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Ferroelectricity in glycine: A mini-review

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Glycine is the simplest natural amino acid, a basic building block for various biomaterials. Supramolecular packing of glycine molecules into three main crystalline polymorphs allows controlling their functional properties, such as piezoelectricity and ferroelectricity. Though piezoelectricity in glycine is well studied and reviewed, its ferroelectric properties were not summarized and analyzed until now. In this mini-review, we briefly discuss glycine polymorphs, their functional properties, and phase transitions, review recent findings on domain structure and polarization switching in β - and γ -glycine, and consider their possible applications in biocompatible photonic and piezoelectric devices.

KEYWORDS

organic piezoelectrics, ferroelectrics, domain structure, amino acids, glycine

Introduction

Amino acid glycine is the simplest building block of various biomaterials and is often considered a symbol of life on our planet. Therefore, it has attracted considerable attention in different research fields, mainly in materials science, pharmacology, and medicine. Glycine plays a key role in many physiological processes, e.g., in cancer cell metabolism, (Jain et al., 2012) and is used to treat various diseases, including ischemic stroke, anxiety, insomnia, schizophrenia, benign prostatic hyperplasia, etc (Gusev et al., 2000; Babić and Babić, 2009). It also serves as a bulking agent in pharmaceutical protein formulations (Horn et al., 2018). On a completely different scale, glycine has been found in the interstellar medium (Kuan et al., 2003; Ioppolo et al., 2021) and in the comas of comets and meteorites, (Elsila et al., 2009; Altwegg et al., 2016) thus providing evidence of the panspermia hypothesis (Wesson, 2010). As for the functional physical properties of crystalline glycine, they largely depend on the supramolecular packing of its molecules into three main polymorphs (α , β , and γ), resulting in different crystallographic structures (Heredia et al., 2012; Guerin et al., 2017; Gleeson et al., 2020; Boldyreva, 2021). It has been a long time established that the α -phase is centrosymmetric (space group $P2_1/n$), in which only surface piezoelectricity and pyroelectricity may exist *via* doping or water incorporation (Piperno et al., 2013; Meirzadeh et al., 2018; Dishon et al., 2020). On the contrary, β and γ phases of glycine are non-centrosymmetric (space groups $P2_1$ and $P3_1$, respectively) (Iitaka, 1960; Iitaka, 1961) and exhibit technologically significant piezoelectric responses, as has been shown by Lemanov in 2000 (Lemanov, 2000).

It was like that until 2012, when another important functional property, ferroelectricity, was reported by Heredia et al. (2012). Using a novel Piezoresponse Force Microscopy (PFM) tool and molecular modeling, it has been shown, that switchable polarization domains exist in γ -glycine microcrystals grown from the solution. Polarization switching was performed by applying DC voltage to the PFM tip at the nanoscale and switchable domains were shown to persist for a long time. That work attracted a wide interest of the research community in different fields and has launched a new round of experimental and theoretical studies of glycine (Bystrov et al., 2014; Bystrov et al., 2015; Bystrov et al., 2016; Guerin et al., 2017; Seyedhosseini et al., 2017; Bai et al., 2018; Tasnim et al., 2018; Hu et al., 2019; Slabov et al., 2019; Bishara et al., 2020; Dishon et al., 2020; Gleeson et al., 2020; Hosseini et al., 2020; Kholkin et al., 2021). Several reviews reported piezoelectric properties of glycine (Tayi et al., 2015; Tofail and Bauer, 2016; Guerin et al., 2017; Maiti et al., 2019; Kim et al., 2020; Li et al., 2020; Boldyreva, 2021; Xu et al., 2021). However, until now, its ferroelectric properties have not been summarized and analyzed.

In this mini-review, we summarize 10 years of rigorous research on ferroelectricity and polarization switching in β -glycine, discuss undesirable phase transitions between polymorphs influencing the ferroelectricity, ways of stabilization of ferroelectric β -phase, and its possible applications in biocompatible photonic and piezoelectric devices.

Polymorphic phases and ferroelectricity

Ferroelectricity is observed for a specific polymorphic state of the glycine— β -phase. Actually, glycine is a model material for studying polymorphism because crystalline glycine can be easily grown from the aqueous solution that, in principle, results in a mixture of different polymorphs— α , β , and γ . That is due to the Ostwald rule of stages, meaning that the less stable β -phase is formed first, (Seyedhosseini et al., 2014) and then more stable γ - and α -phases appear. Several papers discussed various possibilities to grow predominantly one phase or another (Boldyreva et al., 2003a; Lee et al., 2008; Poornachary et al., 2008). For instance, selective growth of single-phase piezoelectric γ -glycine can be achieved by the modification of the solution's pH (Boldyreva et al., 2003a; Lee et al., 2008) or addition of trace amounts of chiral impurities into the aqueous solution, (Poornachary et al., 2008) whereas less stable β -phase can be preferentially grown from the solution in the presence of acetic acid (Drebushchak et al., 2002) or glucose (Gerasimov et al., 2022).

In general, polymorphic crystalline phases can be distinguished by various analytical techniques such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), infrared, Raman, and solid-state nuclear

magnetic resonance (NMR) spectroscopies, and powder X-ray diffraction (Brog et al., 2013). These integral methods allow detecting the presence of tiny amounts of phases in a mixture. However, for local polarization switching experiments by PFM, the polymorphic phase of an individual microcrystal should be determined. In this case, the choice of the methods is quite limited. Roughly, a phase of an individual crystal can be identified by observation of crystals' habits by optical microscopy. Evaporation of the glycine aqueous solution droplet on a substrate leads to the formation of rhombohedral plate-like α -glycine crystals (Figure 1A), β -glycine forms elongated rectangular (needle-like) crystals (Figure 1B), and γ -glycine forms trigonal prisms (Figure 1C) (Iitaka, 1961; Bai et al., 2018). However, this is true for as-grown phases only. Due to polymorphic phase transitions, the crystal's phase may change under various external factors (temperature, gases, mechanical treatment, etc.) (Boldyreva et al., 2003b) without habit modification (Isakov et al., 2014). Therefore, special methods for the phase determination of individual microcrystals should be applied prior to studies of ferroelectricity.

This problem can be partially resolved by PFM, which allows distinguishing the centrosymmetric α -phase (which does not possess any piezoelectric activity) from non-centrosymmetric β - and γ - phases (*a priori* piezoactive). But the distinction between β - and γ - phases is more difficult. PFM measurements in combination with crystal habit observation were used in (Heredia et al., 2012); however, they have led to an erroneous attribution of ferroelectricity to the γ -phase. Further studies (Isakov et al., 2014; Seyedhosseini et al., 2014; Seyedhosseini et al., 2015; Bystrov et al., 2016; Seyedhosseini et al., 2017; Slabov et al., 2019; Vasileva et al., 2019) showed that experimental results reported in (Heredia et al., 2012) could be actually done on β -phase.

The discrimination between β - and γ -phases by PFM can be done based on the determination of the components of the piezoelectric matrix, which are different for β - and γ -phases (Guerin et al., 2017). However, this method requires precise measurements at different crystal faces, which are not always accessible. Therefore, a more convenient method for the determination of the polymorphic phase of an individual microcrystal is confocal Raman microscopy (CRM). Application of this fast and non-destructible method just before the PFM measurements allows excluding possible artifacts with phase determination. CRM is based on the analysis of spectral fingerprints of each phase (Lee et al., 2008; Surovtsev et al., 2011; Seyedhosseini et al., 2014) and was successfully used for distinguishing phases in micro- and nanocrystals of glycine (Seyedhosseini et al., 2014; Zelenovskiy et al., 2016; Seyedhosseini et al., 2017; Slabov et al., 2019) and *in situ* studying an unusual solid-state phase transition (Isakov et al., 2014).

What is especially important is that CRM demonstrated preferable nucleation and stabilization of individual

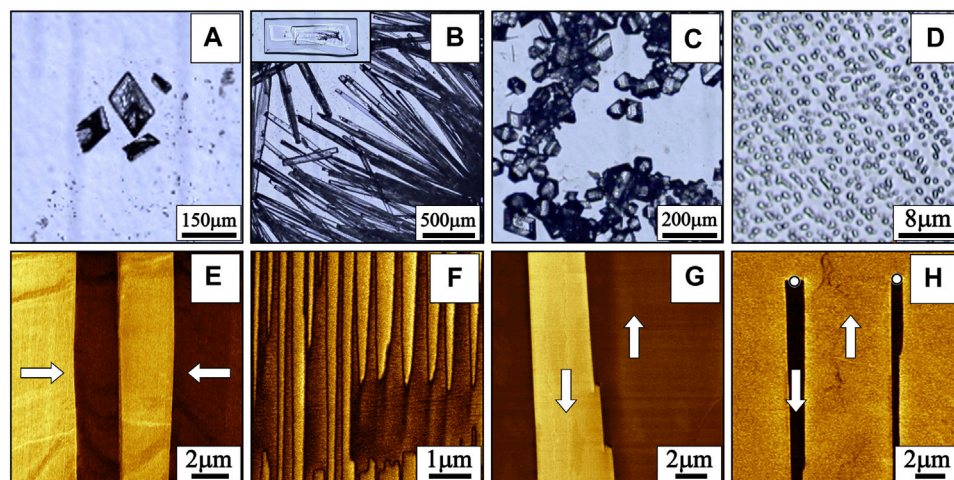


FIGURE 1

Morphology of the glycine microcrystals of different polymorphs: (A) α -phase, (B) β -phase, (C) γ -phase, and (D) microislands of β -glycine. The inset in (B) shows another common morphology of β -glycine crystals well suitable for studies of ferroelectricity. Types of as-grown domains in β -glycine (Vasileva et al., 2019): (E) stripe domains with charged domain walls, (F) quasi-periodic ensembles of needle-like domains, and (G) irregular shaped domains with segmental step-like domain walls. White arrows show the direction of spontaneous polarization. (H) Artificial domains created by the application of an external electric field to the PFM tip.

microcrystals of β -glycine and its quasi-regular arrays of nanocrystals formed *via* evaporative dewetting on a Pt substrate (Figure 1D) (Seyedhosseini et al., 2014; Seyedhosseini et al., 2017). This fact opens the way for studying ferroelectricity in β -glycine and its applications. Preferable β -phase crystallization can be also achieved in nanopores (Hamilton et al., 2008), microfluidic channels (Bhamidi et al., 2015), or under the action of standing surface acoustic waves (Bai et al., 2018). These are promising but more complicated and less studied ways for the ferroelectricity stabilization in glycine.

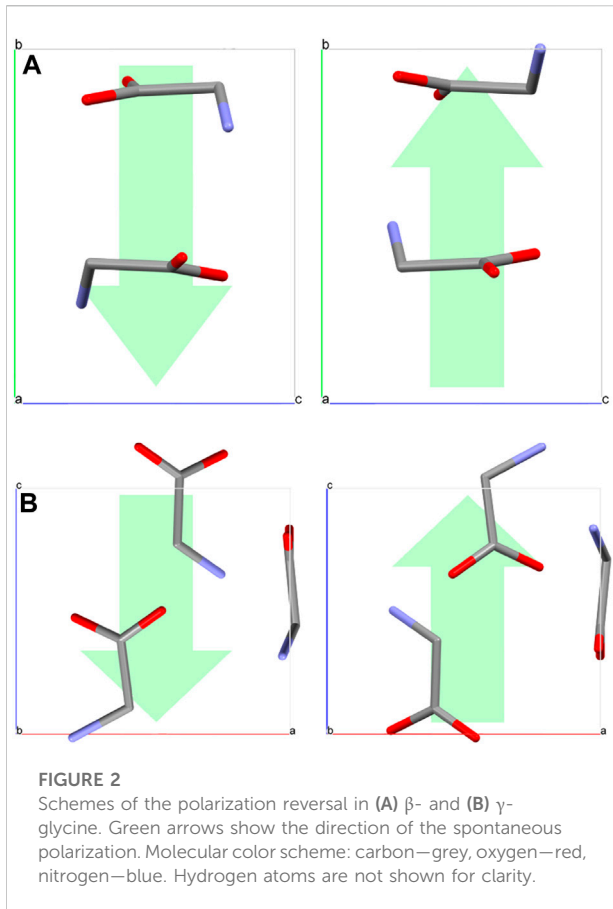
In 2005, the low-temperature calorimetric measurements on β -glycine revealed an anomaly of heat capacity at 252 K (Drebushchak et al., 2005), which was then confirmed by incoherent inelastic neutron scattering (Bordallo et al., 2008; Aree et al., 2013). Other polymorphs did not show such anomaly. The calculations of enthalpy, entropy, and Gibbs energy for all three polymorphs showed that their thermodynamic properties (and thus macroscopic physical properties) are affected by the arrangement of NH_3^+ tails of zwitterions rather than by the crystal structure (Drebushchak et al., 2005). Indeed, though, in the gas phase, the zwitterionic form of glycine molecule is less stable than the neutral one (Palla et al., 1980), it can be stabilized in a solution through the hydrogen bonds formation with water molecules (Basch and Stevens, 1990). In a solid phase, the zwitterionic structure of glycine molecules is also preserved and provides an additional interaction between the molecules (Drebushchak et al., 2005). Therefore, the anomaly in the heat capacity observed in β -

glycine was attributed to a second-order ferroelectric-paraelectric phase transition (Drebushchak et al., 2005).

The detailed phenomenological analysis of this anomaly in terms of the compressible Ising model (Kiraci, 2021) confirmed that conclusion and also demonstrated that the critical exponents in “ferroelectric” ($T < 252$ K) and “paraelectric” ($T > 252$ K) phases are consistent with those predicted from the 3D Ising model and the 2D Potts model, respectively. However, as is shown in detail in the following section, the main features of ferroelectricity, such as domain structures and the ability to switch the polarization by an electric field, well persist in β -glycine at room temperature. Therefore, the observed anomaly at 252 K may be related not to the ferroelectric-paraelectric phase transition but, highly likely, to the transition between two ferroelectric phases. This question requires additional studies.

Domain structures and polarization switching

While piezoelectricity in γ - and β -phases originates from their non-centrosymmetric space groups, its attribution to the class of ferroelectrics can be done only experimentally (Lines and Glass, 1977). PFM can serve as a perfect tool to distinguish not only piezoelectric but also ferroelectric phases due to the domain structure visualization and the polarization switching in a point (Shvartsman et al., 2002; Kalinin et al., 2010; Soergel, 2011). A multitude of recent reports (Isakov et al., 2014;



Seyedhosseini et al., 2014; Seyedhosseini et al., 2015; Bystrov et al., 2016; Hu et al., 2019; Vasileva et al., 2019) have proven that β -glycine is indeed ferroelectric with switchable polarization and diverse domain structures. The as-grown domain structure at nonpolar surfaces of β -glycine crystals, which are usually available for PFM study, consists of three types of domains (Vasileva et al., 2019): 1) stripe-like domains with flat charged domain walls (Figure 1E) appeared due to the variations of defects during the crystal growth; 2) quasi-periodic ensembles of needle-like domains (Figure 1F) appeared under the action of pyroelectric field occurred due to the cooling down of the evaporating droplet; and 3) irregular shaped domains with segmental step-like domain walls (Figure 1G).

Domains can also be created in β -glycine crystals by the application of an external electric field by the PFM tip (Figure 1H). Computer modeling based on density functional theory and molecular-dynamic simulations showed for β -glycine an average coercive field of about 1 V/nm (10^3 kV/mm) (Bystrov et al., 2015; Bystrov et al., 2016), which corresponds to 60 V applied to the PFM tip (Seyedhosseini et al., 2015). In principle, polarization switching in γ -glycine may also be possible, but it requires 4–8 times bigger electric fields (Heredia et al., 2012; Bystrov

et al., 2015). Moreover, the maximum value of the electric field near the apex of the PFM tip with the applied voltage of 100 V is about 3 V/nm only (Seyedhosseini et al., 2015). Higher voltages lead to the electric breakdown of the crystal. Therefore, a single molecule switching in γ -glycine remains a theoretical possibility. Such a big difference in threshold fields for β - and γ -glycine is due to the mechanism of the polarization reversal. As computer modeling demonstrated, (Hu et al., 2019) the spontaneous polarization of β -glycine oriented along the polar crystallographic axis b stems from an ordered arrangement of the $-\text{NH}_3^+$ groups, whereas the polarization switching occurs *via* the change of a dihedral angle between the $-\text{NH}_3^+$ groups and the plane of the carboxyl ($-\text{COO}^-$) groups (Figure 2A). At the same time, polarization reversal of γ -glycine requires the rotation of glycine molecules by 180° around an axis perpendicular to the polar c -axis (Hu et al., 2019) (Figure 2B), which makes the polarization reversal of γ -glycine much more difficult than that of β -phase.

The artificial needle-like domains created by the PFM tip propagate far outside the field area due to the kinks interaction (Vasileva et al., 2019), and their length depends on the applied voltage and pulse duration (Seyedhosseini et al., 2015). PFM tip movement during the voltage application allows the creation of tailored domain structures with different types of domain walls: neutral and charged head-to-head and tail-to-tail (Vasileva et al., 2019). Usually, tail-to-tail domain walls are flat and oriented normally to the polar axis, whereas head-to-head ones are rough and inclined (Vasileva et al., 2019). That allows suggesting that tail-to-tail domain walls possess higher conductivity, accelerating the screening of the depolarization fields created by the bound charges (Schröder et al., 2012; Schröder et al., 2014; Lu et al., 2015). This assumption is supported by the quantum chemical calculations that showed tail-to-tail walls are around seven times more stable than head-to-head ones (Bystrov et al., 2016).

Applications and perspectives

As recently demonstrated (Seyedhosseini et al., 2015; Vasileva et al., 2019), the polarization switching and the evolution of the domain structures in β -glycine crystals are qualitatively similar to those found in uniaxial inorganic ferroelectrics. This observation opens up the possibility of applying the methods of domain engineering developed earlier for the creation of tailored micro- and nanodomain structures in inorganic ferroelectrics (Shur and Ye, 2008) for organic ones, which are highly demanded elements of biocompatible photonic devices. It is known that organic nonlinear optical materials have an advantage over their inorganic counterparts due to their big molecular

polarizability and the ability to tune their properties by chemical modifications (Humar et al., 2017). In the case of crystalline organic ferroelectrics, such as β -glycine, the nonlinear optical properties can be additionally improved by the methods of domain engineering (Shur and Ye, 2008) by the creation of a periodical domain structure. Periodically poled β -glycine crystal can significantly enhance the effectiveness of the second harmonic generation and optical parametric oscillation, (Scrymgeour et al., 2014) thus allowing the usage of glycine in biocompatible photonic devices for quantitative tissue imaging and diseases diagnosis (Campagnola, 2011).

Stabilization of β -glycine crystals by Pt substrate (Seyedhosseini et al., 2014), strong piezoelectric activity exceeding that of classical perovskite piezoelectric ceramics (Heredia et al., 2012; Guerin et al., 2017), and nonlinear susceptibility much higher than that of γ -glycine (Gleeson et al., 2020), make β -glycine a promising functional material for various biomedical applications such as wearable and implantable sensors (Bishara et al., 2020; Hosseini et al., 2020; Li et al., 2020), energy harvesting, (Guerin et al., 2017) and nonlinear optical devices (Seyedhosseini et al., 2014; Gleeson et al., 2020). Recently, the combination of chitosan fibers with β -glycine allowed the creation of a new biodegradable sensor for sub-bandage pressure monitoring with quite high sensitivity in the range from 5 to 60 kPa (Hosseini et al., 2020). However, obtained spherulite-like β -glycine crystal structures demonstrate mainly shear piezoresponse that limits the applicability and sensitivity of the sensor. Another configuration of a sensor with β -glycine crystals confined in the cylindrical nanopores with the polar axis oriented along the pores provided pressure sensitivity as low as 1 Pa (Bishara et al., 2020). The application of inkjet printing suggests additional ways of designing the next-generation biosensors (Buanz and Gaisford, 2017; Slabov et al., 2019).

Though ferroelectricity in γ -glycine still remains a theoretical possibility, it also could be interesting for developing wearable and implantable bioelectronic devices even regardless of its slightly weaker piezoelectric response (Guerin et al., 2017). That is due to its phase stability and the pronounced positive therapeutic effect on cognitive functions and neural activity, as compared with α -glycine (Markel et al., 2011; Malakhin et al., 2012). As far as we know, the biological activity of the β -glycine was not studied yet. The combination of outstanding functional properties, inherent biocompatibility, stability, and direct therapeutic effect can endow γ -glycine-based sensors with additional multi-aspect functions. Recently, they have been grown as wafer-scale films in combination with PVDF (Yang et al., 2021) and demonstrated much higher sensitivity than PVDF polymer patches (Okosun et al., 2021).

Moreover, we suppose that humidity-controlled phase transitions (Isakov et al., 2014) allow, in principle, the

creation of β - γ and β - α “chimera” crystals with the combination of two or even three polymorphic phases in one crystal. Such a combination of phases and thus functional properties may additionally expand possible applications of glycine and other amino acid crystals. At the same time, such devices would be able to disintegrate and resorb after completing their work cycle without any adverse long-term effects (Hosseini et al., 2021).

The idea of the control of functional properties *via* supramolecular packing (Guerin et al., 2017) can probably be also extended to β' , δ , ε , and ζ phases of glycine existing at high pressures (Boldyreva et al., 2005; Dawson et al., 2005; Goryainov et al., 2005; Goryainov et al., 2006). Thus, ε -glycine at about 4.3 GPa belongs to piezoelectric space group Pn , (Dawson et al., 2005) whereas δ -glycine belongs to the centrosymmetric space group $P2_1/a$ (Dawson et al., 2005). Recent computer modeling (Guerra et al., 2020) revealed three more potentially piezoelectric phases of glycine: m , t , and o (space groups $P2_1$, $P4_3$, and $P2_12_12_1$, respectively) that were not observed experimentally yet. These exotic glycine polymorphs are not stable under ambient conditions. However, the possibility of finding ways for their stabilization in further research (as it happened with metastable β -glycine) cannot be ruled out. The authors foresee that such a simple molecule as glycine will bring many more surprises in the future.

Conclusion

In this mini-review, we summarized the recent findings on ferroelectric properties and polarization switching of β - and γ -phases of glycine. We demonstrated that due to the transitions between polymorphic phases, the crystal habit is not a reliable method for choosing the appropriate crystals for the research, and additional phase confirmation by confocal or micro-Raman spectroscopy is highly recommended. Recent experimental and computer simulation studies of domain structures and polarization switching undoubtedly confirmed ferroelectricity in β -glycine, whereas a single molecule switching in γ -glycine still remains a theoretical possibility. Regardless of the metastability of the β -phase, its stabilization inside nanopores or microfluidic channels, as well as at the Pt substrates, allows considering its usage in various applications, whereas the outstanding nonlinear optical properties and the ability to create stable periodical domain structures make β -glycine a promising material for biocompatible photonic devices. We suppose that the combination of two or three polymorphic phases in one crystal is potentially achievable due to the humidity-controlled phase transitions, and searching the ways for effective stabilization of high-pressure polymorphic phases can open new ways for applications of crystals of this remarkable amino acid.

Author contributions

Conceptualization, AK; literature review, PZ, DV, and SV; writing—original draft preparation, PZ; writing—review and editing, SK and AK.

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