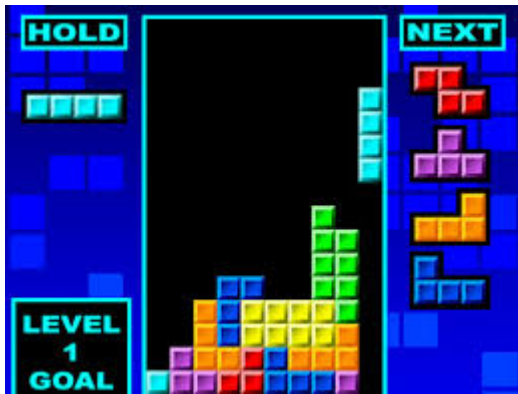
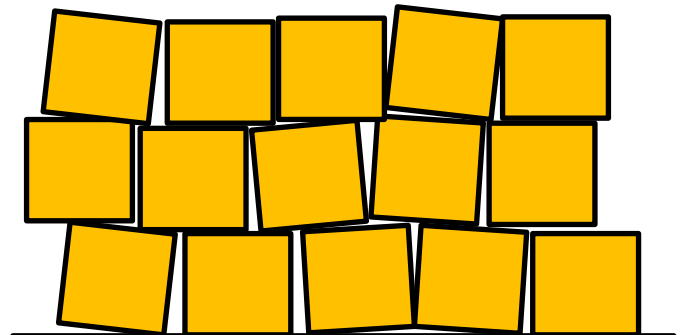


Verre ordinaire (fusion-trempe)

mauvais « packing »



Verre (Dép. Vap.)
« packing » optimal



EFFET « Tetris »



Messages à retenir

Etat vitreux et transition vitreuse dans les matériaux composés de petites molécules organiques

Contraste fort entre interactions intra- et inter-moléculaires → ensemble de propriétés physiques spécifiques

Intérêts :

- sujets physiques originaux: transf. phase, états hors-équilibre, vitrification,...**
- applications (pharmacie, agrochimie)**

Groupe MMT – Laboratoire UMET CNRS 8207 - Université Lille1



<http://umet.univ-lille1.fr/MMT>