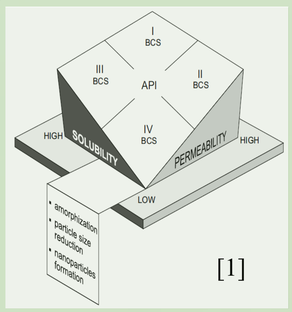
Crystalline *vs* amorphous drugs: the benzodiazepines case-study

Sofia Valenti,[1] Maria del Barrio, [1] Philippe Negrier, [2] Michela Romanini, [2] Roberto Macovez, [1] and Josep Lluis Tamarit

1 Grup de Caracterització de Materials, Departament de Física, Universitat Politècnica de Catalunya, EEBE, Campus Diagonal-Besòs, Av. Eduard Maristany 10-14, 08019 Barcelona, Catalonia, Spain.

2 Université Bordeaux, LOMA, UMR 5798, F-33400 Talence, France CNRS, LOMA, UMR 5798, F-33400 Talence, France



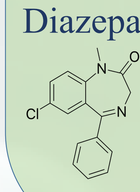
[1]

Bioavailability, strategies and the benzodiazepines

API (active pharmaceutical ingredients) can be poorly water-soluble, hindering the bioavailability of a medicament.
Possible strategies are chemical derivatizations, amorphization and co-dissolutions.

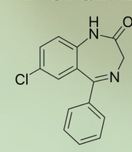
- 322 million people suffer from depression as of 2015 [2]
- 40% of patients with depressive disorders are prescribed **benzodiazepines**

Diazepam (DIA)



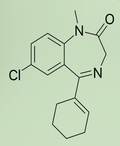
T_g = 317.8 K
T_m = 404.1 K

Nordiazepam (NOR)



T_g = 346.8 K
T_m = 487.0 K

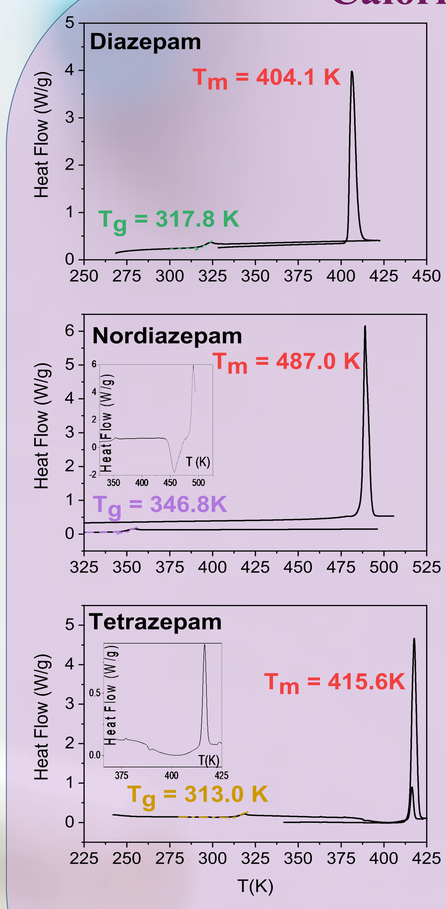
Tetrazepam (TETRA)



T_g = 415.6 K
T_m = 313.0 K

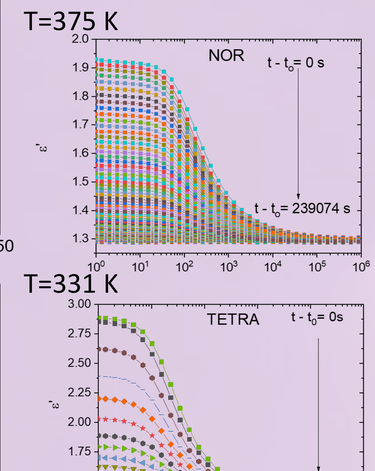
Only one with strong H-bonds

Calorimetry and phase changes



T_g (TETRA) < T_g (DIA) < T_g (NOR)

T_m (DIA) < T_m (TETRA) < T_m (NOR)



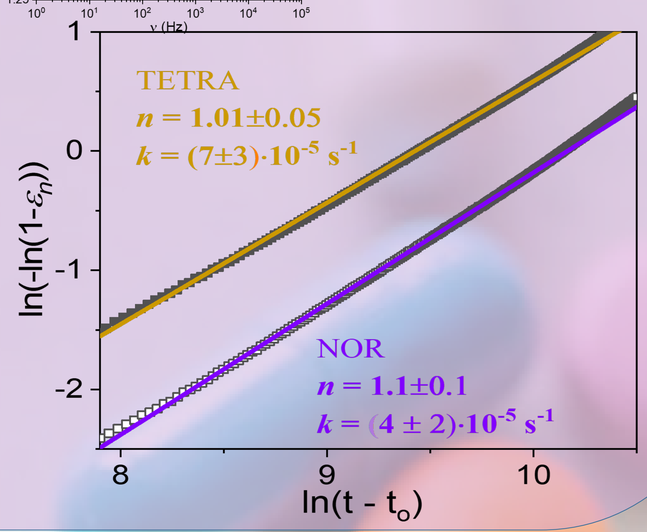
The Avrami law[3]:

$$\varepsilon_n(t) = \frac{\varepsilon_s(t) - \varepsilon_s(SL)}{\varepsilon_s(C) - \varepsilon_s(SL)}$$

$$\varepsilon_n(t) = 1 - \exp(-Z(t - t_o)^n)$$

$$k = Z^{1/n}$$

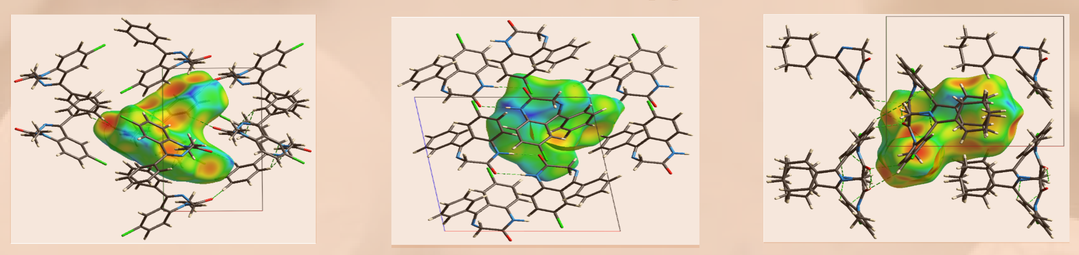
- DIA does not crystallize;
- Same crystal dimensionality (n) for TETRA and NOR;
- TETRA crystallizes faster than NOR.



Crystalline

DIA	NOR	TETRA

Hirshfeld Surfaces [4]



D-H···A	d(H··A) [Å]
C24-H24···O1	2.44
C22-H22···O1	2.53
C13-H13···N2	2.81
C15-H15···N2	2.79

D-H···A	d(H··A) [Å]
C15-H3···O1	2.65
N1-H11···O1	**2.03**
C3-H8···N1	2.79
C6-H10···N2	2.79

D-H···A	d(H··A) [Å]
C2-H2B···O1	2.51
C7-H7···O1	2.61
C10-H10A···O1	2.75
C9-H8···N2	2.70

Lower bond length → **strong** H-bond in NOR
→ lower **Hirshfeld surface/volume**, higher **density, T_m and T_g**

ρ [g cm^{-3}]	V_H [Å^3]	A_H [Å^2]
1.395	332.4	305.9

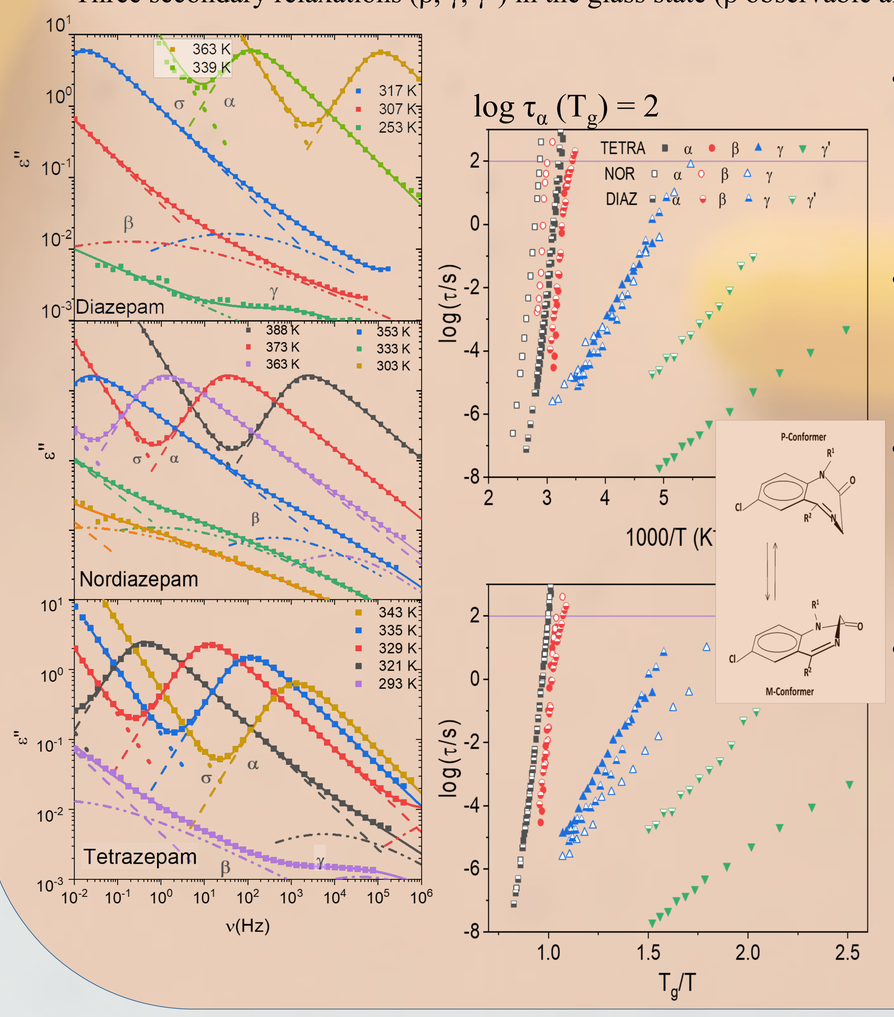
ρ [g cm^{-3}]	V_H [Å^3]	A_H [Å^2]
1.432	308.8	287.2

ρ [g cm^{-3}]	V_H [Å^3]	A_H [Å^2]
1.319	357.2	315.9

vs

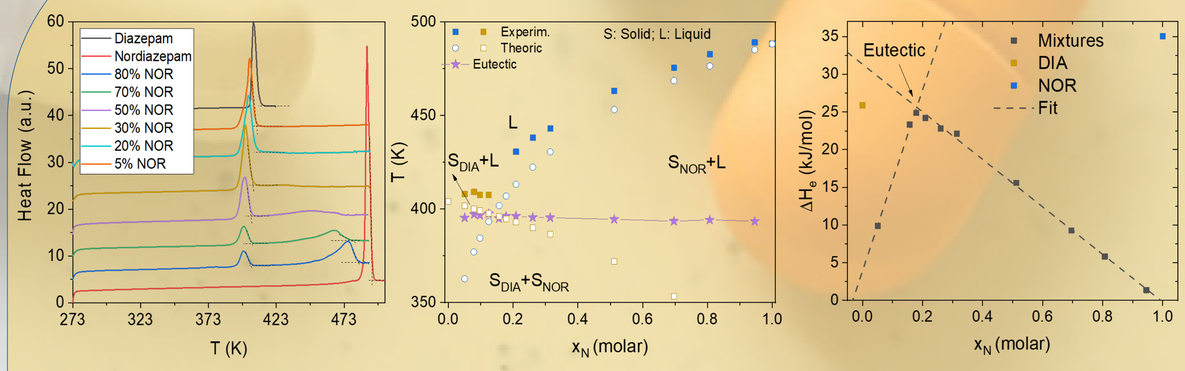
Amorphous

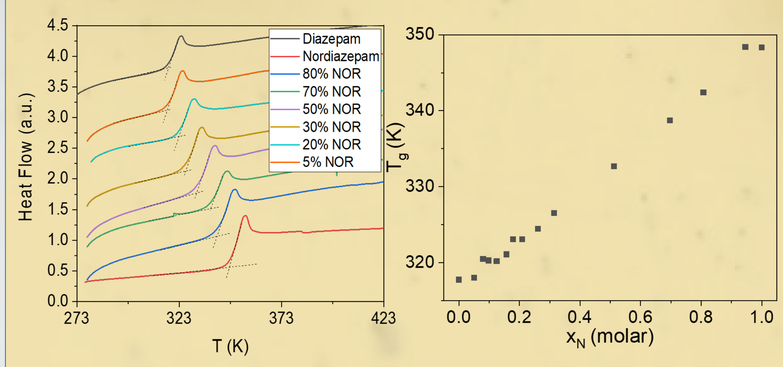
- Primary relaxation (α) in the liquid state (structural and cooperative)
- Three secondary relaxations (β, γ, γ') in the glass state (β observable also in the liquid state)



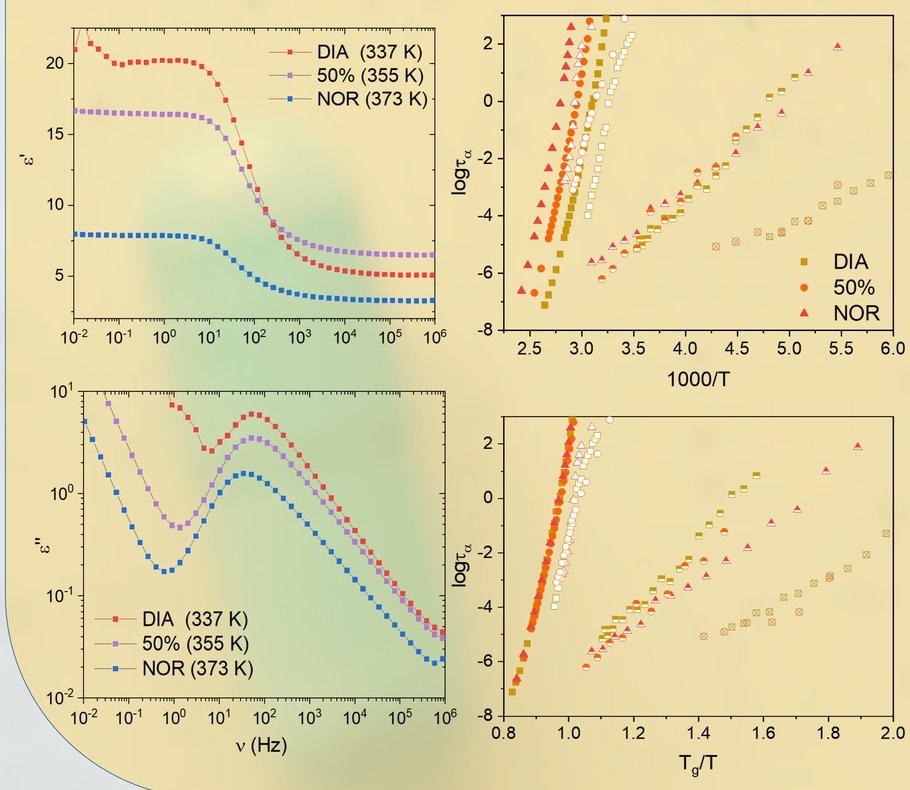
- Same τ_α at same T/T_g → liquid unaffected by H-bonds, crystallization behavior independent of fragility.
- τ_β same at same T/T_g → intermolecular and local, crystallization is independent of T_g (β).
- Same τ_γ at same T → intramolecular, due to inter-conversion dynamics between conformers.
- $\tau_{\gamma'}$ only present in DIA and TETRA → due to the internal rotation along the covalent bond linking the fused double ring with the six-membered carbon ring, hindered by H-bonds.

Co-Dissolutions of NOR and DIA





- Solid solution prepared by mixing with a mortar
- Eutectic concentration = 18% molar
- T_g linear with concentration



- Dielectric constant of 50% mixture in between DIA and NOR
- A single α and **β** process in the 50%
- Same τ_α and τ_β at same T/ T_g
- τ_γ and $\tau_{\gamma'}$ of 50% and DIA coinciding at same T (intramolecular)

References

[1] Rams-Baron, M.; et al. Springer International Publishing AG, Cham, Switzerland, 2018
[2] WHO | Depression and Other Common Mental Disorders. (2017).
[3] Avrami, M., J. Chem. Phys. 1939, 7, 1103–1112.
[4] Spackman, M. A.; Jayatilaka, D., Cryst. Eng. Comm. 2009, 11, 19-32.