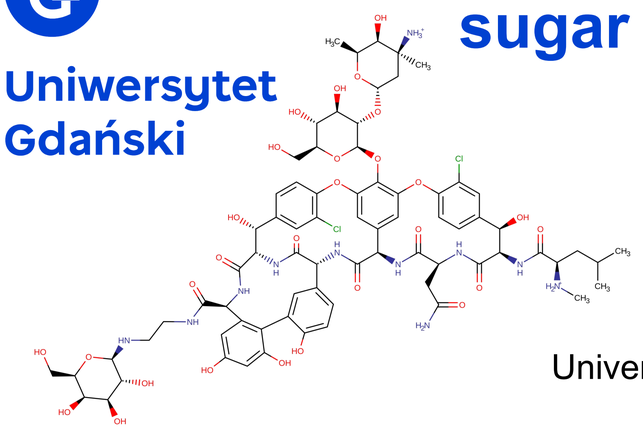
Molecular dynamics study on the influence of C-terminal sugar substitution on dynamics and conformation of vancomycin derivatives



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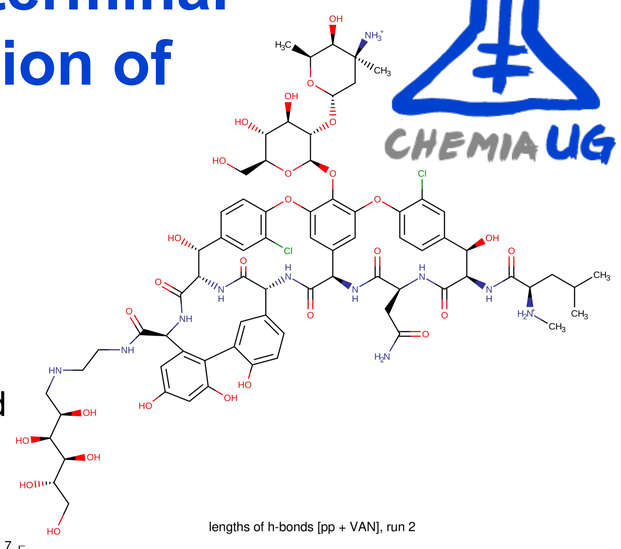


Introduction

Vancomycin (Van) is a glycopeptide antibiotic used in the prophylaxis and treatment of infections caused by Gram-positive bacteria. It prevents incorporation of N-acetylmuramic acid (NAM)- and N-acetylglucosamine (NAG)-peptide subunits into the peptidoglycan (PG) matrix, the major structural component of Gram-positive bacteria cell walls.

We were going to test *in silico* new Van derivatives and their abilities to form an alternative points of interaction with the PG C-terminus. It was meant to serve enhancing of existing Van binding to PG and to counteract possible weakening of the binding caused by bacteria PG mutations.

Extensive dynamic behavior analysis should reveal how the introduced modifications affect binding properties of modified Van.

Rationale

Modifications of the native Van structure were carried out in two different ways. The first modification was an addition of ß-D-galactopyranose or D-glucitol to the C-terminus of Van heptapeptidic macrocyclic ring. The second Van modification was an addition of 10 carbon-long, hydrophobic chain. This chain was added directly to the vancosamine. It's presence can enhance lipophilic effect of the new Van derivative. Such a modification facilitates approaching of the antibiotic molecule to the PG cell-wall layer, as observed in some glycopeptide antibiotics, e.g. telavancin. To find the best Van analog, we applied all these Van structure alterations in all possible combinations. Previous computational investigations revealed that interactions between PG precursor and modified Van C-terminus strongly depends on the distance between PG precursor and a type of sugar added C-terminally. [1]

Methods

All non-standard groups were parametrized for the AMBER *ff03*, and *glycam06* force fields. All partial atomic charges were computed with the RESP protocol. Initial Van structure was based on crystallographic Van structure (PDB ID: 1FVM, chain O) in complex with Ace–Ala–D-iGlu–Lys–D-Ala–D-Ala ligand.

A pentapeptide cell wall precursor (Ace–Ala–D-iGlu–Lys–D-Ala–D-Ala) was added in the position known to form an active complex with Van. This short peptide is known to sufficiently mimic presence of the PG structure and can be used to verify the hypothesis of new bond formation between Van and PG. [2] All Van derivatives with their pentapeptides (PG precursors) were constructed based on this native complex.

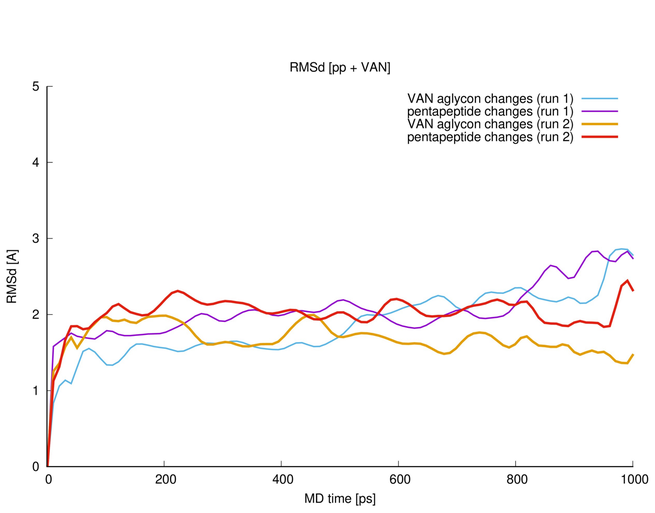
The pre-equilibrated water boxes (TIP3P model) as well as counter ions for charge neutralization, were added to the computational system. The rectangular computational system containing Van derivative in complex with PG precursor was extended by solvation layer by 12 Å in each direction. Geometry of each Van derivative–PG precursor complex was optimized and energy minimized. After initial geometry optimization, the hydrogen bond restraints (applied to five hydrogen bonds) were released to provide mutual adjustment of Van derivative and PG fragment. Initial equilibration with adjustment to 300 K was carried out for 0.5 ns. Subsequently, all complexes were submitted to the 1 ns of isothermal-isobaric (300 K) molecular dynamics MD in the AMBER suite of programs then analyzed. The analysis of results included root mean square deviation (RMSd) calculations and control distances calculations.

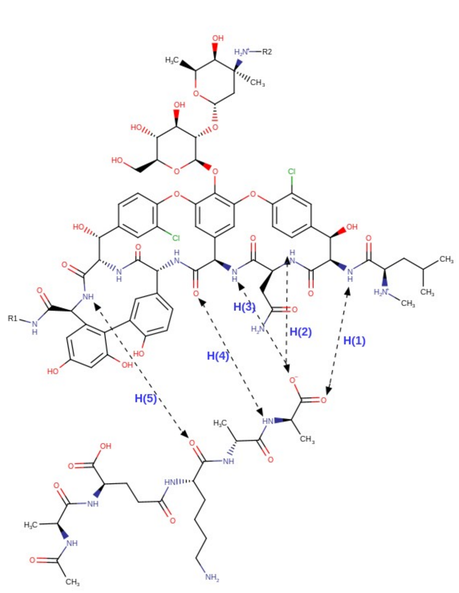
Results

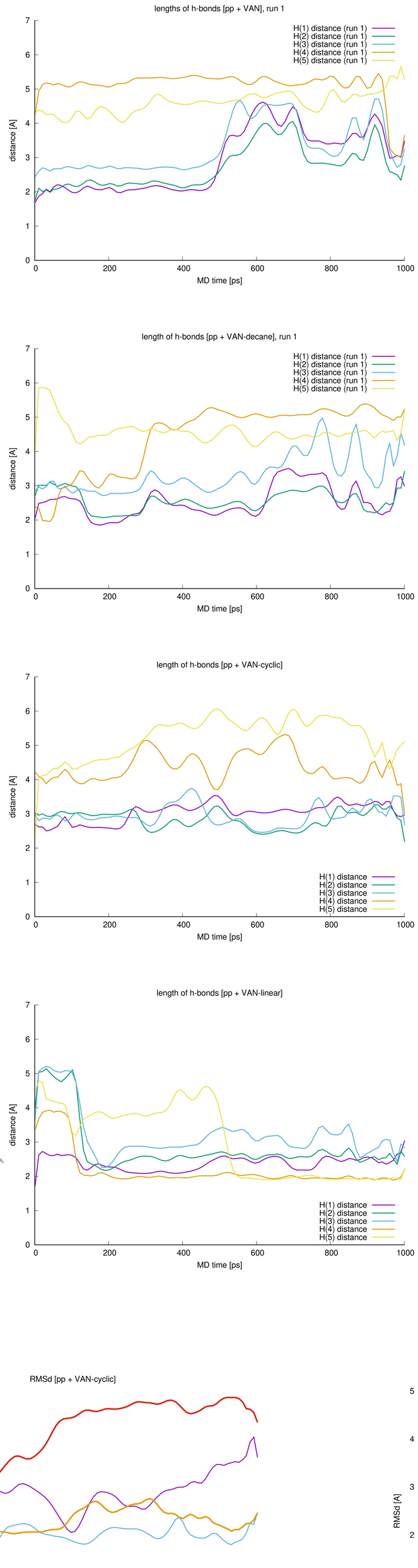
Basing on RMSd changes, total energy changes and most important: changes in length of control distances, we conclude that the most advantageous modification was the C-terminal addition of linear sugar without the presence of decane chain.

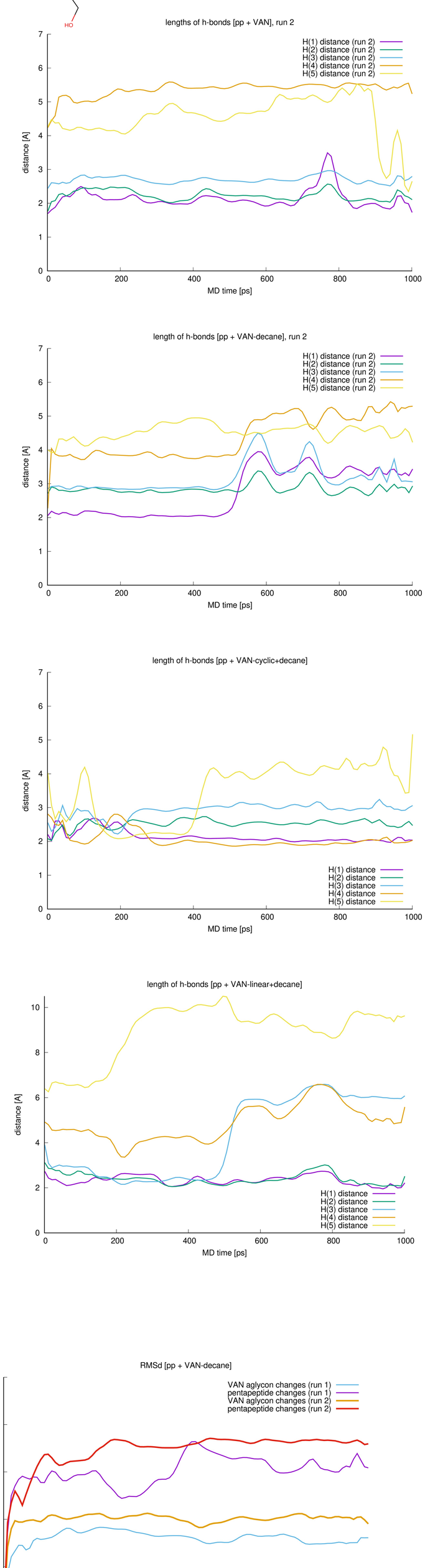
The stabilized distances of all control distances indicate that bonding of such Van analog is advantageous. The modifications not only did not impair the quality of the interaction with the PG, but proved to be even more advantageous in this modeling (see the plots) than in the case of the analogous control distances for the Van complex without modifications.

The second, preferred analog is Van incorporating cyclic sugar with the presence of decane chain on vancosamine. Only one control distance (H(5)) seems to be fluctuating in this case.









References

[1] Ślusarz, R.; Samaszko-Fiertek, J.; Dmochowska, B.; Madaj, J. Molecular dynamics study on the influence of C-terminal sugar substitution on dynamics and conformation of vancomycin derivatives. *Journal of Carbohydrate Chemistry*, **2017**, *36*, 45–58.

[2] Williams, D. H. and Bardsley, B., The Vancomycin Group of Antibiotics and the Fight against Resistant Bacteria, Angew. Chem. Int. Ed. 38, **1999**, 1172–1193.

Acknowledgments

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