Life in Silico (2023) 1(1), 8-12

LIFE IN SILICO
https://life-insilico.com

RESEARCH ARTICLE

OPEN ACCESS

Closer look into HIV-host interactions: Standard Gibbs energy of binding of the gp120 antigen of HIV-1 to the CD4 receptor and monoclonal antibodies

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ARTICLE INFO

Article History:

Received: 29 November 2022
Revised: 25 January 2023
Accepted: 26 January 2023
Available online: 01 February 2023

Edited by: E. S. Istifli

Keywords:

Biothermodynamics of viruses
HIV-1
Binding constant
Gibbs energy of binding
Antigen-receptor binding

ABSTRACT

HIV-1, like other viruses, represents an open thermodynamic system. This is why it is important to know its thermodynamic properties. Virus-host interactions are performed at the membrane as antigen-receptor binding. Antigen-receptor binding represents a chemical reaction, similar to protein-ligand interactions. The driving force for antigen-receptor binding is Gibbs energy of binding. Knowing Gibbs energy of binding, it is possible to estimate the rate of virus binding and entry into host cells. In this paper, binding equilibrium constants and standard Gibbs energies of binding between the HIV-1 gp120 antigen and the CD4 receptor have been reported at 4 °C, 22 °C and 37 °C.

1. Introduction

Biothermodynamics is the youngest subdiscipline of thermodynamics, which has appeared during the second half of the 20th century, at the initiative of Schrödinger (1992). However, the root of biothermodynamics can be traced to the late 18th century, when Lavoisier and Laplace used calorimetry to study metabolic heat released by a guinea pig (Lavoisier & DeLaplace, 1994; Lavoisier & Marquis de Laplace, 1783). Biothermodynamics of viruses, or virothermodynamics, is a part of biothermodynamics that has begun to develop intensely during the last several years (Popovic, 2022b, 2022c).

Organisms represent complex open systems that consist of simple atoms and complex macromolecules, which biologically, chemically and thermodynamically interact with other organisms and their surroundings (Popovic, 2014; Von Bertalanffy, 1950, 1968). Viruses can be understood as complex macromolecular structures, with characteristic empirical formulas (elemental composition) (Degueldre, 2021; Molla et al., 1991; Wimmer, 2006) and thermodynamic properties (Gale, 2018, 2019; Popovic, 2022f; Şimşek et al., 2022), which interact with their host cells (Popovic, 2022d, 2022k, 2022l; Popovic & Minceva, 2020b, 2021). Viruses are obligate intracellular parasites, which hijack their host cell's metabolic machinery, using it for their own multiplication (Popovic & Minceva, 2020a). Viruses interact with their host

Reviewed by:
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e-ISSN:
doi:

cells at the membrane, binding to specific receptors (Gale, 2018, 2019, 2020, 2022). Viruses also interact into a different type of interaction with their host – in the cytoplasm, when they hijack the cell's metabolic machinery (Popovic & Minceva, 2020b). Host cells for SARS-CoV-2 include the epithelial cells of the upper respiratory pathways (Bridges et al., 2022; Ryu & Shin, 2021). Host cells for HIV are human immune cells, such as helper T cells, macrophages and dendritic cells (Cunningham et al., 2010).

HIV is of spherical shape with a diameter of 120 nm. It is composed of two copies of positive-sense single-stranded RNA. Its nucleocapsid is enveloped by a lipid bilayer, which originates from the human host cell, like that of other enveloped viruses. The antigen of HIV is envelope glycoprotein gp120 (Xu et al., 2013). It attaches to the host cell receptor CD4 and chemokine coreceptors (Arrildt et al., 2012; Chan et al., 1997). Antigen-receptor interaction represents a chemical reaction similar to protein-ligand binding (Du et al., 2016; Popovic & Popovic, 2022). The driving force for most chemical processes is Gibbs energy (Balmer, 2010; Demirel, 2007; Popovic, 2022f; Von Stockar, 2013). Thus, Gibbs energy is the driving force for antigen-receptor binding (Popovic, 2022g, 2022i).

RNA viruses exhibit the tendency to mutate (Duffy, 2018). SARS-CoV-2 has mutated several dozen times since 2019 (Popovic, 2022a, 2022g, 2022h, 2022i, 2022j; Popovic & Popovic, 2022), causing multiple waives of pandemic. HIV also exhibits a great genetic variability (Robertson et al., 1995), resulting in change in biological, chemical and thermodynamic properties. But, it has never made pandemic waves as massive as COVID-19. It is important to understand thermodynamic background of viral infection (Head et al., 2022; Mahmoudabadi et al., 2017).

The aim of this paper is to calculate the binding equilibrium constant and standard Gibbs energy of binding for HIV-1. Standard Gibbs energy of binding of HIV-1 will then be compared to those of other viruses.

2. Materials and methods

2.1. Data sources

Dissociation equilibrium constant, K_d, data for HIV-1 were taken from the literature from (Schnittman et al., 1988; Thali et al., 1991; Xu et al., 2013). Xu et al. (2013) reported dissociation equilibrium constants of HIV-1 gp120 antigen to the CD4 receptor and monoclonal antibodies (MAB), at 4 °C. The measurements were made using ELISA. Thali et al. (1991) reported the relative dissociation equilibrium constant of HIV-1 gp120 to CD4 at 37 °C. The measurements were made using immunoprecipitation (Thali et al., 1991). Schnittman et al. (1988) reported dissociation equilibrium constants of HIV-1 gp120 to CD4 at 22 °C. The measurements were made using a custom-developed assay (Schnittman et al., 1988).

2.2. Thermodynamic properties of binding

Dissociation equilibrium constants were used to find binding equilibrium constants, using the equation given below:

$$K_B = \frac{1}{K_d}$$

where K_B is the binding equilibrium constant and K_d is the dissociation equilibrium constant (Du et al., 2016; Popovic & Popovic, 2022). Then, K_B was used to find standard Gibbs energy of binding, through the equation given below:

$$\Delta_B G^0 = -RT \ln K_B$$

where $\Delta_B G^o$ is standard Gibbs energy of binding, R is the universal gas constant and T is temperature (Popovic & Popovic, 2022).

3. Results and discussion

Table 1 shows standard thermodynamic properties of binding for HIV-1, including the binding equilibrium constant, K_B, and standard Gibbs energy of binding, $\Delta_B G^o$. At the temperature of 4 °C, binding equilibrium constant of gp120 to CD4 was found to be K_B = 9.5 10^8 M^{-1}, while its standard Gibbs energy is $\Delta_B G^o$ = -47.63 kJ/mol. At 22 °C, the binding equilibrium constant of gp120 to CD4 is 2 10^8 M^{-1}, while standard Gibbs energy of binding is -46.90 kJ/mol. Also, at 37 °C, binding equilibrium constant of gp120 to CD4 was found to be 1.331 10^8 M^{-1}, while the standard Gibbs energy of binding is -48.24 kJ/mol. On the other hand, at 4 °C, gp120 binds to monoclonal antibodies (MAB) with a binding equilibrium constant of 12 10^8 M^{-1} and a standard Gibbs energy of -48.17 kJ/mol.

Table 1. Thermodynamic properties of binding between gp120 protein of HIV-1 with human CD4 receptors and monoclonal antibodies (MAB)*

Interaction	T (°C)	K_d (nM)	K_B ($\cdot 10^8$ M^{-1})	$\Delta_B G^o$ (kJ/mol)
gp120 with CD4	4	1.053	9.500	-47.63
gp120 with CD4	22	5	2	-46.90
gp120 with CD4	37	7.516	1.331	-48.24
gp120 with MAB	4	0.8333	12.00	-48.17

* The table gives data on temperature, T, dissociation equilibrium constant, K_d, binding equilibrium constant, K_B, and standard Gibbs energy of binding, $\Delta_B G^o$. The K_d data were taken from (Schnittman et al., 1988; Thali et al., 1991; Xu et al., 2013).

In order to infect a host cell, HIV-1 binds, using its antigen glycoprotein 120 (gp120), to the CD4 receptor of the host cell (Figure 1). Biothermodynamic properties of HIV-1 were studied in detail and are available in the literature (Gale, 2020; Myszka et al., 2000). Gibbs energy of antigen-receptor binding (gp120 to CD4) has been reported by Myszka et al. (2000) to be $\Delta_B G^o$ = -49.4 kJ/mol (-11.8 kcal/mol), at 37 °C. Standard enthalpy of binding of gp120 to CD4 at 37 °C was found to be $\Delta_B H^o$ = -264 kJ/mol (-63 kcal/mol) (Myszka et al., 2000). The entropy term for gp120-CD4 binding was found to be $-T\Delta_B S^o$ = 214 kJ/mol (51.2 kcal/mol), at 37 °C (Myszka et al., 2000), which corresponds to a standard entropy of binding of $\Delta_B S^o$ = -691 J/mol K.

Based on the results reported in Myszka et al. (2000), Gale (2020) calculated $\Delta_B H^o$ and $\Delta_B S^o$ values for binding of HIV-1 gp120 to the CD4 receptor. At 4 °C, standard enthalpy of binding of HIV-1 gp120 to the CD4 receptor was found to be $\Delta_B H^o$ = -97.9 kJ/mol, while standard entropy of binding was found to be $\Delta_B S^o$ = -126.01 J/mol K (Gale, 2020; Myszka et al., 2000). At 25 °C, standard enthalpy of binding of gp120 to CD4 was found to be $\Delta_B H^o$ = -198.2 kJ/mol, while standard entropy of binding was found to be $\Delta_B S^o$ = -472.9 J/mol K (Gale, 2020; Myszka et al., 2000).

Based on the reported K_d (Thali et al., 1991; Xu et al., 2013), in this paper, standard Gibbs energy of binding was calculated for HIV-1 at 4 °C and 37 °C. Standard Gibbs energy of binding at 4 °C was found to be -47.63 kJ/mol for gp120 to the CD4 receptor, while the standard Gibbs energy of binding between gp120 and monoclonal antibodies (MAB) was found to be -48.17 kJ/mol, using K_d data from (Xu et al., 2013). The binding equilibrium constant for gp120 to CD4 was found to be K_B = 9.5 10^8 M^{-1}, while that between gp120 and MAB is 12 10^8 M^{-1}, using K_d data from (Xu et al., 2013).

Standard Gibbs energy of binding of HIV-1 to the CD4 receptor at 22 °C was found to be -46.90 kJ/mol, while the equilibrium binding constant is 2 10^8 M^{-1}, using K_d data from (Schnittman et al., 1988). Standard Gibbs energy of binding for HIV-1 gp120 to the CD4 receptor at 37 °C was found to be -48.24 kJ/mol, while the binding equilibrium constant is 1.331 10^8 M^{-1}, using K_d data from (Thali et al., 1991; Xu et al., 2013).

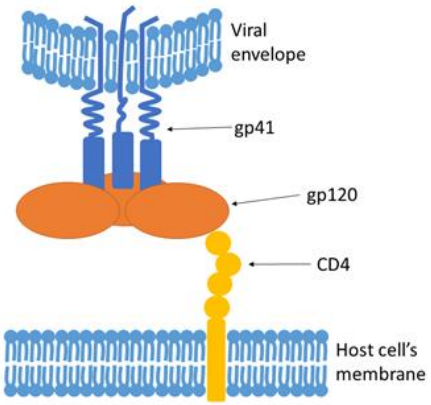

Figure 1. Binding of HIV-1 gp120 antigen to host cell's CD4 receptor
The gp120 proteins form trimers on the surface of the HIV-1 viral envelope, which consists of a lipid bilayer membrane. The gp120 protein attaches to the CD4 receptor on the host cell's membrane. This represents the first step in entry of HIV-1 into host cells.

Inoculation with HIV-1 occurs within the organism at the constant temperature of 37 °C. The first interaction between HIV-1 virus and its host cell occurs at the membrane, representing the binding of the gp120 antigen to the CD4 receptor, at 37 °C. Since the antigen-receptor reaction is a chemical reaction similar to protein-ligand interactions, the driving force for this chemical reaction is Gibbs energy of binding. Gibbs energy of binding, $\Delta_B G$, is proportional to the binding rate, r_B, according to the binding phenomenological equation given below:

$$r_B = -\frac{L_B}{T}\Delta_B G$$

where T is temperature and L_B is the binding phenomenological coefficient (Popovic, 2022e, 2022h). The values of Gibbs energy of binding reported by Myszka et al. (2000), Gale (2020) and this paper are negative. This indicates that the antigen-receptor binding reaction is spontaneous and occurs at a finite rate r_B. The values obtained in the three studies are slightly different. It would be expected that the value of Gibbs energy of binding at 4 °C is less negative than that at 22 °C.

At 37 °C, standard Gibbs energy of binding at 37 °C was reported by Myszka et al. (2000) to be $\Delta_B G^o$ = -49.4 kJ/mol (-11.8 kcal/mol), while Gale (2020) reported -49.26 kJ/mol. In this paper, we report $\Delta_B G^o$ = -48.24 kJ/mol at 37 °C. **Table 2** gives results for Gibbs energies of binding available in the literature (Popovic & Minceva, 2021). Based on **Table 2**, we can conclude that viruses have standard Gibbs energies of binding of the same order of magnitude.

HIV-1 is surrounded by a phospholipid bilayer envelope. In order for the HIV-1 virus to enter the host cell, the viral envelope must fuse with the host cell membrane (Wilen et al., 2012). In order for this to happen, the initial repulsive forces between the heads of the two phospholipid bilayers must be overcome. The energy for this partly comes from the Gibbs energy of binding, which is negative.

Table 2. Standard Gibbs energies of binding reported in the literature*

Name	$\Delta_B G^o$ (kJ/mol)	Reference
Adenovirus	−45.1 to −45.7	(Lortat-Jacob et al., 2001; Popovic & Minceva, 2021)
HIV-1	−53.9 to −47.1	(Balliet et al., 1999; Popovic & Minceva, 2021)
HIV-1 at 37 °C	−49.26	(Gale, 2020; Popovic & Minceva, 2021)
HIV-1 at 25 °C	−57.2	(Gale, 2020; Popovic & Minceva, 2021)
HIV-1 at 4 °C	−63.0	(Gale, 2020; Popovic & Minceva, 2021)
HIV-2	−43.4	(Balliet et al., 1999; Popovic & Minceva, 2021)
Human cytomegalovirus	−53.2	(Balliet et al., 1999; Popovic & Minceva, 2021)
Influenza (3SLN)	−32.6	(Balliet et al., 1999; Popovic & Minceva, 2021)
Influenza (6SLN)	−33.7	(Balliet et al., 1999; Popovic & Minceva, 2021)
Parainfluenza virus 1	−24.0 to −27.8	(Popovic & Minceva, 2021; Tappert et al., 2013)
Parainfluenza virus 2	−21.7 to −30.4	(Popovic & Minceva, 2021; Tappert et al., 2013)
Parainfluenza virus 3	−23.2 to −26.6	(Popovic & Minceva, 2021; Tappert et al., 2013)
Poliovirus	−57.5	(Balliet et al., 1999; Popovic & Minceva, 2021)
Reovirus	−55.2	(Balliet et al., 1999; Popovic & Minceva, 2021)
Vesicular stomatitis virus	−58.3	(Balliet et al., 1999; Popovic & Minceva, 2021)
Arboviruses	−18	(Gale, 2019; Popovic & Minceva, 2021)
SARS-CoV-2	−42.2 to −51.4	(Lan et al., 2020; Popovic & Minceva, 2020a, 2021; Shang et al., 2020; Walls et al., 2020; Wrapp et al., 2020)
Rhinovirus	−28 to −39	(Casasnovas & Springer, 1995)

* For every virus, the table gives $\Delta_B G^o$ and the references from which the values were taken

4. Conclusions

Gibbs energy of binding of the HIV-1 gp120 antigen to the CD4 receptor at 37 °C is -48.24 kJ/mol, at 22 °C it is -46.90 kJ/mol, while at 4 °C it is -47.63 kJ/mol. The determined Gibbs energy of HIV-1 is significantly different from Gibbs energy of binding of other viruses, but is on the same order of magnitude. The negative Gibbs energy of binding of gp120 to CD4 also provides the driving force for merging of the virus envelope with the host cell membrane, during the entry of the virus into the host cell.

Acknowledgments

None.

Conflict of interest

The author confirms that there are no known conflicts of interest.

Statement of ethics

In this study, no method requiring the permission of the "Ethics Committee" was used.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Funding

The author declares that the study did not receive any financial support/grant from any public or private organization.

CRediT authorship contribution statement

Marko Popovic: All stages of the present article was carried out by Marko Popovic.

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Supplementary File

None.

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