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Thermodynamic properties of enzyme-catalyzed reactions involving cytosine, uracil, thymine, and their nucleosides and nucleotides

Robert A. Alberty

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, United States

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Abstract

The standard Gibbs energies of formation of species in the cytidine triphosphate series, uridine triphosphate series, and thymidine triphosphate series have been calculated on the basis of the convention that $\Delta_f G = 0$ for the neutral form of cytidine in aqueous solution at 298.15 K at zero ionic strength. This makes it possible to calculate apparent equilibrium constants for a number of reactions for which apparent equilibrium constants have not been measured or cannot be measured because they are too large. This paper adds fifteen reactants to the database BasicBiochemData3 at MathSource that includes 199 reactants. The standard transformed Gibbs energies of formation of these fifteen reactants are used to calculate apparent equilibrium constants at 298.15 K, ionic strength 0.25 M, and pHs 5, 6, 7, 8, and 9 for thirty two reactions. The p*K*s, standard Gibbs energies of hydrolysis, and standard Gibbs energies of deamination are given for these fifteen reactants.

Keywords: Cytosine; Uracil; Thymine; Nucleotides; Thermodynamics; Apparent equilibrium constants

1. Introduction

This paper extends the calculations of the thermodynamic properties of enzyme-catalyzed reactions involving guanine, xanthine, and their nucleosides and nucleotides [1] to the cytidine triphosphate, uridine triphosphate, and thymidine triphosphate series [2]. These calculations are based on the convention that $\Delta_f G^\circ(\text{cytidine,aq,298.15 K}, I=0)=0$. The calculated species properties are used to calculate apparent equilibrium constants for thirty two enzyme-catalyzed reactions at pHs 5 to 9. The requirement for these calculations is that moities of these reactants must appear on both sides of the catalyzed reactions. The calorimetric research by Boeiro–Goates and coworkers [3–5] has eliminated this requirement for reactions involving the ATP and IMP series. Species data for 199 biochemical reactants are stored in BasicBiochemData3 [6]. This has made it possible to calculate apparent equilibrium constants of many enzyme-catalyzed reactions [7].

The reactions that connect the reactants in the CTP, UTP, and TTP series are represented schematically in Eq. (1). The reactions in the vertical direction are

$$\begin{array}{ccccc}
\text{CTP} & = & \text{UTP} & = & \text{TTP} \\
\| & & \| & & \| \\
\text{CDP} & = & \text{UDP} & = & \text{TDP} \\
\| & & \| & & \| \\
\text{CMP} & = & \text{UMP} & = & \text{TMP} \\
\| & & \| & & \| \\
\text{cytidine} & = & \text{uridine} & = & \text{thymidine} \\
\| & & \| & & \| \\
\text{cytosine} & = & \text{uracil} & = & \text{thymine}
\end{array} \tag{1}$$

hydrolysis reactions, but H_2O and other reactants are not shown. The first column of equal signs in the horizontal direction are deaminase reactions, but the H_2O and ammonia are not shown. The second column of arrows in the horizontal direction is discussed later in connection with the TTP series.

Abbreviations: CTP, cytidine triphosphate; CDP, cytidine diphosphate; CMP, cytidine monophosphate; UTP, uridine triphosphate; UDP, uridine diphosphate; UMP, uridine monophosphate; TTP, thymidine triphosphate; TDP, thymidine diphosphate; CMP, thymidine monophosphate.

E-mail address: alberty@mit.edu.

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Calculations of the standard Gibbs energies of formation $\Delta_f G^\circ$ of species of the cytidine triphosphate series, the uridine triphosphate series, and the thymidine triphosphate series are based on the convention that $\Delta_f G^\circ$(cytidine,aq,298.15 K, $I=0$)$=0$. The apparent equilibrium constants for all the reactions that are indicated by equal signs and more can be calculated at 298.15 K, ionic strengths from zero to about 0.35 M, and pHs in the range 5 to 9. The apparent equilibrium constants are not presented for all of these possible reactions, but tables are given of reactions for the CTP series, the UTP series, and the TTP series with their EC numbers [8] to show that the apparent equilibrium constants can be calculated with the assistance of BasicBiochemData3 [6] for more reactions than those shown in Eq. (1).

The thermodynamic connection between the CTP series and the UTP series is provided by the assumption that the $\Delta_r G^\circ$ for the deamination of cytidine is equal to the $\Delta_r G^\circ$ for the deamination of adenosine [1]. The thermodynamic connection between the UTP series and the TTP series is obtained by use of the assumption that $\Delta_f G^\circ$(uracil,aq,298.15 K, $I=0$)$=\Delta_f G^\circ$(thymine, aq,298.15 K, $I=0$), based on related pairs of species.

2. Calculation of standard Gibbs energies of formation of the species of the CTP series

Since it is currently not possible to connect species in the CTP series with the elements in their reference states, $\Delta_f G^\circ$(cytidine^0, 298.15 K, $I=0$)$=0$ is adopted as a convention of the thermodynamic tables. It is assumed that the CTP series is like the ATP series with respect to phosphate hydrolysis constants and deamination equilibrium constants so that the $\Delta_f G^\circ$ for the ATP series can be used to calculate the $\Delta_f G^\circ$ of species in the CTP. The $\Delta_f G^\circ$ of the two most highly charged species of ATP, ADP, and AMP and the electrically neutral species of adenosine and adenine [6] are given in Table 1, where the electric charges of the species are shown.

Two things have to be done to Table 1 to make it apply to the CTP series. The first is to add 194.50 kJ mol^{-1} to each of the values in this table because $\Delta_f G^\circ$(cytidine,aq,298.15 K, $I=0$)$=0$. This does not change the p*K*s of the phosphate groups or the equilibrium constants for the chemical reactions of hydrolysis of the most highly charged species. The second is to use the p*K*s of the pyrimidine rings in the CTP series to calculate the $\Delta_f G^\circ$ of the species with a hydrogen ion bound by the pyrimidine ring. Since p*K*(adenine,298.15 K, $I=0$)$=4.20$ and p*K*(cytosine,298.15 K, $I=0$)$=4.60$ [9,10], the ring p*K*s in the CTP series are taken to be 0.40 larger than in the ATP series: namely, CTP(5.08), CDP (4.76), CMP(4.40), cytidine(3.87), and cytosine(4.60). As the pH is reduced to this range, the cytosine ring picks up a hydrogen ion.

Table 1
Some of the standard Gibbs energies of formation in the ATP series at 298.15 K and zero ionic strength [6][a,b]

Reactant	$\Delta_f G^\circ$/kJ mol^{-1}	
ATP	−2768.10(−4)	−2811.48(−3)
ADP	−1906.13(−3)	−1947.10(−2)
AMP	−1040.45(−2)	−1078.86(−1)
Adenosine	−194.50(0)	
Adenine	313.40(0)	

[a] The charges of the species are shown in parentheses.

[b] The number of digits in this and subsequent tables does not signify the accuracy in terms of significant figures. The information in any thermodynamic table is in the differences between values. For example, in Table 2 the difference between the first two values is 43.38 kJ mol^{-1}. This can be used to calculate the p*K* of CTP: $43.38/(8.31451\times0.29815\times2.303)=7.60$. Table 2 involves the assumption that the p*K* of CTP is the same as the p*K* of ATP because the phosphate groups are pretty far removed from the structural differences between ATP and CTP.

Table 2
Thermodynamic properties of the species in the CTP series at 298.15 K and zero ionic strength[a]

	$\Delta_f G^\circ$/kJ mol^{-1}	z	N_H
CTP	−2573.60	−4	12
	−2616.98	−3	13
	−2645.98	−2	14
CDP	−1711.63	−3	12
	−1752.60	−2	13
	−1779.77	−1	14
CMP	−845.95	−2	12
	−884.36	−1	13
	−909.45	0	14
Cytidine	0	0	13
	−22.09	1	14
Cytosine	507.90	0	5
	481.64	1	6

[a] The charge number is represented by z, and the number of hydrogen atoms is represented by N_H.

This yields the species data in Table 2 that can be used to calculate standard transformed Gibbs energies of formation $\Delta_f G'^\circ$ at 298.15 K, pHs in the range 5 to 9, and ionic strengths in the range zero to about 0.35 M. The charge on the species is z, and the number of hydrogen atoms it contains is N_H. The standard transformed Gibbs energies of formation of these reactants can be calculated at 298.15 K and desired pHs and ionic strengths using the Mathematica program calcdGmat [11].

3. Calculation of standard Gibbs energies of formation of species in the UTP series

The $\Delta_f G^\circ$ for the species in the UTP series can be calculated from the $\Delta_f G^\circ$ for some of the species in the CTP series in a three-step process. The first step is to select the $\Delta_f G^\circ$ in the CTP series that contain information that applies to the UTP series.

Table 3
Some of the standard Gibbs energies of formation in the CTP series at 298.15 K and zero ionic strength that are used in calculating species properties in the UTP series[a]

Reactant	$\Delta_f G^\circ$/kJ mol^{-1}	
CTP	−2573.06(−4)	−2616.98(−3)
CDP	−1711.63(−3)	−1752.60(−2)
CMP	−845.95(−2)	−884.36(−1)
Cytidine	0(0)	
Cytosine	507.90(0)	

[a] The charges of the species are shown in parentheses.