Section III
Perspective

Thermodynamics and Kinetics of Drug Binding, First Edition. Edited by György M. Keserü and David C. Swinney.

16
Thermodynamics and Binding Kinetics in Drug Discovery

György M. Keserü and David C. Swinney

16.1
Introduction

Understanding drug action at the molecular level to guide the rational design of new medicines is facilitated by understanding the kinetics and thermodynamics of drug binding. A therapeutically useful, safe drug response involves the availability of the drug molecule for binding to the target and the translation of the binding to a selective physiologic response. Binding kinetics and thermodynamics are associated with energetic profiles in which the thermodynamics provides the energetic driving force and binding kinetics describes the rates of transitions between energetic minima. The binding process involves the desolvation of the medicine, formation of an initial collision complex with a physiological molecule known as the target, followed by the formation of stable drug–target bimolecular complexes. The stability, duration, and structure of the drug–target complexes contribute to selective physiologic responses.

The intrinsic biophysical characteristics of a non-covalent bimolecular interaction are quantitative parameters useful to help correlate the chemistry of the molecular interaction to physiological and pharmaceutical function. For example, fractional occupancies are used to predict effective blood levels and functional responses, whereas crystal structures, which arguably represent free energy minimums, are used to help design molecules that bind to the drug target. While this way of using thermodynamic and kinetics measurements provides valuable information for drug discovery, the complexities of biological systems are difficult to quantitate using these parameters. The biophysical details of the chemical interactions can be further quantitated in terms of entropy and entropy, and association and dissociation rates.

There is compelling evidence that the thermodynamic and kinetic parameters contribute to the safe, selective therapeutic response, and usefulness of specific medicines [1–5]. Clearly, high affinity associated with large negative free energy (ΔG) and slow dissociation kinetics (k_{off}) are an important feature of drug binding. However for a drug to be a safe medicine, the binding must provide a selective

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response that leads a tolerable therapeutic index. In this chapter, we discuss how the different features of thermodynamics and binding kinetics can contribute to selectivity and an increased therapeutic index.

16.2 Reaction Coordinate

The reaction coordinate is useful to describe binding energetics (Figure 16.1a). The free energy difference between two stable energy states in equilibrium is related to K_d by the equation $\Delta G_0 = -\mathrm{RTln}\, K_d$. The time it takes to transition from one state to another via the transition state is determined by the height of the energy barrier between these states. This time is determined by the kinetic rates for the transition, k_{on} and k_{off}.

The translation of the kinetic rates to a physiological response is shaped by the magnitude of competing rates and the equilibrium state of the system. The outcome of the competing rates is dependent on the relative energy barriers of a thermodynamically stable state (Figure 16.1b) [6]. If one barrier is much lower than the other, then this rate will be faster, regardless of their magnitudes. The closer the system is to equilibrium, the less the outcome will depend upon competing kinetic rates and the more it will depend on the relative thermodynamic stabilities reflected in the equilibrium constants. In contrast, the further the system is from equilibrium, the more the outcome is determined by competing kinetic rates as opposed to equilibrium constants and concentrations (Figure 16.1b).

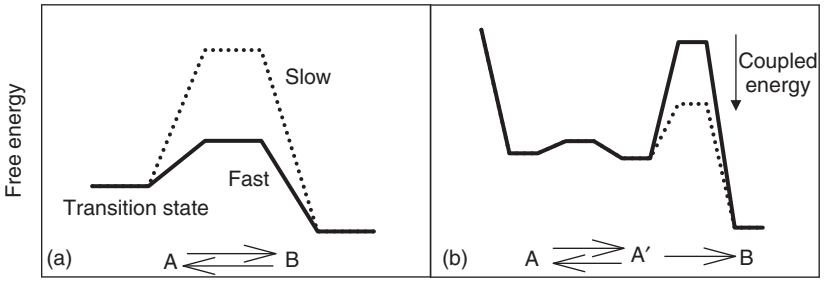

Figure 16.1 Energetic description of biochemical transitions. (a) Energetics of a simple equilibrium reaction; the position of the equilibrium is determined by the relative energy between A and B, while the height of the barrier describes the rate of transition between the two states. Equilibrium with a high barrier is reached slowly, whereas equilibrium with a low barrier is achieved rapidly. (b) Boundaries to accessible states are determined by the height of the energy barrier. Solid line; A and A′ are in equilibrium and B is not accessible because of a high energy barrier. Dashed line; the barrier to B is lowered by energy provided by a coupled system such as drug binding, enzyme catalysis, and induced conformational changes. This is an example of a kinetically controlled reaction. (Reproduced with permission from Bentham Science Publishers © 2006 Ref. [6].)

16.3
Competing Rates

The consequence of competing rates on an outcome will depend on the relationship to equilibrium. Competing reactions at equilibrium are consider under thermodynamic control while those not at equilibrium are consider under kinetic control. An example of this behavior in chemistry is seen with the Diels–Alder reaction of cyclopentadiene with furan can produce two isomeric products. At room temperature, kinetic reaction control prevails and the less stable endo isomer **2** is the main reaction product. At 81 °C and after long reaction times, the chemical equilibrium can assert itself and the thermodynamically more stable exo isomer **1** is formed. The exo product is more stable by virtue of a lower degree of steric congestion, while the endo product is favored by orbital overlap in the transition state (Figure 16.2).

It has been proposed that this type of control in biologic systems translates to switch-like behavior for kinetic control and adjustable behavior for kinetic control [7]. In the following section we will discuss the role of binding kinetics and thermodynamics in thermodynamic, kinetic, and conformational controlled reactions and the contributions to selectivity and a therapeutic index.

16.4
Thermodynamic Controlled Process – Competing Rates under Equilibrium Conditions

The effect of binding on drug design is generally evaluated via equilibrium binding and in most cases reflects binding modes observed in crystal structures of drug bound to a drug target. The binding free energy, ΔG, is due to the difference in binding free energy between free and bound drug and is related to the equilibrium dissociation constant, K, by the equation $\Delta G = -n\mathrm{RT}(1/K_i)$. Since the K_i equals $k_\mathrm{off}/k_\mathrm{on}$ the K_i will correlate with k_off for a series of molecules where the association constants are identical, such as when the binding is diffusion controlled.

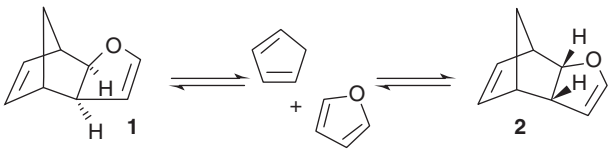

Figure 16.2 Diels–Alder reaction of cyclopentadiene with furan.

This will translate to function when the biology is directly related to the equilibrium occupancy of the target. When the system is at equilibrium competition from an endogenous physiological effector (substrate for enzymes, ligand for receptor) may shift a dose–response curve to higher doses; higher concentrations of drug will be required to maintain the same fraction of occupancy in order to achieve the same response.

When there is a potential for mechanism-based toxicity (on-target toxicity) thermodynamic controlled equilibrium binding can provide an advantage by limiting the fractional occupancy. Reducing fractional occupancy will reduce the toxicity, but also will reduce the activity. Accordingly, this approach will be useful only in systems where lower occupancies provide sufficient efficacy. The tolerability of atypical antipsychotics such as clozapine, the memantine NMDA antagonist, and rapidly reversible NSAIDs has been attributed to the fast off rates that allow equilibrium with an endogenous effector to limit the mechanism-based toxicity [8–10].

16.5 Kinetics Controlled Processes – Competing Rates under Non-equilibrium Conditions

The challenge to achieve an efficient response can be difficult in the presence of high concentrations of competitive effectors due to lower fractional occupancy. This is exemplified by resistance of the ATP-competitive kinase inhibitors gefitinib and erlotinib to the epidermal growth factor receptor (EGFR) kinase. The resistance is due to mutations that alter the ATP binding site in such a way that they increase the affinity of the EGFR kinase domain for ATP. The functional consequence of these resistance mutations is therefore to enable ATP to compete more effectively with gefitinib and erlotinib [11].

It can be difficult to maintain competitive inhibition in the kinetic context of open systems (constant supply of substrates and elimination of products). Westley and Westley have concluded that substrate competitive inhibitors cannot be expected (and do not) provide effective long-term inhibition in simple open systems [12]. The competition can be minimized in nonequilibrium systems in which competing rates create irreversible behavior. For example, irreversible covalent binding medicines are effective medicines that eliminate competition. Reversible inhibitors with slow dissociation rates can achieve a similar response. The functional consequences have been described as insurmountable behavior and pseudo irreversibility. This behavior has been ascribed to a number of different medicines including the angiotensin receptor blockers such as candesartan [13] and is discussed in work of George Vauquelin in Chapter 14 of this book.

The effect of dissociation rates (residence time) to extend pharmacodynamics to outlast pharmacokinetics is another example of a competing rate. In this case,

the dissociation rate for drug from its target must be greater than the elimination half-life.

16.6 Conformational Controlled Process – Kinetics as a Diagnostic for Conformational Change

Slow binding kinetics provide a diagnostic for ligand specific conformational changes. Ligand-specific conformations are predicted to be associated with the slow binding kinetics. Due to the dynamics of conformational changes, it is a challenge to determine SAR associated with the conformational changes based on equilibrium binding and structural studies. Binding kinetics can provide a diagnostic of the role of specific amino acids in ligand induced conformational changes. This was recently described in for allosteric ligand binding to the CCR5, the co-receptor for HIV-1 infections [14]. The mechanism for the slow binding kinetics was proposed to involve rearrangement of the large, flexible binding site to form complementary interactions with the CCR5 ligands. The requirement of E283 for maraviroc, F109 for aplaviroc, and E283 and W86 for vicriviroc suggests that both initial RA and subsequent, R′A complexes are in the pocket described in the maraviroc bound structure of Tan and co-workers (2013). The structural differences between RA and R′A are due to dynamic rearrangement in the same binding pocket. Initial ligand association with the receptor (RA) involves contribution of these anchoring interactions deep in the large CCR5 binding pocket. The RA complex then slowly transitions to a most stable state (R′A). It was speculated that the initial dynamic, flexible RA state will sample the conformational space and transition to a more stable, longer lasting state when a transition state complementary to the structure of the small molecule ligand is identified. The transition state and subsequent final state are unique to each ligand. The ligand specific interactions are then translated to ligand-specific surface conformations of the receptor that are differentially recognized by the GP120 of HIV-1. It was concluded that the differential binding of the antagonists to the CCR5 receptor is determined by contributions from residues that stabilize the binding as well as residues in the transition states to ligand-specific stable complexes (R′A). A kinetic mutation finger print was used to identify the residues involved in the ligand-specific conformational changes. Identification of interactions between the receptor and small molecule that contribute to the unique dynamic transitions could inform chemical design toward changing the binding dynamics while retaining binding affinity. In this case, the slow binding kinetics provide a diagnostic for ligand-specific conformational changes and the kinetic mutant fingerprint infer to identify of specific interactions associated with ligand-specific conformational changes [14].

16.7 The Value of Thermodynamics Measurements to Drug Discovery

Identification of suitable chemical starting points and their subsequent optimization are the most important objectives in drug discovery programs. Although the basic principles of selecting the starting points are extensively discussed, the guidelines of multidimensional optimizations are less than straightforward. The optimization efforts are typically affinity driven and it is assumed that the binding and translation of binding are at equilibrium. Accordingly, medicinal chemistry teams look to focus on other properties such as specificity and selectivity toward the target, physicochemical, and ADME features, and other drug-like properties. Starting from the thermodynamic principles of ligand binding we show here that thermodynamic measurements could contribute to the parallel optimization of multiple parameters and therefore help drug discovery teams identifying promising compounds with balanced properties.

In thermodynamic terms, the optimization of the binding affinity means improving the binding free energy that have two components; the binding enthalpy and the binding entropy. Both enthalpic and entropic components might contribute positively or negatively to the binding free energy and consequently to the binding affinity. Specific interactions such as hydrogen bonds, salt bridges, van der Waals contacts represent enthalpic rewards while desolvation of polar groups results in enthalpic penalty. Entropic rewards are usually associated to the desolvation of the ligand upon binding to the target protein while conformational changes at both the ligand and the receptor side yield entropic penalties (Figure 16.3).

Based on these considerations, the optimization efforts might result in different thermodynamic consequences. The introduction of a polar group could improve the binding enthalpy when specific polar interactions with optimal geometry are

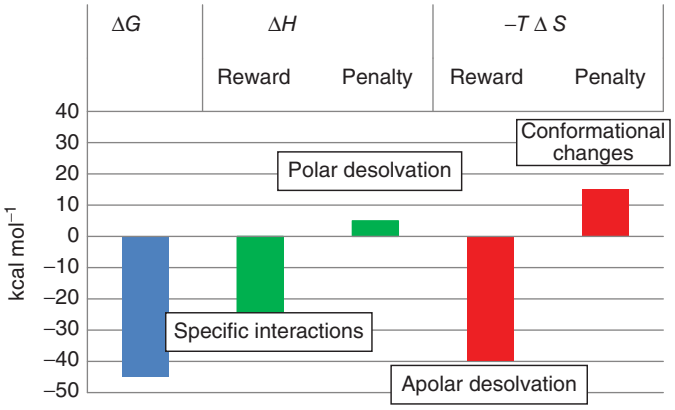

Figure 16.3 Enthalpic (ΔH) and entropic ($-T\Delta S$) components of the binding free energy (ΔG).

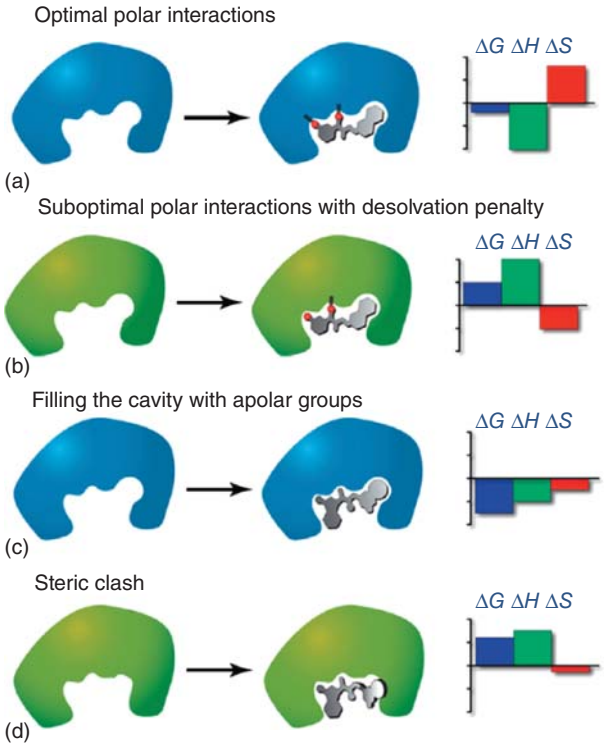

Figure 16.4 Thermodynamic consequences of introducing polar and apolar groups. Adapted with permission from Ref. [15], Copyright © 2011 Elsevier B.V.

formed (Figure 16.4a). If the polar group is positioned incorrectly then mostly the enthalpic penalty of polar desolvation is realized (Figure 16.4b). Adding non-polar groups might be enthalpically advantageous when an apolar cavity is filled (Figure 16.4c). Since apolar interactions are typically less dependent on orientation, the suboptimal fit to the binding cavity would still give some entropic reward; however, steric classes – while the entropic reward due to ligand desolvation is present – cause drastic enthalpic penalties (Figure 16.4d). Consequently, thermodynamic data are best used in connection with structural information that help to understand the thermodynamic consequences of stepwise structural optimization of the compounds.

Thermodynamics impacts the physicochemical and consequently the ADMET profile of the compounds, in addition to the affinity of the ligand binding. In Chapter 4 we showed that enthalpically driven optimizations typically provide better quality compounds than those obtained from entropically driven processes. Good physicochemical and drug-like properties that contribute to more promising ADMET profiles [16] improve the quality of candidate medicines. Freire *et al.* suggested that the quality of interactions of the ligand and the

accompanying binding thermodynamics profile impact selectivity against off-targets [15]. As discussed previously, enthalpically optimized compounds have carefully positioned ligand-binding site atom pairs to achieve the maximal gain in binding enthalpy (Figure 16.4a). The interactions originally designed for the target-binding site are oriented sub-optimally for the off-targets, and therefore do not yield the enthalpic reward realized for the target. The off-target affinity of the ligand will be limited since they will have the same desolvation penalty of the polar ligand atoms (Figure 16.4b). In contrast, entropically optimized compounds have less positional constraints and desolvation of the apolar moieties can result in entropy gain independently on the binding environment (Figure 16.4c). These compounds have therefore higher chance forming attractive interactions with off-targets. This hypothesis was first demonstrated on HIV-1 protease compounds by Kawasaki and Freire [15] measuring the thermodynamic profiles on the primary target HIV-1 protease and cathepsin D and pepsin as off-targets. The impact of binding thermodynamics on selectivity was demonstrated by two pairs of compound. For the first pair, the introduction of two methyl groups into a phenyl moiety resulted in $-11.2\,\text{kJ mol}^{-1}$ gain in binding free energy due to the more favorable enthalpy contribution of the methylated derivative (Figure 16.5). This effect is a result of the optimal occupancy of a small cavity around the aryl moiety that is well oriented and the methyl groups can form desirable contacts. The selectivity toward pepsin and cathepsin D increased from 12- to 157-fold and 72- to 2464-fold, respectively. In the second pair, the thioether moiety was replaced by the sulfonyl-methyl group that resulted in $1.2\,\text{kJ mol}^{-1}$ decrease in binding free energy. However, the binding enthalpy improved from -34.3 to $-50.6\,\text{kJ mol}^{-1}$, and the entropy contribution deceased by $11.2\,\text{kJ mol}^{-1}$. The introduced sulfonyl group establishes a strong hydrogen bond with Asp30

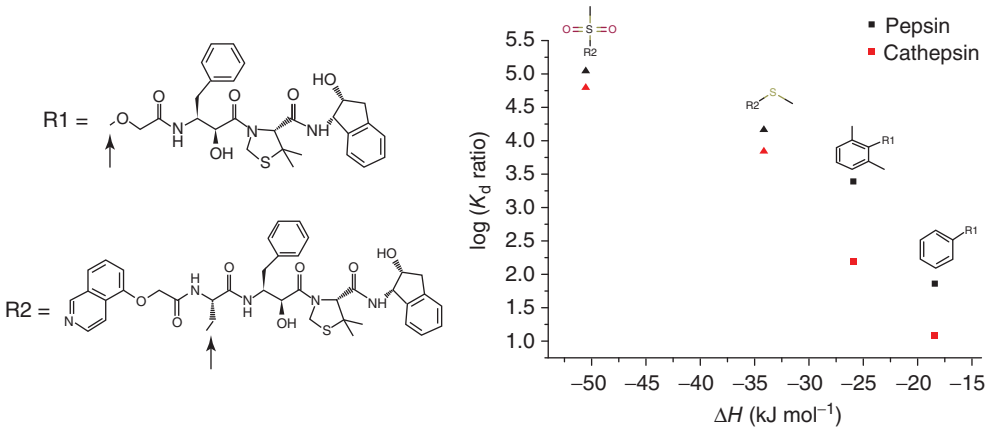

Figure 16.5 Correlation between binding free energy difference and binding enthalpy for HIV-1 protease inhibitors. Adapted with permission from Ref. [17], Copyright © 2011 Elsevier B.V.

of the protease, as evident in the crystal structure. The selectivity against pepsin and cathepsin D increased by seven- and ninefold. The authors suggested that maximal selectivity can be achieved by introducing a few very strong hydrogen bonds toward the primary target protein. H-bonds have very rigorous distance and angular constraints. Consequently, suboptimal H-bonds formed with the off-target protein are penalized and this result in large decrease in the corresponding binding free energy. The overall picture of the four compounds suggests that as the enthalpy contribution to binding free energy is increased, the compounds are more specific to the primary target. It is interesting to note that among these four compounds, the compound with the most favorable binding enthalpy has the highest selectivity and not the one with the highest affinity. This observation has been further validated for a collection of drug targets including matrix metalloprotease MMP12, aldose reductase ALR1, thrombin, cannabinoid receptors, and mitogen-activated protein kinase 14 (MAPK14) having thermodynamic profiles and selectivity data published [17].

The relationship between binding thermodynamics and target specificity was investigated on a dataset containing 19 marketed drugs with thermodynamic and broad specificity assay profiles (Table 16.1) [17].

Table 16.1 shows that binding of three HIV-1 protease inhibitors Nelfinavir, Indinavir, and Saquinavir are entropy driven. Ritonavir binding is also entropy driven, but the enthalpy contribution is more favorable than that for the first

Table 16.1 Broad assay profile and binding thermodynamics data for 19 marketed drugs.

Drug	Target	DrugMatrix	Cerep	ΔG (kJ mol^{-1})	ΔH (kJ mol^{-1})	$-T\Delta S$ (kJ mol^{-1})
Nelfinavir	HIV-1 protease	7.0	—	−53.5	13	−66.5
Indinavir	HIV-1 protease	3.0	7	−51.8	7.6	−59.4
Saquinavir	HIV-1 protease	11.0	18	−54.3	5.0	−59.3
Ritonavir	HIV-1 protease	8.0	15	−57.3	−18.0	−39.3
Amprenavir	HIV-1 protease	2.0	3	−55.2	−28.8	−26.4
Flupenthixol	Dopamine D2	—	52	−47.7	15.2	−62.9
Haloperidol	Dopamine D2	18.0	27	−53.2	−12.8	−40.4
Alizapride	Dopamine D2	—	13	−42.3	−50.8	8.6
Metoclopramide	Dopamine D2	6.0	19	−41.4	−54.8	13.4
Sulpiride	Dopamine D2	2.0	10	−41.9	−88.6	46.7
Fluvastatin	HMG-CoA reductase	1.0	5	−37.6	0.0	−37.6
Cerivastatin	HMG-CoA reductase	0.0	4	−47.7	−13.8	−33.9
Pravastatin	HMG-CoA reductase	0.0	1	−40.5	−10.5	−30.0
Atorvastatin	HMG-CoA reductase	0.0	—	−45.6	−18.0	−27.6
Clozapine	Histamine H1	26.0	44	−47.9	72.0	−119.9
Diphenhydramine	Histamine H1	11.0	29	−43.6	22.6	−66.2
Pindolol	Beta-blocker	1.0	9	−49.6	−21.3	−28.3
Isoproterenol	Beta-blocker	1.0	5	−50.2	−143.2	92.9
Novobiocin	DNA gyrase		0	−42.7	−51.8	9.2

group. Amprenavir binding is characterized by balanced entropy–enthalpy contributions. The change from entropy driven binding to more balanced thermodynamic profile is also reflected in the selectivity profile. Amprenavir hits only 2 targets out of ~134 involved in the DrugMatrix panel and 3 out of 185 in Cerep profiling. In contrary, Saquinavir hits 11 targets on the DrugMatrix assay panel and 18 on the Cerep panel.

Enthalpy contribution of the five drugs acting on dopamine D2 receptor possess significant, −0.91 linear correlation coefficient (r) with the number of hit targets on the Cerep profile. The entropy-driven binding of Flupenthixol is translated into high promiscuity, hitting 52 targets (Table 16.1). In contrast, the enthalpy-driven binding of Sulpiride highlights the enhanced complementarity to the target binding site, and results in significantly reduced promiscuity. Ligands of the dopamine D2 target show univocal tendencies on the DrugMatrix and the Cerep profile.

In case of HMG-CoA reductase inhibitors, Fluvastatin binding is entropy driven, while Cerivastatin, Pravastatin, and Atorvastatin binding have increased enthalpy contribution. Accordingly, Fluvastatin, Cerivastatin, and Pravastatin hits 5, 4, and 1 target on the Cerep assay panel, respectively. The increasing selectivity is in line with the entropy-promiscuity relationships, since the decreasing binding entropy results in lower promiscuity.

Binding of the histamine H1 ligands is entropy driven. Accordingly, Clozapine and Diphenhydramine are highly promiscuous compounds hitting 26 and 11 targets on DrugMatrix, 44 and 29 targets on the Cerep profile, respectively.

Thermodynamics profiles of beta blockers revealed that Pindolol binding is balanced in terms of enthalpy and entropy contributions, while Isoproterenol binding is entirely enthalpy-driven. Thermodynamic profiles are in line with their medium and low promiscuity, respectively.

The last example discussed is Novobiocin, a selective compound characterized by enthalpy-driven binding and correspondingly no off-target activity on the Cerep panel. This compound is specific, with no promiscuity issue reported.

Finally, we investigated the relationship between thermodynamics profiles and observed hit rates (Figure 16.6) for the 17 drugs tested on the Cerep assay profile.

Although differences in binding site characteristics and measurement conditions might impact the results of this analysis we found that compounds hitting a higher number of targets have more remarkable entropy and typically less favorable enthalpy contributions. It is worth mentioning here that higher affinity achieved by entropy-driven optimization do not necessary result in high selectivity (significant negative correlation coefficients), in contrast to those with lower affinity but higher enthalpy contributions.

Although the investigation of binding thermodynamics demonstrated its true value in the optimization of binding affinity, physicochemical and ADMET properties, target specificity, and selectivity, there are a number of limitations that make the interpretation of thermodynamic profiles challenging. First it should

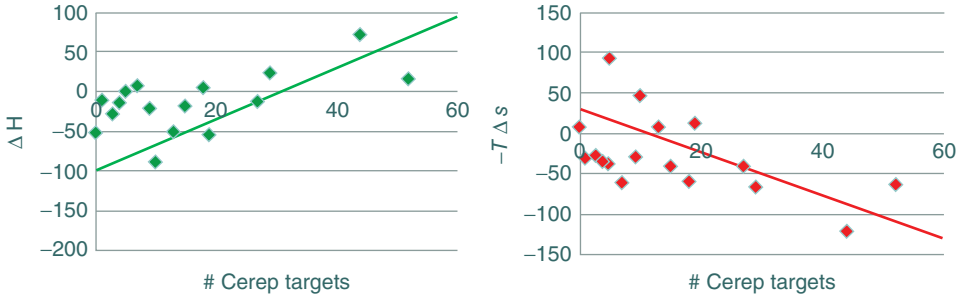

Figure 16.6 Relationship of enthalpic and entropic components of binding free energy (kJ mol^{-1}) and the number of targets hit on the Cerep broad assay profile for 17 marketed drugs.

be considered that both isothermal titration calorimetry and van't Hoff-based approaches provide the net value of thermodynamics parameters that are usually the sum of multiple changes occurred during the binding event. Structural interpretation of the thermodynamic profile might therefore be ambiguous. Here we would like to mention only two complicating factors: the role of binding site water molecules and the cooperativity of polar and nonpolar interactions. These phenomena would result that the introduction of apolar functionalities yields enthalpic reward and vice versa, adding polar groups might turn the enthalpically driven binding of the ligand to entropically favored one (Figure 16.7). The carbonic anhydrase case study of Whitesides and coworkers demonstrate the first scenario when adding a phenyl group to thiophene-sulfonamide (Figure 16.7a)

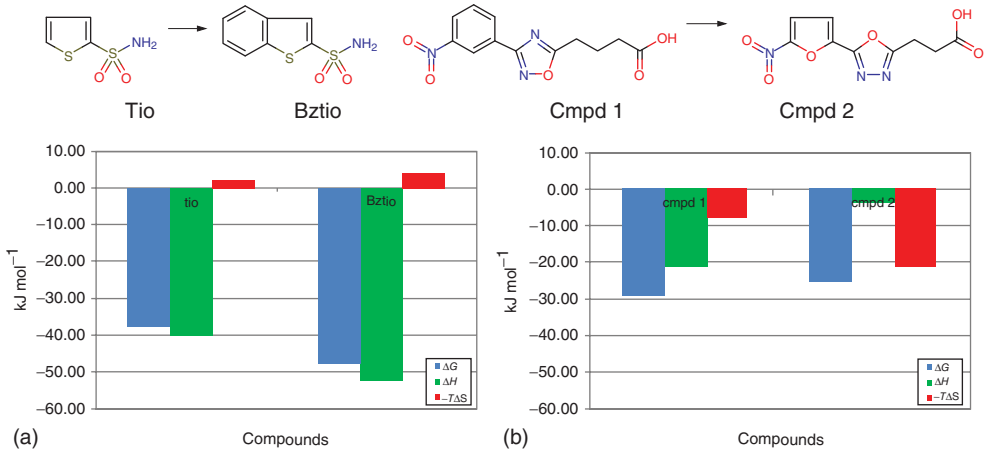

Figure 16.7 Enthalpic (a) and entropic (b) optimizations by the introduction of apolar and polar groups, respectively.

resulted in enthalpic reward [18]. In this case, the introduction of the apolar phenyl group yielded enthalpically more favorable binding that was interpreted on the basis of binding site water molecules. This unexpected change in the thermodynamic profile was rationalized by an enthalpically disfavored water molecule that was displaced by the phenyl extension of the ligand. The opposite situation was observed for aldose reductase inhibitors when introducing polar heteroatoms (Figure 16.7b) resulted in entropically driven binding [19]. In this case, the more polar ligand formed suboptimal polar interactions within the binding site and therefore the enthalpic penalty of polar desolvation compensated the limited enthalpic reward.

The observed cooperativity between hydrogen bonding and hydrophobic interactions complicates the interpretation of thermodynamic profiles further. Klebe and coworkers showed that the formation of lipophilic contacts and the corresponding desolvation of their binding site avoided the formation of optimal hydrogen bonds [20] for a series of thrombin inhibitors. Consequently, the effect of polar and apolar interactions and their impact on the thermodynamic profile could not be separated. Furthermore, the mutually competing and partially compensating enthalpic and entropic effects of polar and apolar moieties resulted in non-additivity of their free energy contributions to ligand binding.

Despite the limitations discussed above, thermodynamics-guided optimizations became more and more frequent in the medicinal chemistry practice. The identification of enthalpic starting points is now supported by plate-based nanocalorimetry [21] and enthalpic screening protocols such as SITE [22]. Analyzing the biomedical literature, we identified 30 documented cases when the investigation of thermodynamic profiles contributed to medicinal chemistry optimizations [23]. Comparing changes in physicochemical profiles and ligand efficiency indexes one can conclude that in contrast to conventional HTS-based optimizations, thermodynamics-guided optimizations provided compounds having similar parameters to that of the successful lead optimizations (Table 16.2).

Considering that similar to successful lead optimizations thermodynamics-guided processes were able to improve the affinity with remarkably reduced

Table 16.2 Physicochemical and ligand efficiency changes in medicinal chemistry optimizations.

Process	*n*	pPot change	MW change	logP change	LE change	SILE change	LLE change	LELP change
HTS based optimization [24]	335	1.39	51.5	0.27	0.02	0.58	1.1	0.1
Lead optimization successful [25]	60	2.08	89.9	0.05	0.01	0.85	2.1	−1.1
Thermo optimization	30	1.27	63.8	0.01	0.01	0.37	1.22	0.09

inflation of physicochemical properties, we feel that investigation of binding thermodynamics might contribute significantly to the success of medicinal chemistry programs in drug discovery projects.

16.8 Complementarity of Binding Kinetics and Thermodynamic to Discover Safer Medicines

Overall thermodynamics quantitates the difference in energetics between two states in equilibrium and binding kinetics depends on the energetics of the barriers to the states (Figure 16.1a). In more complex systems, the thermodynamic and kinetic parameters are features that contribute to selectivity and a tolerable therapeutic index, each in their own way. Currently, the underlying principles of how thermodynamics and kinetics provide selectivity are beginning to be revealed, but are still not absolutely clear. As described in this chapter, in some cases the enthalpic component will correlate with better affinity and selectivity to the on-target by providing a more exact fit for the binding site. The binding kinetics describes the rate of the binding process and can contribute to selectivity via the equilibrium state of the system and relationship to competing rates. Kinetics and thermodynamics of drug binding are complementary in providing increased selectivity.

So far in this chapter (and in this book) binding kinetics and thermodynamics have been generally discussed separately with the exception of defining the relationships in the reaction coordinate. Clearly, both describe the aspects of the binding process and the discussions above related to defining how the individual features (K_d, k_{on}, k_{off}, ΔG, ΔH, ΔS) relate to drug action and optimization. At this point, there is not enough of an understanding to predict how thermodynamics and kinetics can be integrated with the exception of the case in which thermodynamics stabilization of the ground state in a simple bimolecular reaction increases the kinetic barrier and corresponding k_{off} by lowering the ground state energy. We have limited understanding of thermodynamic properties that control the transition states.

Perhaps the biggest technical challenge for drug discovery is to identify molecules and their binding modes and corresponding molecular mechanisms of actions (MMOAs) that provide a safe and effective response. Intrinsic to the interaction is the binding kinetics and thermodynamics. Historically, binding kinetics and thermodynamics have been thought of almost exclusively in terms of free energy and affinity as molecular descriptors for activity. It is now clear that the features of binding kinetics and thermodynamics will also influence selectivity and thereby the therapeutic index and usefulness of a medicines. This chapter and book describes some of the recent advances to understand the underlying principles and apply these to drug discovery. We believe that effective use of binding kinetics and thermodynamics can help optimize drug candidates to selective, safer medicines.

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