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Polymorphism in a benzo[*b*][1,4]diazepine derivative: crystal structure, phase behavior and selective influence of solvents

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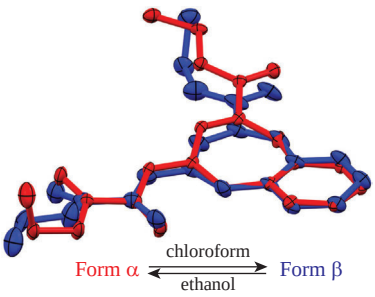
Ethyl 4-[(*Z*)-3-ethoxy-2,3-dioxopropylidene]-4,5-dihydro-1*H*-benzo[*b*][1,4]diazepine-2-carboxylate forms two polymorphic modifications α and β, which differ in molecular conformations, as well as in the dimension of H-bonded supramolecular motifs in crystals that are a 1D chain or a 0D dimer, respectively. The formation of polymorphs can be controlled by choice of the solvent used. Crystallization from a solution in a polar protic solvent, ethanol, results in the thermodynamically favorable α-form, while using a low-polarity solvent, chloroform, and melt crystallization lead to the metastable β-form.



Keywords: polymorphism, crystal structure, phase behavior, crystallization, π···π interaction, hydrogen bonds.

Polymorphism consists in the differences in the crystal structure of the same compound at the molecular and supramolecular levels, which is reflected in both physical and physicochemical properties, such as crystal morphology, stability, melting behavior and solubility.[1] It is important to note that the difference in solubility between two or more crystalline modifications can provide different pharmacokinetics for them. Hence, the development of approaches to the detection of polymorphs and the direct production of the desired form is of undoubted interest. In this regard, crystallization from a solution or the melt is considered an attractive and convenient method that can be used not only to prepare a stable modification and some metastable forms but also to study the crystallization process and the phenomenon of polymorphism.[2] It is worth noting that the crystallization of the melt can be controlled by the cooling rate, but this method was found to be limited by the thermal stability of the organic compound at elevated temperatures. At the same time, for crystallization from solution, one can easily change several parameters of a thermodynamic and kinetic nature that affect the nucleation and further growth of crystals. These parameters include temperature conditions, the nature of solvents differing in dielectric constant, polarity, viscosity and other properties, the initial concentration of the solution, the crystallization method (for example, evaporation, liquid–liquid and vapor diffusion) and impurities or additives.[2–5] Moreover, an essential characteristic of crystallization is the ability to scale up and conduct both batch and continuous processes.[2] The published works report the correlation between the nature of solvents and the crystal structures of polymorphic modifications. Thus, aprotic and low-polarity solvents often promote the formation of hydrogen-bonded dimers as supramolecular building blocks.[6–12]

In this article, we compared the crystal structures of two polymorphic modifications of ethyl 4-[(*Z*)-3-ethoxy-2,3-dioxopropylidene]-4,5-dihydro-1*H*-benzo[*b*][1,4]diazepine-2-carboxylate **1** that can be obtained in individual forms by preferential crystallization of compound **1** from polar protic ethanol and low-polarity aprotic chloroform. Compound **1** is readily derived from diethoxalylacetone (dimethyl 2,4,6-trioxoheptanedioate)[13,14] when exposed to *o*-phenylenediamine in methanol (Scheme S1, see Online Supplementary Materials). Next, we carried out crystallization from different solvent systems and a melt-induced phase transformation. Notably, compound **1** belongs to benzodiazepines, an important class of organic compounds, exhibiting pharmacological activities, such as antibacterial, anticancer, anti-inflammatory, antidepressant, anticonvulsant and analgesic.[15–18]

Two polymorphic modifications of compound **1**, designated as α (α-**1**) and β (β-**1**), crystallize in the space groups $P2_1/c$ and $P\bar{1}$, respectively, with only one molecule in an asymmetric cell. These polymorphs α-**1** and β-**1** form dark red crystals, easily distinguishable by their dissimilar habit, namely prisms and needles, respectively (Figure S1, see Online Supplementary Materials). According to the data of single-crystal X-ray diffraction,† the α and β forms are characterized at the molecular level by the different

† *Crystal data for* α-**1**. $C_{17}H_{18}N_2O_5$, dark red prism (0.556 × 0.373 × ×0.265 mm), M = 330.33, monoclinic, space group $P2_1/c$ (no. 14), a = 11.4514(6), b = 13.4050(8) and c = 11.6910(7) Å, β = 118.7410(10)°, V = 1573.54(16) Å^3, Z = 4, Z' = 1, T = 100(2) K, d_{calc} = 1.394 g cm^{-3}, μ(MoKα) = 0.104 mm^{-1}, F(000) = 696, $T_{max/min}$ = 0.9489/0.9018. 18441 reflections were collected (2.028° ⩽ θ ⩽ 28.780°, index ranges: –15 ⩽ h ⩽ 15, –17 ⩽ k ⩽ 18, –15 ⩽ l ⩽ 15), 4028 of which were unique (R_{int} = 0.0236, R_σ = 0.0199, completeness to θ_{max} 98.5%). The refinement

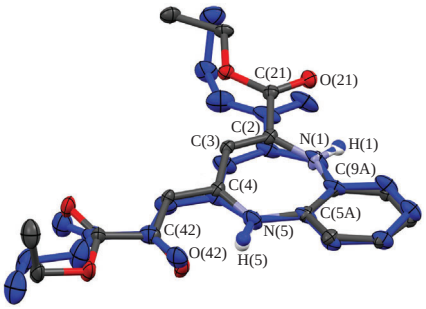


Figure 1 Overlay of the molecules of compound **1** extracted from the crystal structures of polymorphs α (colors by elements) and β (blue). ORTEP is shown with anisotropic ellipsoids for non-hydrogen atoms at the 50% probability level. Except for H(1) and H(5), hydrogen atoms and minor disorder components are omitted for clarity.

conformation of the benzo-fused 7-membered diazepine ring. This difference is shown in Figure 1 and can be described by the dihedral angles C(9A)–N(1)–C(2)–C(3), C(3)–C(4)–N(5)–C(5A) and C(2)–C(3)–C(4)–N(5). Their values are respectively –26.80(18)°, 17.92(16)° and 10.35(16)° for the α form and –5.9(6)°, 8.1(5)° and –2.0(5)° for the β form. Hence, in the first case, the conformation of the benzo-fused diazepine ring is a half-boat, and two nitrogen atoms turn out to be somewhat pyramidal, while in the second case, both the ring conformation and configurations of nitrogen atoms are almost planar. Interestingly, in the case of the β form, the terminal ethyl groups were found to be disordered over two positions with the contribution of the main components of 0.503(7) for the C(2) pivot arm and 0.66(2) for the C(4) pivot arm. Since the disorder persists for the β polymorph also at room temperature, it probably has the statistic nature.

Differences between the conformations of molecules can be associated with the different supramolecular organization of crystals, caused primarily by hydrogen bonds (Table 1) and π···π interactions. So, for the α modification, intermolecular hydrogen bonds of the N–H···O=C type are formed with both sides of the molecule plane, leading to the formation of 1D zigzag chains along the 0*b* axis [Figure 2(*a*)]. In the case of the β form, hydrogen

Table 1 Geometrical parameters of classical inter- and intramolecular H-bonds in polymorphs α and β of compound **1**.

Polymorph	D–H···A	*d*(D–H)/Å	*d*(H···A)/Å	*d*(D···A)/Å	∠DHA/deg
α	N(1)–H(1)···O(42)[a]	0.884(15)	2.179(15)	2.9665(12)	148.2(12)
	N(5)–H(5)···O(21)[b]	0.867(15)	2.593(14)	3.1171(12)	119.9(11)
	N(1)–H(1)···O(21)	0.884(15)	2.225(14)	2.6575(12)	109.8(11)
	N(5)–H(5)···O(42)	0.867(15)	1.918(15)	2.6563(12)	142.1(13)
β	N(1)–H(1)···O(21)[c]	0.86(2)	2.42(3)	3.255(3)	163(3)
	N(1)–H(1)···O(21)	0.86(2)	2.22(3)	2.669(3)	112(2)
	N(5)–H(5)···O(42)	0.87(2)	2.03(3)	2.727(3)	136(2)

[a] Symmetry operation: $1-x$, $y-½$, $½-z$. [b] Symmetry operation: $1-x$, $y+½$, $½-z$. [c] Symmetry operation: $-x$, $2-y$, $1-z$.

bonds of this type arise when identical sides of the planes of two molecules approach each other, resulting in the formation of planar centrosymmetric dimers as the main 0D crystallographic motif [Figure 2(*b*)]. Further chain formation with classical H-bonds does not occur, probably due to steric hindrance.

Interestingly, the structural difference between the crystalline forms α and β can be easily detected at the next level of crystal organization. In the α modification, two adjacent diazepine rings related by the inversion center interact through the homoatomic π···π contact C(3)···C(4) [Figure 3(*a*)], which connects the H-bonded chains into two-dimensional corrugated layers. At the same time, in the β form, π···π staking is more expanded and is realized mainly between two adjacent planar fragments C(21)–C(2)–C(3) and C(41)–C(42)–C(43) [Figure 3(*b*)]. Consequently, due to the π···π contacts, the H-bonded dimers in the β polymorph associate, forming 1D ribbons. 3D crystal structures of the α and β modifications, built due to all non-covalent interactions, are characterized by packing indices of 71.0 and 70.1%, respectively.

Preliminary quantum-chemical calculations, which were carried out at a single point for molecules with a geometry taken from the crystal structures, suggest that the conformation with a nonplanar diazepine moiety, realized in the crystal of polymorph α, appears to be the most stable, including due to the stronger intramolecular hydrogen bond N(5)–H(5)···O(42).

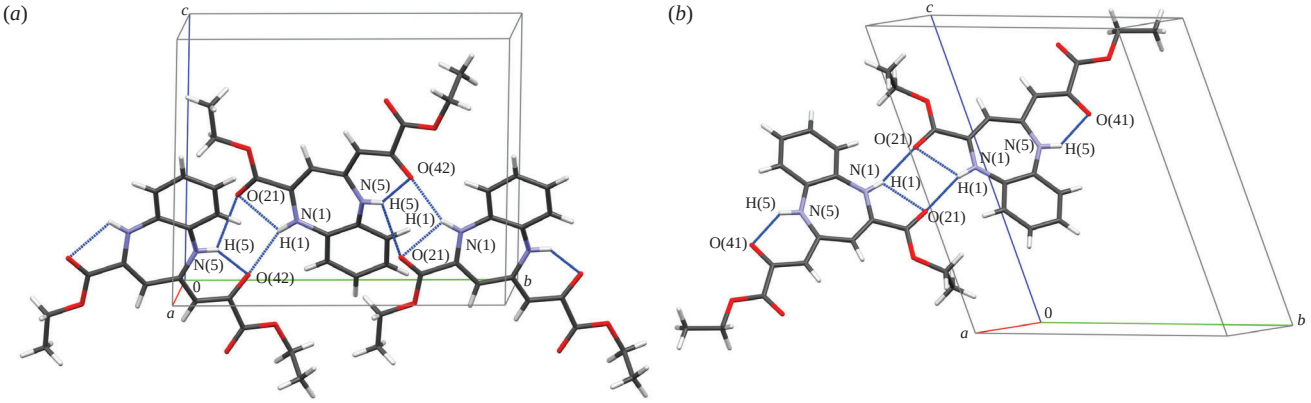


Figure 2 Fragments of molecular packing in the crystals of (*a*) polymorph α-**1** and (*b*) polymorph β-**1**, demonstrating two types of the supramolecular organization of the main crystal-forming motifs: a zigzag chain and a centrosymmetric dimer, respectively. Hydrogen bonds N–H···O are shown by blue dashed lines.

of 227 parameters with no restraints converged to $R_1 = 0.0366$ and $wR_2 = 0.0923$ for 3429 reflections with $I > 2\sigma(I)$ and $R_1 = 0.0445$ and $wR_2 = 0.0971$ for all data with $S = 1.041$ and largest diff. electron density, peak/hole: 0.326/–0.217 e Å^{-3}. The crystals were grown by slow evaporation of an ethanol solution at room temperature.

Crystal data for β-**1**. $C_{17}H_{18}N_2O_5$, dark red needle (0.561×0.063×0.040 mm), $M = 330.33$, triclinic, space group $P\bar{1}$ (no. 2), $a = 5.425(3)$, $b = 11.666(7)$ and $c = 14.060(9)$ Å, $\alpha = 113.388(9)°$, $\beta = 95.061(9)°$, $\gamma = 96.102(8)°$, $V = 803.7(9)$ Å^3, $Z = 2$, $Z' = 1$, $T = 100(2)$ K, $d_{calc} = 1.365$ g cm^{-3}, μ(MoKα) = 0.102 mm^{-1}, $F(000) = 348$, $T_{max/min} = 0.9580/0.6217$. 6709 reflections were collected ($1.925° \leqslant \theta \leqslant 25.343°$, index ranges: $-6 \leqslant h \leqslant 6$, $-13 \leqslant k \leqslant 14$, $-15 \leqslant l \leqslant 16$), 2900 of which were unique ($R_{int} = 0.0612$, $R_\sigma = 0.0891$, completeness to θ_{max} 98.4%). The refinement of 267 parameters with 103 restraints converged to $R_1 = 0.0550$ and $wR_2 = 0.1222$ for 1667 reflections with $I > 2\sigma(I)$ and $R_1 = 0.1094$ and $wR_2 = 0.1456$ for all data with $S = 0.997$ and largest diff. electron density, peak/hole: 0.233/–0.281 e Å^{-3}. The crystals were grown by slow evaporation of a chloroform solution at room temperature.

CCDC 2086558 and 2086559 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

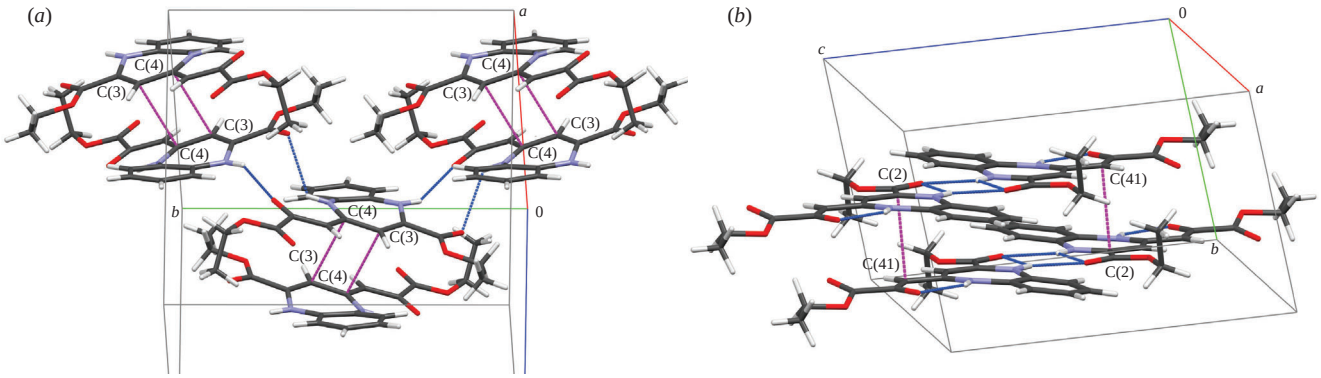


Figure 3 Fragments of molecular packing in the crystals of (*a*) polymorph α-**1** and (*b*) polymorph β-**1**, demonstrating two types of π···π interactions. Hydrogen bonds N–H···O and π···π contacts are shown by blue and magenta dashed lines, respectively.

Thermally induced phase behavior was studied by differential scanning calorimetry. Upon heating the α phase obtained from an ethanol solution, an endothermic process corresponding to melting is observed (146.5 °C, 104 J g^{-1}). In contrast, the β phase crystallized from a chloroform solution exhibits a more complex behavior, namely a sequence of endothermic, exothermic and again endothermic events. This picture is typical for the case of melting of a metastable form, cold crystallization of a more thermodynamically stable one and its subsequent melting.[19–21] Thus, the β phase melts at about 123 °C, forming a supercooled melt. The latter crystallizes, forming the more thermodynamically favorable α phase. Finally, the newly obtained α phase melts when it reaches the melting point (Figure S2).

Crystallization of the melt in an aluminum crucible occurs only after a few hours at 20 °C. The phase thus obtained is characterized by melting at *ca.* 123.3 °C, complicated by the slow cold crystallization of the α form. We believe that, in our case, the metastable but kinetically more preferable β phase is formed from the melt, and its melting was observed as described above.[22] The difference in the melting of the β form obtained from the melt and solution can be explained by the presence in the latter case of a sufficient amount of α-form crystals, which acted as seeds.

Next, we investigated the crystallization of compound **1** from solvents of various polarities, *viz.* ethanol, acetone, dichloromethane, diethyl ether, chloroform and toluene, upon evaporation at room temperature. The experiments were repeated at least three times; the composition of the obtained solid phases was controlled by powder X-ray diffraction (Figures S4–S7). As a result, only two solvents provide selective crystallization of a specific form: ethanol and chloroform give the phases α and β, respectively. From acetone and diethyl ether, the α polymorph is primarily formed, while dichloromethane leads mainly to the β form. Toluene promotes the formation of a mixture of the polymorphic modifications. Interestingly, prolonged crystallization from solutions (without solvent evaporation) allows one to observe the crystallization of needles corresponding to the β form, which recrystallize over time into prisms (the α form).[19] This observation is one more evidence of the thermodynamic favorability of the α polymorph at the temperatures studied and entirely agrees with the DSC results.

These results suggest that the formation of an H-bonded dimer as a supramolecular building block may be preferable from solvents that cannot effectively participate in H-bonding. Of course, other factors, such as the width of the metastable zone for the nucleation of each polymorph or the temperature regime, are not considered and can be significant. In general, our conclusion is consistent with the published data.[6–12]

In summary, in the solid state, benzodiazepine **1** exists in two polymorphic modifications, α and β, differing in the conformation of molecules and the supramolecular organization of the crystals. The dimer-based polymorph β turned out to be metastable and primarily crystallized from chloroform and methylene chloride solutions or the melt. The chain-based polymorph α is thermodynamic stable at the temperatures studied and primarily crystallizes from solvents that can participate in the H-bond formation.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.03.041.

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