



Investigating structural features which control the dissolution of bioactive phosphate glasses: Beyond the network connectivity



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ABSTRACT

We have used classical molecular dynamics simulations to characterise the structure of three compositions of silver-containing phosphate glasses with 45 mol% P_2O_5 , 30 mol% CaO , and varying amounts of Na_2O and Ag_2O . These compositions all have the same network connectivity, allowing us to highlight two other structural features which will affect the glass dissolution. Firstly, the number of different phosphate chains bonded to each modifier atom was computed and it was observed that silver and sodium bind to roughly the same number of phosphate chains, despite the differences in their local environments. Secondly, the clustering of modifier cations was characterised and shown to be enhanced at low concentrations of sodium and silver, but not to exist for calcium.

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1. Introduction

Very many different types of glasses are implanted into the body for medical reasons. Because of its amorphous structure, glass is not restricted to specific stoichiometries, as crystalline materials are. This means that glass has a wider range of possible compositions, and the properties of an amorphous implant can be tuned to optimise the efficacy of the therapy by varying the glass composition.

Glasses implanted into the body will react chemically with their local environment [1,2], and many will degrade [3,4]. Understanding the degradation is crucial [5]: the dissolution products of 45S5 bioglass are useful and promote the creation of new bone [6], by contrast, aluminosilicate glass compositions used for radiotherapy must be as durable as possible [7]. If a glass is to deliver a drug or nutrient at a specific rate, then its dissolution needs to be precisely controlled [8,9]. Much recent research work has sought to improve our understanding of glass dissolution processes and the structural and compositional features that affect them.

In principle, the factors which control glass dissolution are wide-ranging and could include the glass structure at various length scales, the diffusion of ions through the glass and their exchange between the surface and environment, changes in the glass surface structure, the solution chemistry and pH, among others. However, despite these possibilities, a good understanding of the glass dissolution can often be obtained from its bulk atomic structure alone, which is useful

because the bulk structure is accessible from experiment and computer simulation.

The most important structural parameter which affects the dissolution of a glass is the *network connectivity* [10,11]. The network connectivity (NC) is defined as the average number of bridging oxygen (BO) atoms bound to a network-forming cation, where a BO atom is defined as an oxygen atom which is chemically bound to two network polyhedra. Oxygen atoms which do not connect two network polyhedra are called non-bridging oxygen (NBO) atoms. The NC depends critically on composition because the inclusion of network-modifying cations such as sodium or calcium typically breaks T–O–T bonds (where T is a network former, phosphorus in these glasses) causing the formation of NBO and decreasing the network connectivity [12].

High values of NC typically indicate a well-connected glass network which is not prone to dissolution and is not bioactive. Lower values indicate a fragmented, disconnected network which has many reactive sites and is both prone to dissolution and bioactive. 45S5 bioglass, which is highly bioactive and bonds to both bone and soft tissue, has a NC of 1.9; likewise, bioactive phosphate glasses which have 45 mol% P_2O_5 [3] have NCs of 1.8. Whilst bioactivity is difficult to define and is certainly not a precise function of NC, Hill [11] identified that compositions with NC as high as 2.6 can still be bioactive, but Tilocca identified that compositions with NC greater than 3.0 are bioinactive and very durable [12,13].

It was clear from its first uses [10,11] to describe glass structure, that the NC cannot capture all of the structural features which affect the dissolution. Recently, we and others have shown through computer simulation other features of the glass structure, particularly present at length

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Table 1
The simulated compositions (mol%) and their densities.

Composition	P ₂ O ₅	Na ₂ O	Ag ₂ O	CaO	Density (g cm ⁻³)
A5	45.0	20.0	5.0	30.0	2.707
A10	45.0	15.0	10.0	30.0	2.854
A15	45.0	10.0	15.0	30.0	3.001

scales beyond the first neighbour shell, which are also pertinent. We briefly outline some here:

- i. Clustering of network-modifying cations, such as Na, Ca, Ag, Sr, Y. These cations are not necessarily distributed evenly throughout the glass [13–16], and cluster together, which decreases bioactivity [12].
- ii. Mesoscale segregation of network. The NC can vary spatially throughout the material: for example, fluorinated 45S5 bioglass separates into silicate-rich and silicate-poor regions due to fluorine's preferential bonding to the network modifiers in the glass [17,18], which does not happen for fluorinated phosphate-based glass [19].
- iii. Modifier-chain bonding. For phosphate-based bioactive glasses with <50 mol% P₂O₅, the dissolution is controlled by the bonding of the phosphate chains to the modifier atoms [20], such that small changes in the Na/Ca ratio, which do not alter the NC, lead to order-of-magnitude changes in the dissolution rate [3,21].

In this work, we use an example multicomponent system, i.e., a silver-containing phosphate-based bioactive glass, with 45 mol% P₂O₅ and varying amounts of Na₂O, Ag₂O and CaO. In addition to the interest from the glass structure perspective, silver-containing glasses are known to be antibiotic [8,22]. Substituting Ag₂O for Na₂O leads to a decrease in glass dissolution rate [22] for glasses with 50 mol% P₂O₅. There is no evidence for mesoscale segregation of this system, and so we will concentrate on the other two factors, namely: clustering of modifier cations, and the nature of network-modifier-chain bonding and its changes with composition. These properties are accessible through the use of molecular dynamics (MD) simulation techniques, which have been used not just to study glass properties, but also to connect the atomic structure of glass to its use as biomedical implants [12,13,15,16,20,23–25]. In this work, we use classical MD, in which the interatomic forces are approximated by an empirical expression. Although this approximation can introduce errors, it also reduces the computational expense sufficiently to allow us to model systems containing thousands of atoms, which are large enough to look at modifier-chain bonding and clustering. Smaller, more accurate, models created with first-principles MD, in which the forces are computed from a quantum-mechanical

representation of the electronic structure, are not large enough to allow this.

2. Methods

Classical molecular dynamics simulations were performed using the DLPOLY code [26] using a formal-charge, polarizable interatomic force field previously used by us to describe silver-containing [27] and other [20,28] phosphate-based bioactive glasses, in simulations which have given glass structures in agreement with experiment.

The simulation methodology used is identical to that in Ref. [27], which we outline briefly here. Models containing about 2000 atoms were prepared by randomly and independently placing atoms into a cubic periodic box of the appropriate density, subject to the constraint that no atom be closer to another than within ~85–90% of the expected interatomic separation. The densities of these compositions were extrapolated from the experimentally measured density of the Ag-free composition [29], using our knowledge of how Ag₂O substitution for Na₂O affects the density of very similar glass compositions [27]. After a short zero-temperature relaxation, the simulation was run in an NVT ensemble for 50 ps at 2500 K to equilibrate the liquid. The temperature was then reduced in units of 100 K, and at each temperature, the simulation was run for 50 ps, corresponding to a cooling rate of ~2 K/ps. At 300 K, the simulation was run for 250 ps, the last two-thirds of which forms the production run. All data stated are averaged over snapshots taken from this run. Simulated compositions and densities are given in Table 1.

Although this cooling rate is substantially faster than that used to prepare glasses experimentally, simulated cooling rates of this order of magnitude have been used to prepare accurate structural models of glasses in agreement with experimental results using classical molecular dynamics simulations [28,30].

3. Results

Pictures of the models at 300 K are given in Fig. 1.

Because the local silver environment in phosphate-based glasses has been studied before [27], as has the structure of Ag-free phosphate glasses [20,28], we mention them only in the context of those structural features which most profoundly affect the dissolution, which have not yet been characterised for these glasses.

The modifier–oxygen bond lengths and coordination numbers are given in Table 2. The coordination numbers are broken down into bonding to bridging and non-bridging oxygen atoms. Although all modifier atoms prefer to bond to NBO, when more than one are present, they “compete” to satisfy their preferred bonding environment [31]. This

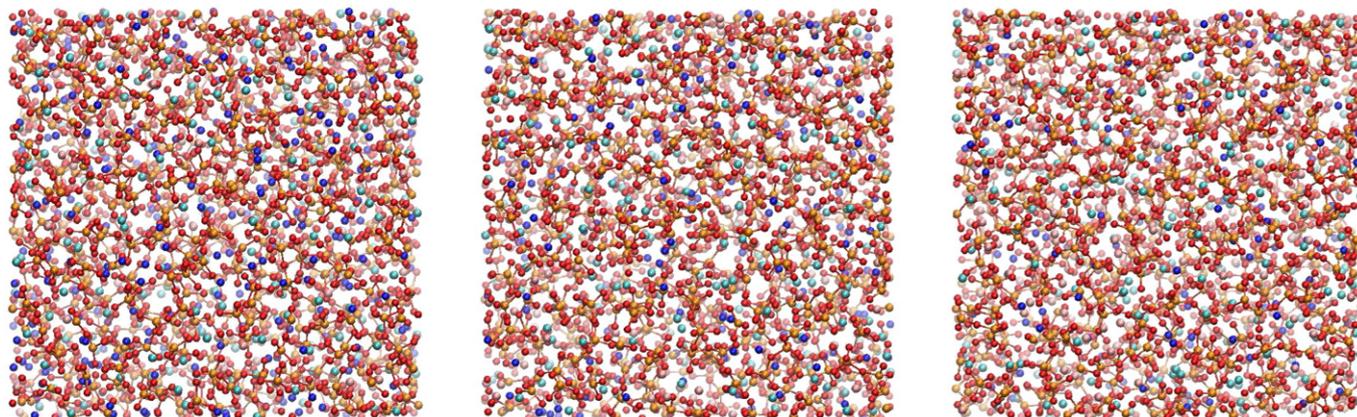


Fig. 1. Views of the A5 (left), A10 (middle) and A15 (right) compositions. The colours are red (oxygen), tan (phosphorus), dark blue (sodium), light blue (calcium) and pink (silver).

Table 2

Bond lengths and coordination numbers to all oxygen atoms (CN), to bridging oxygen atoms only (CN(BO)), and to non-bridging oxygen atoms only (CN(NBO)). Cutoffs are 3.2 Å for all modifier–oxygen pairs.

	Ag–O	Na–O	Ca–O
A5			
Bond length (Å)	2.30	2.35	2.33
CN	5.88	6.34	6.37
CN (BO)	1.15	1.18	0.36
CN (NBO)	4.73	5.16	6.01
A10			
Bond length (Å)	2.29	2.36	2.33
CN	5.59	6.33	6.32
CN (BO)	0.89	1.21	0.40
CN (NBO)	4.69	5.12	5.92
A15			
Bond length (Å)	2.27	2.37	2.33
CN	5.46	6.17	6.23
CN (BO)	0.89	1.28	0.40
CN (NBO)	4.57	4.89	5.83

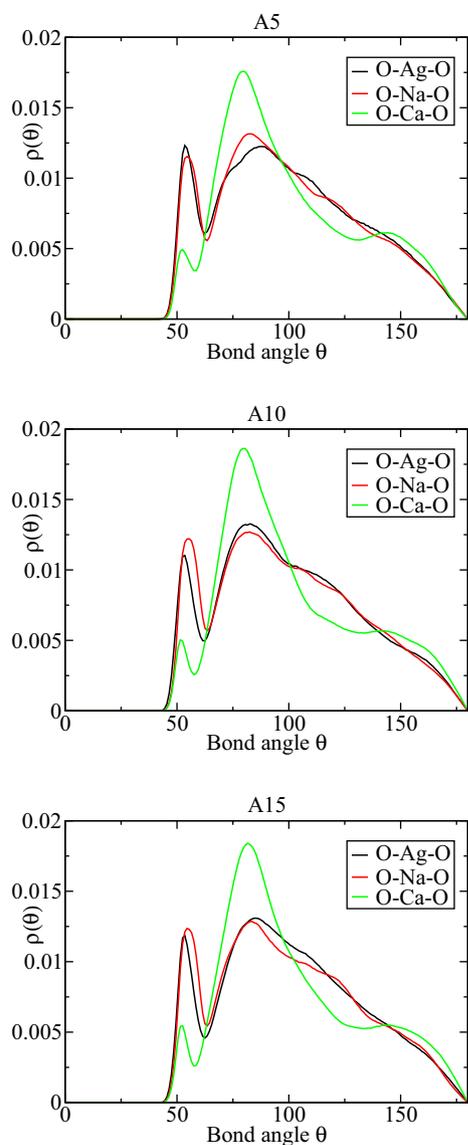


Fig. 2. Oxygen–modifier–oxygen bond-angle distributions for the A5 (top), A10 (middle) and A15 (bottom) compositions. The colours are black (O–Ag–O), red (O–Na–O), green (O–Ca–O).

Table 3

The distribution (in %) of numbers n of phosphate chains bound to different modifier atoms for the glass compositions studied.

	n (%)							Average
	0	1	2	3	4	5	6	
A5								
Ag	0	0	16	44	38	2	0	3.26
Na	0	0	14	49	35	3	0	3.25
Ca	0	0	5	26	41	26	2	3.94
A10								
Ag	0	2	15	52	28	3	0	3.21
Na	0	0	16	45	35	2	0	3.16
Ca	0	0	4	27	52	16	1	3.83
A15								
Ag	0	3	14	49	32	4	0	3.01
Na	0	2	25	47	25	2	0	3.21
Ca	0	0	7	33	44	16	2	3.73

means that the NBO/BO ratio often differs around different modifier atoms, affecting the bioactivity [15,20].

Oxygen–modifier–oxygen bond-angle distributions for the three compositions are given in Fig. 2. Although modifier atoms typically have rather broad bond-angle distributions, reflecting the wide range of possible bonding environments, there are often differences between the different modifiers, particularly in the amount of “intra-tetrahedral” bonding, in which a modifier atom bonds to two atoms from the same phosphate PO_4 tetrahedron [16,20].

As mentioned in the introduction, different modifier atoms bond to different numbers of phosphate chains. The oxygen atoms in the first coordination shell of the modifier atoms are also bonded to PO_4 phosphate tetrahedra which are parts of these phosphate chains. The distribution of numbers of phosphate chains bonded to each type of modifier atom was calculated and is given in Table 3.

Clustering of modifier cations was assessed by comparing the observed number of atoms N_{obs} in a coordination sphere to that which would be expected if the modifier cations were distributed homogeneously throughout the sample N_{hom} and computing the ratio $r = N_{obs}/N_{hom} = (\text{CN} + 1) / (\frac{4}{3}\pi r_c^3 \rho)$, where CN is the M–M coordination number of the central modifier atom M, r_c is the cutoff radius, and ρ is the number density of modifier atoms in the model [13,14,32]. In this work, r_c is set to 5 Å, as in Ref. [14]. Clustering ratios are reported in Table 4. Values of $r > 1$ imply that clustering is occurring, with a ratio $r = 1$ implying that the atoms are distributed as if randomly.

4. Discussion

As outlined in the introduction, in this work we are interested in the structural features which affect the dissolution of phosphate glasses, other than the network connectivity. To remove any influence of changes in the NC from our results, the glass compositions chosen here have been constructed such that they all have the same NC.

The local atomic environment of silver in related phosphate glasses has already been discussed at length [27], as has the structure of Ag-free phosphate glasses [20,28], and so we confine this discussion to those structural features which are likely to affect the glass dissolution.

In glasses with < 50 mol% P_2O_5 , the structure is made up of finite-length unbranched chains of PO_4 phosphate tetrahedra, bound to the

Table 4

The clustering ratios r for the different modifier atoms M.

M	A5	A10	A15
$r(\text{Ag})$	2.0	1.5	1.3
$r(\text{Na})$	1.1	1.2	1.5
$r(\text{Ca})$	1.0	0.9	1.0

modifier atoms, in this case, sodium, calcium and silver. For Ag-free glasses, we have shown [20] that Na binds to fewer chains than Ca does, and that increasing the Ca/Na ratio of the glass will make the glass less prone to dissolution, as seen experimentally [3], because of the increased amount of cross-linking between different phosphate chains. We know from experiment [22] that substituting Ag₂O for Na₂O reduces the dissolution rate for glasses with 50 mol% P₂O₅.

The silver ion has a single charge, as does the sodium ion, and the effects of changing the Ag/Na ratio are likely more subtle. We see from Table 3 that silver and sodium typically bond to roughly the same number of phosphate chains (3.0–3.3 for Ag, 3.2–3.3 for Na).

Although the two ions have the same charge, Ag⁺ is slightly larger, with an ionic radius of 1.29 Å compared to 1.16 Å for Na⁺. The field strength of an ion is defined [31] as the ionic charge divided by the square of the interatomic distance, and the distance will be larger for a larger ion. Ag⁺ therefore has a field strength between that of sodium and calcium, and will therefore [31] be bonded to a number of BO that is less than that of sodium but more than that of calcium, as we confirm from Table 2. This could imply that a silver ion is bound to more phosphate chains than a sodium ion, because BO will connect two phosphate tetrahedra, which are part of the same chain by definition. This will mean that for a given number of tetrahedra chemically bonded to a modifier atom, there could be fewer chains bonded to a silver ion than to a sodium ion.

However, two effects mitigate this trend. Firstly, silver has a smaller coordination number than sodium (Table 2), reducing the potential number of phosphate chains in its first coordination shell. Secondly, sodium and silver have similar amounts of “intra-tetrahedral” bonding, that is, bonding to two oxygen atoms from the same PO₄ tetrahedron, which is visible from the similar intensities of the peaks at ~60° in the O–Ag–O and O–Na–O bond-angle distributions (Fig. 2). This implies a similar number of phosphate chains in the coordination shell of these two ions.

We have previously identified that the field strength of the modifier ions affects the dissolution of the glass containing them, and that modifier atoms with higher field strengths will likely bind to more phosphate chains, e.g., substituting a lower-field-strength modifier by a higher-field-strength modifier will increase glass durability [3,20,22]. It is clear from this study, though, that this is not always the only or dominant effect.

Clustering of modifier cations is known to inhibit bioactivity [12] by strengthening the glass network, although the exact mechanism is unknown. Clustering can be characterised from simulation through the calculation of the clustering ratio *r*.

From Table 4, we see that calcium is distributed homogeneously throughout the glass, with *r* very close to 1 for all compositions. Silver and calcium both cluster slightly (*r* > 1) but seem to cluster together more at lower concentrations: silver has its highest clustering ratio for the A5 composition, and sodium has its highest clustering ratio for the A15 composition, which has the lowest amount of sodium. This phenomenon has also been observed when yttrium clusters in aluminosilicate glasses [13].

These clustering ratios are not much larger than one, and hence are unlikely to be detrimental to the bioactivity of the glass, as similar ratios have been reported for compositions known to be bioactive [14,15], but this clustering could affect other properties of these glasses, for example, the dynamics of silver ion release and hence the glass's antibacterial properties.

5. Conclusion

To conclude, we have looked at compositions of Ag-containing phosphate glasses with identical network connectivities in order to

characterise the effect of structural features on the bioactivity and dissolution. By doing so, we have highlighted some structures – in this case, phosphate–modifier bonding and modifier clustering – which affect the dissolution of these bioactive glasses.

It is rather challenging to disentangle the effects of these structures on the dissolution rate. The experimental data [22] that we have, are on glasses with 50 mol% P₂O₅ which has a NC of 2.0 and therefore a polymeric structure, so it is possible that our simulated data are not directly comparable. For our simulated compositions, we observe that silver and sodium ions are bound to about the same number of phosphate chains which would imply that the change in dissolution has a different cause. Each of these two ions clusters spatially, and this is enhanced at low concentration, but the precise connection between changes in the clustering ratio and dissolution is unknown. This underlines the fact, as mentioned in the introduction, that the dissolution of these glass compositions can depend on several properties of the glass.

Therefore, although these features may not form a complete picture of the glass dissolution, in order to optimise these glasses for a specific dissolution rate, for example for a specific therapy, they must be taken into account.

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