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Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. **00(0)** 1-13 (2026)
JSCS–13721
Original scientific paper
Published DD MM, 2026

December armageddon: Biothermodynamic analysis of rhinoviruses based on calculation of Gibbs energy of antigen-receptor binding and biosynthesis of rhinovirus particles

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(Received 11 January; revised 12 February; accepted 8 April 2026)

Abstract: The subject of this research is a battle that is repeated every year and spreads epidemically on different territories, causing a large number of infected cases and casualties. Infections with rhinovirus are well known to the biomedical sciences. However, for deeper understanding of causes of rhinovirus disease and virus-host interaction (infection) it is necessary to understand it from the perspective of chemistry and biothermodynamics. This paper presents the empirical formulas, the driving forces of rhinovirus-host interactions, as well as a mechanistic model of virus-host interactions at the cell membrane and in the cytoplasm. Based on the described data, conclusions are presented about why 50% of infections of upper respiratory pathways are caused by rhinoviruses. For the first time, Gibbs energies of biosynthesis of virus particles of Rhinoviruses A2, B3 and C15, as well as Gibbs energy of binding of Rhinovirus A2 are presented, which are needed to understand the lifecycle of rhinoviruses.

Keywords: enthalpy; entropy; growth reactions; empirical formulas; molar mass.

INTRODUCTION

Rhinovirus is the most common cause of seasonal respiratory infections. It's estimated that the rhinovirus is the cause of 50% of all viral respiratory infections. Rhinovirus belongs to RNA viruses.[1,2] The rhinovirus virion is unenveloped.[3,4] The virion consists of 60 copies each of the structural proteins VP1, VP2, VP3 and VP4.[5-8] The viral structural proteins form a capsid that surrounds a single-stranded positive-sense RNA genome.[9,10] Rhinoviruses are classified into RV-A, RV-B and RV-C species, each of which contains many subvariants.[11,12]

From above we can conclude that rhinovirus represents a macromolecular assembly that consists of nucleotides and amino acids. As such, the rhinovirus can

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https://doi.org/10.2298/JSC260111019P

be understood, not just as a biological, but also as a chemical entity.[13] Due to their chemical nature, viruses can be characterized by an empirical formula, as well as thermodynamic properties (enthalpy, entropy and Gibbs energy).[14] Rhinovirus performs life processes inside host cells.[15] In its essence, life processes represent chemical reactions, which obey the laws of chemical kinetics and thermodynamics, and are led by a driving force. For example, binding of viruses to host cells is a reaction similar to protein-ligand interactions.[14,16] It is led by a driving force – Gibbs energy of binding.[14,17] Virus multiplication also represents a reaction of polymerization of amino acids into viral proteins and nucleotides into viral nucleic acid,[13,41-45] which undergo self-assembly into virus particles.[23,46,47] A virus in the life process of multiplication performs hijacking of cell metabolic machinery, as well as material resources of host cells (nucleotides, amino acids etc.).[18-20] The reaction of polymerization is led by its driving force – Gibbs energy of biosynthesis.[21,22] Finally, the synthetized virus parts undergo the process of self-assembly and accumulate inside the host cell, which with time can lead to cell lysis and increase in the number of virus particles inside the host organism.[23] The consequence of cell lysis is damage to function and morphology of the tissue of the host organism.[13,24]

The aim of this paper is to chemically and thermodynamically characterize the rhinovirus and make a comparison with other known viruses that have been described in the literature. Moreover, the known lifecycle of viruses is described with the fundamental physicochemical laws that describe the virus-host interactions.

METHODS

Data sources

The genetic sequences of the rhinoviruses were taken from the NCBI database.[25] The analyzed genetic sequences can be found under the accession numbers: X02316.1 for rhinovirus A2, NC_038312.1 for rhinovirus B3 and GU219984.1 for rhinovirus C15.

The protein sequences of the rhinoviruses were taken from the UniProt database.[26] The analyzed protein sequences can be found under the accession numbers: P04936 for rhinovirus A2, Q82081 for rhinovirus B3 and E5D8F2 for rhinovirus C15 (PTM / Processing section). The morphology of the rhinovirus particles was taken from 5-8.

The dissociation equilibrium constants, K_d, of the rhinoviruses A2 and B3 were taken from the literature[27,28]. They were measured with atomic force spectroscopy and surface plasmon resonance.[27,28]

Atom counting method

The molecular formulas, empirical formulas and molar masses of the rhinoviruses were calculated with the atom counting method, as described in the literature[29,30]. The atom counting method is a computational approach for calculation of chemical properties of macromolecules and macromolecular assemblies.[29,30] It is applied with a computer program, which goes along the genetic and protein sequences and adds atoms that come from nucleotide and amino acid residues.[29,30] For macromolecular assemblies, the numbers of atoms coming from constituent

molecules are multiplied by the number of their copies of the molecules in the macromolecular assembly.[29,30]

Patel-Erickson-Battley model

Thermodynamic properties of live matter of rhinoviruses were calculated with the Patel-Erickson-Battley model, as described in the literature[13,14]. Based on the empirical formula, the degree of reduction, E, was calculated with the equation

$$E = 4n_C + n_H - 2n_O - 0\,n_N + 5n_P + 6n_S \quad (1)$$

where n_C, n_H, n_O, n_N, n_P and n_S are the numbers of carbon, hydrogen, oxygen, nitrogen, phosphorus and sulfur atoms in the empirical formula.[31,32] Then the Patel-Erickson equation was used to find standard enthalpy of combustion, $\Delta_C H^o$, of live matter[31,32]

$$\Delta_C H^0(bio) = -111.14\ \frac{kJ}{C-mol} \times E \quad (2)$$

Standard enthalpy of combustion was then converted into standard enthalpy of formation, $\Delta_f H^o$, of live matter with Hess's law, as described in the literature[13,32].

The Battley equation was used to calculate standard molar entropy, $S_m{}^o$, of live matter based on its empirical formula

$$S_m^0(bio) = 0.187\ \sum_J \frac{S_m^0(J)}{a_J} n_J \quad (3)$$

where $S^o{}_m(J)$ is standard molar entropy of element J, a_J number of atoms of element J in its standard state elemental form, n_J the number of atoms of element J in the empirical formula of live matter and the summation is made over all J elements that are present in the live matter.[33,34] Moreover, standard entropy of formation, $\Delta_f S^o$, of live matter was calculated with the modified Battley equation[33,34]

$$\Delta_f S^0(bio) = -0.813\ \sum_J \frac{S_m^0(J)}{a_J} n_J \quad (4)$$

Standard Gibbs energy of formation, $\Delta_f G^o$, of live matter was calculated based on its standard enthalpy of formation, $\Delta_f H^o$, and standard entropy of formation, $\Delta_f S^o$, with the equation

$$\Delta_f G^0(bio) = \Delta_f H^0(bio) - T\Delta_f S^0(bio) \quad (5)$$

where T is temperature.[13]

The Patel-Erickson-Battley model has been widely used in research on thermodynamic properties of organisms.[49,50] It gives results in good agreement with experimental data.[33,34,50] The uncertainty in $\Delta_C H^o$ calculated with the Patel-Erickson equation is 5.36%.[50] The uncertainty in $S_m{}^o$ calculated with the Battley equation is 19.7%.[33,34]

Biosynthesis reactions and thermodynamic properties

Biosynthesis reactions are macrochemical equations that show how new live matter is produced from nutrients by organisms[13,14,48]. The biosynthesis reactions of viruses have the form

$$\text{(Amino acid)} + O_2 + HPO_4^{2-} + HCO_3^- \rightarrow \text{(Bio)} + SO_4^{2-} + H_2O + H_2CO_3 \quad (6)$$

where (Amino acid) represents amino acids with the empirical formula $CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472}$ and (Bio) represents the empirical formula of new live matter. Amino acids are the source of energy, carbon, nitrogen and sulfur.[1,13,14] O_2 is the electron acceptor.[13,14,35] HPO_4^{2-} is the source of phosphorus.[1,13] SO_4^{2-} is an additional metabolic product that takes excess sulfur.[13,14] HCO_3^- and H_2CO_3 form a bicarbonate buffer that maintains constant pH.[13,14]

The biosynthesis reactions and thermodynamic properties of live matter were used to calculate thermodynamic properties of biosynthesis with Hess's law

$$\Delta_{bs}H^0 = \sum_{products} \nu\, \Delta_f H^0 - \sum_{reactants} \nu\, \Delta_f H^0 \quad (7)$$

$$\Delta_{bs}S^0 = \sum_{products} \nu\, S_m^o - \sum_{reactants} \nu\ S_m^o \quad (8)$$

$$\Delta_{bs}G^0 = \sum_{products} \nu\, \Delta_f G^0 - \sum_{reactants} \nu\, \Delta_f G^0 \quad (9)$$

where $\Delta_{bs}H^o$ is standard enthalpy of biosynthesis, $\Delta_{bs}S^o$ standard entropy of biosynthesis, $\Delta_{bs}G^o$ standard Gibbs energy of biosynthesis and ν represents a stoichiometric coefficient .[13,14]

Antigen-receptor binding

Thermodynamic properties of antigen-receptor binding of rhinoviruses were calculated with the methodology of thermochemistry, as described in the literature[13,14,16]. Antigen-receptor binding represents a chemical reaction similar to protein-ligand interactions.[13,14,16] The reaction of antigen-receptor binding is

$$(\text{An}) + (\text{Re}) \rightleftarrows (\text{An-Re}) \quad (10)$$

where (An) is the free virus antigen, (Re) the free host cell receptor, while (An-Re) the antigen-receptor complex.[13,14,16] The dissociation equilibrium constant, K_d, is given by the equation

$$K_d = \frac{[An][Re]}{[An-Re]} \quad (11)$$

where [An], [Re] and [An-Re] are the concentrations of the free virus antigen, free host cell receptor and antigen-receptor complex.[13,14,16] The binding equilibrium constant, K_B, was calculated from K_d with the equation[13,14,16]

$$K_B = \frac{1}{K_d} = \frac{[An-Re]}{[An][Re]} \quad (12)$$

Standard Gibbs energy of binding, $\Delta_B G^o$, was calculated from K_B with the equation

$$\Delta_B G^0 = -RT \ln K_B \quad (13)$$

where T is temperature and R is the universal gas constant.[13,14,16]

RESULTS AND DISCUSSION

Rhinovirus by its morphology might not be quite the simplest, but it belongs to simpler (and smaller) virus particles. It can be characterized chemically by an empirical formula, which is different than those of all other viruses and thermodynamic properties that represent the driving force for physiological processes that comprise the lifecycle of the virus. Having in mind its simplicity, it can be expected that the process of virus multiplication proceeds relatively rapidly compared to other larger viruses. Indeed, as was said in the introduction, infections by rhinovirus comprise a half of all respiratory viral infections.

Rhinovirus A is characterized by the empirical formula $CH_{1.4750}O_{0.3938}N_{0.2973}P_{0.0222}S_{0.0060}$, which is different than that of the JN.1 variant of SARS-CoV-2 $CH_{1.6390}O_{0.2841}N_{0.2300}P_{0.006439}S_{0.003765}$ (Reference 36) or Coxsackievirus A $CH_{1.4665}O_{0.4007}N_{0.2963}P_{0.023292}S_{0.005318}$ (Reference 30). The molar mass of a Rhinovirus particle is 7.961 MDa. Molar masses of other viruses are

219.2 MDa for the virion of the JN.1 variant of SARS-CoV-2[36] and 8.16 MDa for the virion of Coxsackievirus A[30]. The molar mass of the rhinovirus is similar to that of Coxsackievirus, while the molar mass of a SARS-CoV-2 particle is 27 times greater. The reason is that a SARS-CoV-2 particle is more complex and contains, except for the nucleocapsid, a lipid envelope with viral spike and membrane proteins. Empirical formulas of rhinoviruses are given in Table I. Molecular formulas of rhinoviruses are given in Table II.

Thermodynamic properties of live matter of rhinovirus particles are given in Table III. Enthalpies of formation of rhinovirus particles are negative, which means that the particles have a lower total energy content than their constituent elements. The reason for this is attraction of valence electrons of less electronegative elements (C, H, P and S) by more electronegative O and N. Entropies of the virions are positive, which is in agreement with the third law of thermodynamics. Gibbs energies of formation of the virions are negative. This means that the usable energy content of the virions is lower than that of their constituent elements.

TABLE I. Empirical formulas of rhinoviruses. The empirical formulas have the form $CH_{nH}O_{nO}N_{nN}P_{nP}S_{nS}$, where n_H, n_O, n_N, n_P and n_S are the numbers of H, O, N, P and S atoms present in live matter per carbon atom.

Name	n_H	n_O	n_N	n_P	n_S	Mr (g C-mol^{-1})
Rhinovirus A2	1.4750	0.3938	0.2973	0.0222	0.0060	24.84
Rhinovirus B3	1.4861	0.3986	0.2958	0.0225	0.0053	24.89
Rhinovirus C15	1.4727	0.3918	0.2962	0.0223	0.0068	24.82

TABLE II. Molecular formulas of rhinoviruses. The molecular formulas have the form $C_{mC}H_{mH}O_{mO}N_{mN}P_{mP}S_{mS}$, where m_C, m_H, m_O, m_N, m_P and m_S are the total numbers of C, H, O, N, P and S atoms in the virus particles. Mr(tot) represent the total molar masses of the virus particle.

Name	m_C	m_H	m_O	m_N	m_P	m_S	Mr(tot) (MDa)
Rhinovirus A2	320500	472733	126204	95297	7102	1920	7.961
Rhinovirus B3	319933	475467	127510	94635	7208	1680	7.965
Rhinovirus C15	319244	470164	125080	94557	7119	2160	7.924

Based on the empirical formulas, biosynthesis reactions of the rhinoviruses were formulated and are presented in Table IV. The biosynthesis reaction of rhinovirus A is

$$1.3232\ CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472} + 0.4343\ O_2 + 0.0222\ HPO_4^{2-} + 0.0032\ HCO_3^- \rightarrow CH_{1.4750}O_{0.3938}N_{0.2973}P_{0.0222}S_{0.0060} + 0.0237\ SO_4^{2-} + 0.1382\ H_2O + 0.3263\ H_2CO_3 \quad (14)$$

where $CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472}$ is the empirical formula of amino acids and $CH_{1.4750}O_{0.3938}N_{0.2973}P_{0.0222}S_{0.0060}$ is the empirical formula of the newly synthetized virions.

Changes in thermodynamic properties of the biosynthesis reactions are given in Table V. Standard enthalpies of biosynthesis of rhinoviruses are negative. The negative enthalpies contribute favorably to thermodynamic feasibility of the biosynthesis reactions. Entropies of biosynthesis of rhinoviruses are negative, due to assembly of simpler precursors like amino acids into more complex virus particles. Gibbs energies of biosynthesis of virus particles are negative, which means that the biosynthesis process is thermodynamically favorable.

TABLE III. Thermodynamic properties of live matter of rhinoviruses: standard enthalpy of formation, $\Delta_f H^o$, standard molar entropy, $S_m{}^o$, and standard Gibbs energy of formation, $\Delta_f G^o$.

Name	$\Delta_f H^o$ (kJ C-mol^{-1})	$S_m{}^o$ (J C-mol^{-1} K^{-1})	$\Delta_f G^o$ (kJ C-mol^{-1})
Rhinovirus A2	-86.07	32.14	-44.41
Rhinovirus B3	-87.76	32.34	-45.85
Rhinovirus C15	-85.38	32.06	-43.82

TABLE IV. Biosynthesis reactions of rhinoviruses. The biosynthesis reactions have the form (Amino acid) + O_2 + HPO_4^{2-} + HCO_3^- → (Bio) + SO_4^{2-} + H_2O + H_2CO_3, where (Amino acid) represents amino acids with empirical formula $CH_{1.798}O_{0.4831}N_{0.2247}S_{0.022472}$ and (Bio) represents new live matter.

Name	Reactants					Products			
	Amino acid	O_2	HPO_4^{2-}	HCO_3^-	→	Bio	SO_4^{2-}	H_2O	H_2CO_3
Rhinovirus A2	1.3232	0.4343	0.0222	0.0032	→	1	0.0237	0.1382	0.3263
Rhinovirus B3	1.3163	0.4260	0.0225	0.0036	→	1	0.0243	0.1333	0.3199
Rhinovirus C15	1.3180	0.4261	0.0223	0.0011	→	1	0.0229	0.1409	0.3192

Biosynthesis reactions show how new virus particles are produced from nutrients during multiplication of viruses. Every process in nature is led by a driving force.[37,38] Chemical reactions are led by a driving force – Gibbs energy.[37,39,40] Phenomenological equations belong to nonequilibrium thermodynamics and show how rates of processes depend on their driving forces.[37,39,40] The biosynthesis rate, r_{bs}, depends on Gibbs energy of biosynthesis, $\Delta_{bs}G^o$, according to the biosynthesis phenomenological equation

$$r_{bs} = -\frac{L_{bs}}{T}\Delta_{bs}G \qquad (15)$$

where L_{bs} is the biosynthesis phenomenological coefficient.[13,14,37] According to the biosynthesis phenomenological equation, an organism with more negative Gibbs energy of biosynthesis will have a higher biosynthesis rate.

A viral infection represents an interaction between a virus and its host organism. The interaction occurs at the chemical level. The virus enters into the host cell and performs hijacking of the host metabolic machinery to multiply in a chemical process that requires energy and nutrients. The host cell also uses the metabolic machinery, energy and nutrients for the chemical reactions of reparation of damages that appear during life processes. Therefore, the virus-host interaction represents a competition for the metabolic machinery, energy and nutrients. Virus multiplication and host cell reparation are competitive chemical reactions. According to the biosynthesis phenomenological equation, the reaction with a greater driving force (more negative Gibbs energy) will dominate in the competition.

TABLE V. Thermodynamic properties of biosynthesis of rhinoviruses: standard enthalpy of biosynthesis, $\Delta_{bs}H^o$, standard entropy of biosynthesis, $\Delta_{bs}S^o$, and standard Gibbs energy of biosynthesis, $\Delta_{bs}G^o$.

Name	$\Delta_{bs}H^o$ (kJ C-mol^{-1})	$\Delta_{bs}S^o$ (J C-mol^{-1} K^{-1})	$\Delta_{bs}G^o$ (kJ C-mol^{-1})
Rhinovirus A2	-202.58	-34.32	-192.59
Rhinovirus B3	-198.85	-33.75	-189.04
Rhinovirus C15	-198.64	-33.53	-188.89

TABLE VI. Thermodynamic properties of antigen-receptor binding of rhinoviruses: dissociation equilibrium constant, K_d, binding equilibrium constant, K_B, and standard Gibbs energy of binding, $\Delta_B G^o$. VLDLR1-8 is a soluble native-like recombinant VLDLR (very-low-density-lipoprotein receptor) fragment that encompasses the entire ligand binding domain, which is fused to maltose binding protein (MBP) at the N-terminus and to His_6 at the C-terminus. ICAM-1 is Intercellular Adhesion Molecule 1 (also known as CD54). The K_d values were taken from.[27,28] The $\Delta_B G^o$ value of Rhinovirus B3 was taken from.[28]

Name	Interaction	K_d (M)	K_B (M^{-1})	$\Delta_B G^o$ (kJ mol^{-1})
Rhinovirus A2	Virion and VLDLR1-8	2.40E-08	4.17E+07	-43.49
Rhinovirus B3	Virion and ICAM-1	8.3E-07	1.20E+06	-34.72

Rhinoviruses infect the tissues of the respiratory tract.[1] Figure 1 shows Gibbs energies of biosynthesis of rhinoviruses and their host tissue. Gibbs energy of biosynthesis of the respiratory tract is -49.76 kJ C-mol^{-1}.[24] Gibbs energies of biosynthesis of rhinoviruses are between -188.89 kJ C-mol^{-1} and -192.59 kJ C-mol^{-1}. Therefore, rhinoviruses are characterized by a much greater driving force of multiplication, in the form of more negative Gibbs energy of biosynthesis, than their host tissue. According to the biosynthesis phenomenological equation, due to

the greater driving force, the biosynthesis rate of the rhinovirus is higher than that of its host cells. This means that the metabolic machinery of infected host cells will produce more new virus particles than host cell components. Moreover, production of new virus particles will consume more nutrients and energy. Therefore, the virus performs hijacking of host metabolic machinery, due to more negative Gibbs energy of biosynthesis.

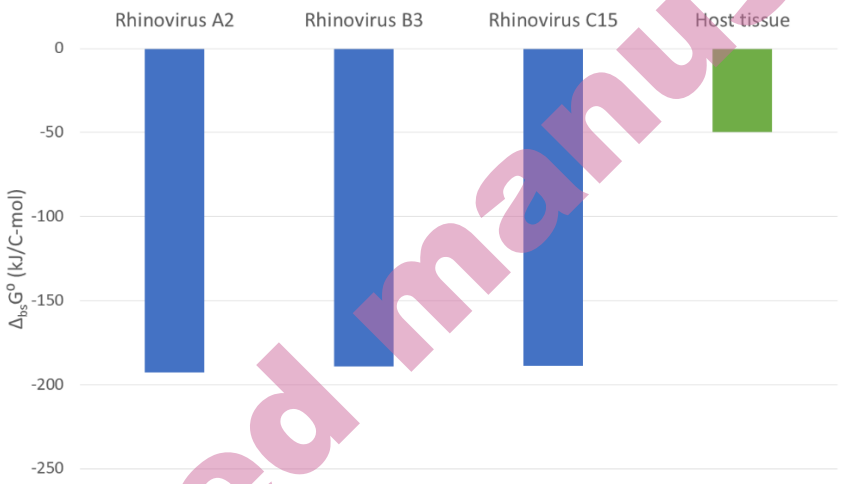

Fig 1: Gibbs energies of biosynthesis of rhinoviruses and their host tissue. Gibbs energy of biosynthesis represents the driving force of virus multiplication in host cells.[13]

The initial interaction between the virus and its host cell occurs at the cell membrane with antigen-receptor binding. The process of antigen-receptor binding is a chemical reaction similar to protein-ligand interactions. The driving force of the antigen-receptor binding reaction is Gibbs energy of binding. Table VI presents Gibbs energies of antigen-receptor binding of rhinoviruses. Rhinoviruses have negative Gibbs energies of binding, which means that the antigen-receptor binding process is favorable. Due to the favorable Gibbs energy change, the virus can enter into the host cells and perform the infection process.

Viruses interact with their host organisms during infection. Infections with different viruses can lead to different signs and symptoms of disease, even if they multiply in the same host tissue. Rhinovirus and SARS-CoV-2 perform infections of the respiratory tract. Gibbs energies of biosynthesis of rhinoviruses are between -188.89 kJ C-mol^{-1} and -192.59 kJ C-mol^{-1}. As of March 2026, the dominant SARS-CoV-2 variant world-wide is the XFG variant, while JN.1 has been designated as a variant of interest by WHO.[51,52] Gibbs energy of biosynthesis of the XFG variant of SARS-CoV-2 is -221.75 kJ/C-mol.[14] Gibbs energy of biosynthesis of the JN.1 variant of SARS-CoV-2 is -221.74 kJ C-mol^{-1}.[36] Gibbs energy of biosynthesis of the XFG and JN.1 variants of SARS-CoV-2 are more

negative than those of rhinoviruses. The more negative Gibbs energy of biosynthesis means that the XFG and JN.1 variants of SARS-CoV-2 have a greater driving force of multiplication inside host cells. This means that the XFG and JN.1 variants of SARS-CoV-2 will multiply inside host cells at a greater rate, according to the biosynthesis phenomenological equation. The greater rate of multiplication leads to production of more virus particles and greater damage to host tissues. Greater damage of host tissues leads to more pronounced signs and symptoms of disease. This means that the XFG and JN.1 variants of SARS-CoV-2 are characterized by a greater pathogenicity than rhinoviruses. Therefore, rhinoviruses produce less pronounced signs and symptoms of disease and are characterized by a lower pathogenicity than SARS-CoV-2 due to their lower driving force of multiplication (less negative Gibbs energy of biosynthesis).

The COVID-19 pandemic has shown how suddenly an emerging virus can appear and how rapidly it can spread all over the world. This is why it is important to have a method to predict the risk posed by an emerging virus for human health early after its appearance. This is often difficult since very little information if known about viruses soon after their appearance. The biothermodynamic methodology applied in this research uses genetic and protein sequence data that can be collected early during an epidemic of an emerging virus. It allows to predict the driving forces of antigen-receptor binding (Gibbs energy of binding) and virus multiplication inside host cells (Gibbs energy of biosynthesis). Based on these properties it is possible to analyze the severity of signs and symptoms and pathogenicity of the virus. This provides an advantage in analysis of risks posed by emerging viruses to human health.

CONCLUSIONS

Chemical and thermodynamic properties of rhinoviruses A, B and C are reported, which include molecular formulas, empirical formulas, molar masses, biosynthesis reactions and thermodynamic properties of live matter, biosynthesis and binding. Chemical and thermodynamic properties of rhinoviruses are different than those of other viruses described in the literature.

During infection, virus multiplication and host cell reparation are chemical reactions that compete for energy and nutrients. Rhinoviruses have a much more negative Gibbs energy of biosynthesis than their host cells. This means that rhinovirus multiplication has a much greater driving force than host cell reparation. Due to the greater driving force of virus multiplication, the host metabolic machinery will produce more new virus particles than host cell components needed for reparation. Virus multiplication will also consume more energy and nutrients. This means that rhinoviruses hijack the metabolism of their host cells due to their greater driving force of multiplication in the form of more negative Gibbs energy of biosynthesis.

Different viruses that interact with the same tissue during infection lead to signs and symptoms of different severity. Rhinoviruses and SARS-CoV-2 are respiratory viruses. However, Gibbs energy of biosynthesis of the XFG and JN.1 variants of SARS-CoV-2 are more negative than those of rhinoviruses, which means that the XFG and JN.1 variants of SARS-CoV-2 have a greater driving force of multiplication. Due to the greater driving force, according to the biosynthesis phenomenological equation, the XFG and JN.1 variants of SARS-CoV-2 will multiply faster and produce more new virus particles and greater damage to host tissue. The greater damage to host tissues will lead to more severe signs and symptoms of disease, as well as greater pathogenicity of the XFG and JN.1 variants of SARS-CoV-2. Therefore, different driving forces of multiplication lead to differences in the severity of signs and symptoms of disease and pathogenicity between rhinoviruses and SARS-CoV-2. The biothermodynamic methodology described in this research can be used in analysis of risks posed to human health by emerging viruses.

NOMENCLATURE

VLDLR1-8 is a soluble native-like recombinant VLDLR (very-low-density-lipoprotein receptor) fragment that encompasses the entire ligand binding domain, which is fused to maltose binding protein (MBP) at the N-terminus and to His_6 at the C-terminus. ICAM-1 is Intercellular Adhesion Molecule 1 (also known as CD54).

Acknowledgements: This work was supported by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia (Grant No. 451-03-136/2025-03/200026).

Author statement: Marko E. Popović: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing; Marijana Pantović Pavlović: Validation, Resources, Writing - Review & Editing, Funding acquisition; Marija Mihailović: Validation, Resources, Writing - Review & Editing, Funding acquisition

ИЗВОД

ДЕЦЕМБАРСКИ АРМАГЕДОН: БИОТЕРМОДИНАМИЧКА АНАЛИЗА РИНОВИРУСА ЗАСНОВАНА НА ПРОРАЧУНУ ГИБСОВЕ ЕНЕРГИЈЕ АНТИГЕН-РЕЦЕПТОР ВЕЗИВАЊА И БИОСИНТЕЗЕ ЧЕСТИЦА РИНОВИРУСА

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Предмет овог истраживања је битка која се понавља сваке године и епидемијски се шири на различитим територијама, узрокујући велики број заражених случајева и жртава. Инфекције риновирусом су добро познате биомедицинским наукама. Инфекције риновирусима су добро познате биомедицинским наукама. Међутим, за дубље разумевање узрока болести риновируса и интеракције вирус-домаћин (инфекције) неопходно је

разумети је из перспективе хемије и биотермодинамике. Овај рад представља емпиријске формуле, *driving force* интеракција риновирус-домаћин, као и механистички модел интеракција вирус-домаћин на ћелијској мембрани и у цитоплазми. На основу описаних података, изнети су закључци о томе зашто је 50% инфекција горњих дисајних путева узроковано риновирусима. По први пут су представљене Гибсова енергија биосинтезе вирусних честица Риновируса *A2*, *B3* и *C15*, као и Гибсова енергија везивања Риновируса *A2*, које су потребне за разумевање животног циклуса риновируса.

(Примљено 11. јануара; ревидирано 12. фебруара; прихваћено 8. априла 2026.)

REFERENCES

1. S. Riedel, J. A. Hobden, S. Miller, S. A. Morse, T. A. Mietzner, B. Detrick, T. G. Mitchell, J. A. Sakanari, P. Hotez, R. Mejia, *Jawetz, Melnick and Adelberg's Medical Microbiology, 28th ed.*, McGraw-Hill, New York, NY, USA, 2019 (ISBN-13: 978-1260012026)
2. D. Bouzid, O. Hadad, M. Bertine, N. Houhou-Fidouh, A. Mirand, X. Duval, V. Bunel, R. Borie, J. C. Lucet, D. Descamps, B. Visseaux, *Int. J. Infect. Dis.* **118** (2022) 144–149 (https://doi.org/10.1016/j.ijid.2022.02.055)
3. S. Ljubin-Sternak, T. Meštrović, *Viruses* **15** (2023) 825 (https://doi.org/10.3390/v15040825)
4. L. Andrup, K. A. Krogfelt, K. S. Hansen, A. M. Madsen, *Am. J. Infect. Control* **51** (2023) 938–957. (https://doi.org/10.1016/j.ajic.2022.12.005)
5. C. Esneau, N. Bartlett, Y. A. Bochkov, Rhinovirus structure, replication, and classification. in *Rhinovirus infections*, N. Bartlett, P. Wark, D. Knight, Eds., Academic Press, Cambridge, MA, USA, pp. 1-23 (https://doi.org/10.1016/B978-0-12-816417-4.00001-9)
6. D. Gil-Cantero, C.P. Mata, L. Valiente, A. Rodríguez-Huete, A. Valbuena, R. Twarock, P. G. Stockley, M. G. Mateu, J. R. Castón, *Commun. Biol.* **7** (2024) 1501 (https://doi.org/10.1038/s42003-024-07213-2)
7. M. G. Rossmann, E. Arnold, J. W. Erickson, E. A. Frankenberger, J. P. Griffith, H. J. Hecht, J. E. Johnson, G. Kamer, M. Luo, A. G. Mosser, *Nature*, **317** (1985) 145–153 (https://doi.org/10.1038/317145a0)
8. A. R. Alsayed, A. Abed, M. J. Al Shawabkeh, R. R. Aldarawish, M. Al-Shajlawi, N. Alabbas, *Pharmacy Practice (Granada)* **22** (2024) 1 (https://dialnet.unirioja.es/servlet/articulo?codigo=9414131)
9. S. Maitra, J. Rajak, A. Ghoshal, B. Roy, S. Ghosh, A. K. Mitra, A. Kumer, B. Dhara, *Health Sci. Rep.* **8** (2025) e70922 (https://doi.org/10.1002/hsr2.70922)
10. C. Esneau, N. E. Bryant, S. L. Johnston, N. W. Bartlett, *CMI Comms.* **2** (2025) 105081 (https://doi.org/10.1016/j.cmicom.2025.105081)
11. A. C. Palmenberg, J. E. Gern, *Methods Mol. Biol.* **1221** (2014) 1–10 (https://doi.org/10.1007/978-1-4939-1571-2_1)
12. W. Li, B. Yu, J. Zhou, Y. Wang, B. Xue, J. Pan, Y. Ran, X. Yang, X. Wang, F. Yang, H. Li, *Virol. J.* **18** (2021) 174 (https://doi.org/10.1186/s12985-021-01645-6)
13. M. E. Popović, V. Tadić, M. Popović, *Virology*, **603** (2025) 110319 (https://doi.org/10.1016/j.virol.2024.110319)
14. M. E. Popović, M. Stevanović, V. Tadić, *Virology*, **614** (2026) 110742 (https://doi.org/10.1016/j.virol.2025.110742)

15. S. L. Kerr, C. Mathew, R. Ghildyal, *Viruses*, **13** (2021) 629 (https://doi.org/10.3390/v13040629)
16. X. Du, Y. Li, Y.-L. Xia, S.-M. Ai, J. Liang, P. Sang, X.-L. Ji, S.-Q. Liu, *Int. J. Mol. Sci.* **17** (2016) 144 (https://doi.org/10.3390/ijms17020144)
17. M. E. Popović, V. Tadić, D. Pei, *Therm. Sci.* (2025) (http://dx.doi.org/10.2298/TSCI250729209P)
18. S. S. Bappy, M. M. Haque Asim, M. M. Ahasan, A. Ahsan, S. Sultana, R. Khanam, A. Z. Shibly, Y. Kabir, *Rev. Med. Virol.* **34** (2024) e2505 (https://doi.org/10.1002/rmv.2505)
19. M. Özilgen, B. Yilmaz, *Int. J. Energy Res.* **45** (2021) 1157–1160 (https://doi.org/10.1002/er.5883)
20. B. Şimşek, M. Özilgen, F. Ş. Utku, *Energy Storage*, **4** (2022) e298 (https://doi.org/10.1002/est2.298)
21. M. J. Assael, G. C. Maitland, T. Maskow, U. von Stockar, W. A. Wakeham, S. Will, *Commonly Asked Questions in Thermodynamics, 2nd ed.*, CRC Press, Boca Raton, FL, USA, 2022 (https://doi.org/10.1201/9780429329524)
22. U. von Stockar, J. Liu, *Biochim. Biophys. Acta*, **1412** (1999) 191–211 (https://doi.org/10.1016/s0005-2728(99)00065-1)
23. P. Buzón, S. Maity, P. Christodoulis, M. J. Wiertsema, S. Dunkelbarger, C. Kim, G. J. L. Wuite, A. Zlotnick, W. H. Roos, *Sci. Adv.* **7** (2021) eabg0811 (https://doi.org/10.1126/sciadv.abg0811)
24. M.E. Popović, M. Popović, G. Šekularac, M. Pantović Pavlović, *J. Serb. Chem. Soc.* **89** (2024) 807-822 (https://doi.org/10.2298/JSC240322051P)
25. E. W. Sayers, J. Beck, E. E. Bolton, J. R. Brister, J. Chan, R. Connor, M. Feldgarden, A. M. Fine, K. Funk, J. Hoffman, S. Kannan, C. Kelly, W. Klimke, S. Kim, S. Lathrop, A. Marchler-Bauer, T. D. Murphy, C. O'Sullivan, E. Schmieder, Y. Skripchenko, A. Stine, F. Thibaud-Nissen, J. Wang, J. Ye, E. Zellers, V. A. Schneider, K. D. Pruitt, *Nucleic Acids Res.* **53** (2025) D20–D29 (https://doi.org/10.1093/nar/gkae979)
26. UniProt Consortium, *Nucleic Acids Res.* **53** (2025) D609–D617 (https://doi.org/10.1093/nar/gkae1010)
27. C. Rankl, F. Kienberger, L. Wildling, J. Wruss, H. J. Gruber, D. Blaas, P. Hinterdorfer, *Proc. Natl. Acad. Sci. U.S.A.* **105** (2008) 17778–17783 (https://doi.org/10.1073/pnas.0806451105)
28. J. M. Casasnovas, T. A. Springer, *J. Biol. Chem.* **270** (1995) 13216–13224 (https://doi.org/10.1074/jbc.270.22.13216)
29. M. Popovic, *Comput. Biol. Chem.* **96** (2022) 107621 (https://doi.org/10.1016/j.compbiolchem.2022.107621)
30. M. E. Popović, G. M. Šekularac, V. M. Tadić, M. R. Pantović Pavlović, *Therm. Sci.* **28** (2024) 4737-4757 (https://doi.org/10.2298/TSCI240429213P)
31. S. A. Patel, L. E. Erickson, *Biotechnol. Bioeng.* **23** (1981) 2051-2067 (https://doi.org/10.1002/bit.260230910)
32. E. H. Battley, *Thermochim. Acta* **309** (1998) 17-37 (https://doi.org/10.1016/S0040-6031(97)00357-2)
33. E. H. Battley, *Thermochim. Acta* **326** (1999) 7-15 (https://doi.org/10.1016/S0040-6031(98)00584-X)
34. E. H, Battley, J. R. Stone, *Thermochim. Acta* **349** (2000) 153-161 (https://doi.org/10.1016/S0040-6031(99)00509-2)

35. K. Annamalai, *Systems*, **9** (2021) 54 (https://doi.org/10.3390/systems9030054)
36. M. E. Popović, M. Stevanović, M. Mihailović, *J. Serb. Chem. Soc.* **89** (2024) 305-320 (https://doi.org/10.2298/JSC240119019P)
37. Y. Demirel, *Nonequilibrium Thermodynamics: Transport and Rate Processes in Physical, Chemical and Biological Systems, 3rd ed*., Elsevier, Amsterdam, Netherlands, 2014 (ISBN: 9780444595812)
38. R. T. Balmer, *Modern Engineering Thermodynamics*, Academic Press, Cambridge, MA, USA, 2010 (https://doi.org/10.1016/C2009-0-20199-1)
39. K. J. Hellingwerf, J. S. Lolkema, R. Otto, O. M. Neijssel, A. H. Stouthamer, W. Harder, K. van Dam, H. V. Westerhoff, *FEMS Microbiol. Lett.* **15** (1982) 7-17 (https://doi.org/10.1111/j.1574-6968.1982.tb00028.x)
40. H. V. Westerhoff, J. S. Lolkema, R. Otto, K. J. Hellingwerf, *Biochim. Biophys. Acta*, **683** (1982) 181–220 (https://doi.org/10.1016/0304-4173(82)90001-5).
41. F. Fenner, P. A. Bachmann, E. P. J. Gibbs, F. A. Murphy, M. J. Studdert, D. O. White, Structure and Composition of Viruses, in *Veterinary Virology*, Accademic Press, 1987, pp 3–19)https://doi.org/10.1016/B978-0-12-253055-5.50005-0)
42. M. Y. Chen, S. S. Butler, W. Chen, J. Suh, *WIRE Nanomed. Nanobiotech.* **11**(3) (2019) e1545 (https://doi.org/10.1002/wnan.1545)
43. S. Himbert, M. Chapman, D. Deamer, M. C. Rheinstädter, *Sci. Rep*. **6** (2016) 31285 (https://doi.org/10.1038/srep31285)
44. J. Lee, K. J. Schwarz, D. S. Kim, J. S. Moore, M. C. Jewett, *Nature Comm.* **11**(1) (2020) 4304 (https://doi.org/10.1038/s41467-020-18001-x)
45. A. S. Spirin, L.P. Gavrilova, Stages of Translation. In: The Ribosome. Molecular Biology Biochemistry and Biophysics / Molekularbiologie Biochemie und Biophysik, vol 4. Springer, Berlin, Heidelberg (1969) (https://doi.org/10.1007/978-3-642-88446-7_8)
46. R. F. Garmann, A. M. Goldfain, V. N. Manoharan, *PNAS* **116**(45) (2019) 22485–22490 (https://doi.org/10.1073/pnas.1909223116)
47. R. D. Cadena-Nava, M. Comas-Garcia, R. F. Garmann, A. L. Rao, C. M. Knobler, W. M. Gelbart, *J. Virol.* **86**(6) (2012) 3318–3326 (https://doi.org/10.1128/JVI.06566-11)
48. U. Von Stockar, Live cells as open non-equilibrium systems. In Urs von Stockar, ed., *Biothermodynamics: The Role of Thermodynamics in Biochemical Engineering*, Lausanne: EPFL Press, (2013) 399-421 (https://doi.org/10.1201/b15428)
49. M. Ozilgen, E. Sorguven Oner, *Biothermodynamics: Principles and Applications* (1st ed.). CRC Press. (2016) (https://doi.org/10.1201/9781315374147)
50. M. Popovic, *Heliyon*, **5**(6) (2019) e01950. (https://doi.org/10.1016/j.heliyon.2019.e01950)
51. WHO (2026). WHO COVID-19 dashboard – Summary [Online] World Health Organization. Available at: https://data.who.int/dashboards/covid19/summary?n=c (Accessed on March 25, 2026)
52. NextStrain (2026) Genomic epidemiology of SARS-CoV-2 with subsampling focused globally over the past 6 months [Online] Available at: https://nextstrain.org/ncov/open/global/6m (Accessed on March 25, 2026).