UC Davis
UC Davis Previously Published Works

Title

Validation of Enthalpy–Entropy Compensation Mechanism in Partial Amide Bond Rotation

Permalink

Journal

ISSN

Authors

Guerra, Jacob
Bajwa, Bhvandip
Kumar, Prarthana
et al.

Publication Date

DOI

Validation of Enthalpy−Entropy Compensation Mechanism in Partial Amide Bond Rotation

Jacob Guerra, Bhvandip Bajwa, Prarthana Kumar, Salvador Vazquez, Viswanathan V. Krishnan,* and Santanu Maitra*

Cite This: *ACS Omega* 2020, 5, 9348−9355

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The concept of enthalpy−entropy compensation (EEC) is one of the highly debated areas of thermodynamics. The conformational change due to restricted double-bond rotation shows a classic two-site chemical exchange phenomenon and has been extensively studied. Fifty-four analogs of *N,N*-diethyl-*m*-toluamide (DEET) as a model system were synthesized to study the thermodynamics of the partial amide bond character using nuclear magnetic resonance (NMR) spectroscopy. Line-shape analysis as a function of temperature is used to estimate the chemical exchange. Eyring analysis was then used to convert the chemical exchange rates to determine the transition state enthalpy and entropy of the molecules. The experimental design follows selective variations that perturb one aspect of the molecular system and its influence on the observed thermodynamic effect. The results of the study demonstrate that amide bond resonance in analogs of DEET follows an EEC mechanism. Simple modifications made to DEET's structural motif alter both the enthalpy and entropy of the system and were limited overall to a temperature compensation factor, T_β = 292.20 K, 95% CI [290.66, 293.73]. We suggest EEC as a model to describe the kinetic compensation seen in chemical exchange phenomena in analogs of DEET.
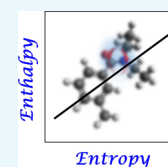
1. INTRODUCTION

The concept of enthalpy−entropy compensation (EEC) was first pointed out by Constable.[1] Since that time, this concept has been widely discussed in the literature either for or against the validity of EEC and covered in detail by many excellent reviews.[2−5] While the concept has been successfully demonstrated in a wide range of systems from single molecules[6] to larger molecular systems,[2] we demonstrate here that the thermodynamics of amide partial double-bond rotation also follows the EEC. *N,N*-Diethyl-*m*-toluamide (DEET) is used here as a model system to exploit chemical exchange caused by restricted rotation about the amide bond using nuclear magnetic resonance (NMR) spectroscopy.

The partial double-bond character in the C−N bond of the amides is due to the resonance interaction between the lone pair of electrons on the nitrogen atom and the carbonyl π system. The rotational barrier leads to observable spectral changes in the NMR time scale leading to studies that include a range of small molecules to proteins.[7−10] For more than 50 years, the chemical exchange phenomenon has been studied, first shown in *N,N*-dimethyl-formamide.[11−14] The extensive use of NMR line-shape, defined as dynamic nuclear magnetic resonance (DNMR) spectroscopy, is popular in undergraduate physical−organic laboratories[15] with sustained interest in the broader field of NMR spectroscopy.[8,10,16−24]

In this study, simple modifications to DEET's motif were made, and 54 analogs were synthesized to study the thermodynamic parameters: enthalpy $\Delta H^{\ddagger}$ and entropy $\Delta S^{\ddagger}$ of the transition state of the partial amide bond rotation. It is believed that electronic and steric interactions of substituents

in analogs of DEET have some effect on the amide bond character given that the amide functional group, generally known as a carboxamide group, has both σ and π bonds. Resonance in the amide bond occurs when the nitrogen atom's lone pair of electrons delocalizes into the carbonyl group's π system. The rotation about the dihedral angle (O−C−N−C) generally has two unique rotational energy barriers due to the extent of resonance.[25] The fast or slow exchange limit between equilibrium conformations occurs with low or high activation energy barriers, respectively, where DEET shows classic two-site chemical exchange associated with the following thermodynamic parameters: $\Delta H^{\ddagger}$ = 59.8 ± 1.1 kJ/mol and $\Delta S^{\ddagger}$ = 10.9 ± 0.9 J/(mol K).[23] Here, molecular collisions do not contribute to the likelihood of overcoming energy barriers; the chemical exchange between conformations is strictly a first-order process.

The exchange rates (k_{ex}, s^{-1}) were derived from the line-shape analysis of the classic two-site exchange spectrum of the methylene peak resonances (N−CH$_2$−) of the DEET molecules. An Eyring plot was used to determine the activation enthalpy $\Delta H^{\ddagger}$ (kJ/mol) and the entropy $\Delta S^{\ddagger}$ (J/(mol K)) affecting partial amide bond rotation for 54 analogs of DEET. In this work, we further demonstrate that entropy and enthalpy
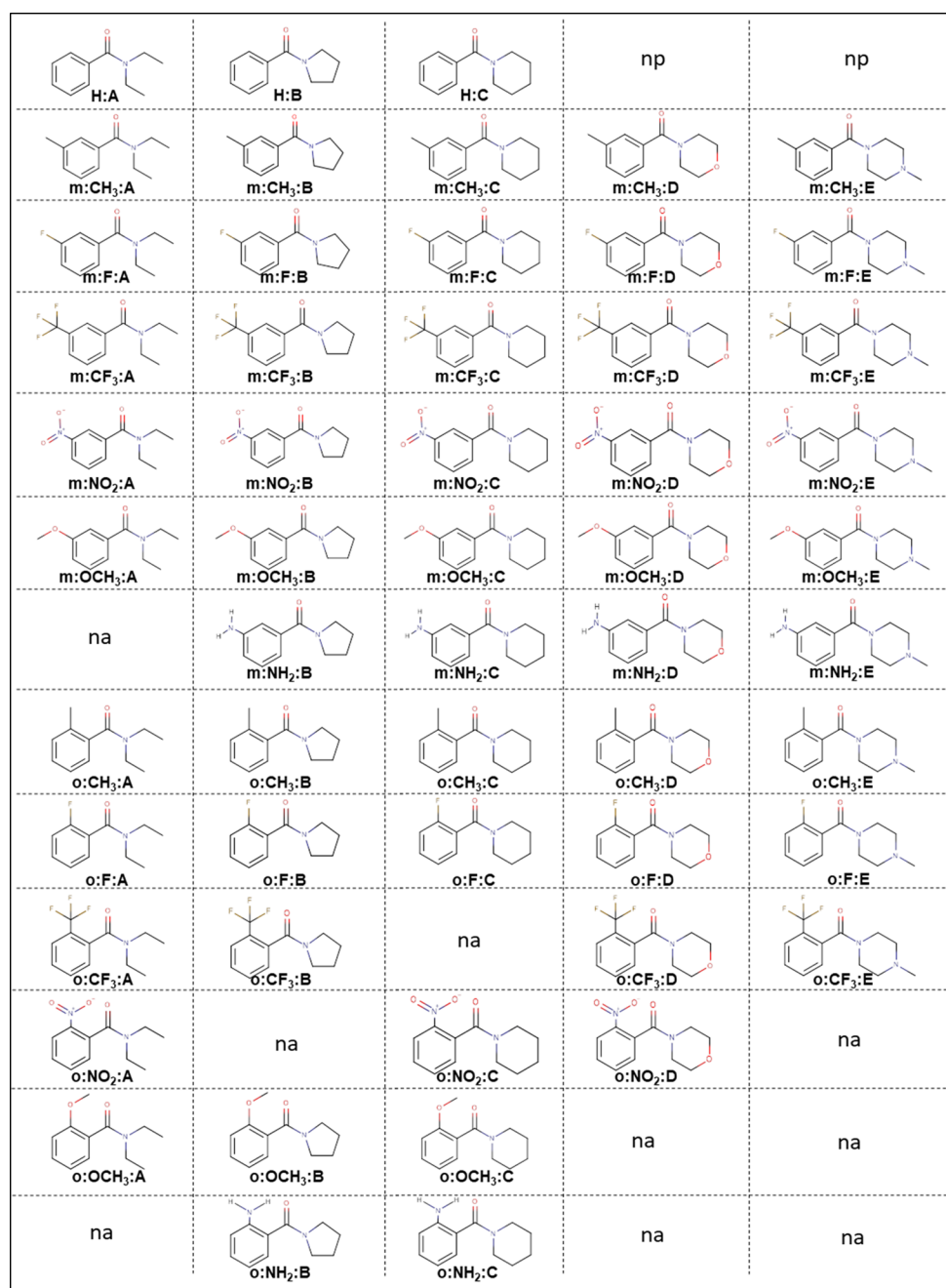
Figure 1. Molecules in the series of DEET. The columns represent the functional group substitutions at ortho (*o*) or meta (*m*) positions with the corresponding groups $-CH_3$, $-F$, $-CF_3$, $-NO_2$, $-OCH_3$, or $-NH_2$. The letters along the row represent an amine substitution with A (diethylamine), B (pyrrolidine), C (piperidine), D (morpholine), and E (1-methylpiperazine). Cells with "np" or "na" represent molecules that were either "not performed" or "not available", respectively.

changes measured in analogs of DEET follow an enthalpy–entropy compensation (EEC) mechanism and are limited to a relatively small window of Gibbs energy of the transition state in the temperature range of 278−331 K. We also demonstrate the use of an EEC plot as a statistical means to describe the linear correlation as having physical thermodynamic meaning in transition state theory, specifically that chemical exchange herein follows a kinetic compensation effect.

2. METHODS

2.1. DEET Analog Design. In this series, *meta*- and *ortho*-substituted analogs were chosen because *meta* positions more

closely resemble the structure of DEET (see Figure 1), and *ortho*-substituted analogs had revealed unprecedented conformational sites in previous studies.[22,23] Aromatic substituents varied in size and electronic properties. The aromatic *meta* position is an inductive contributing site; however, resonance contributes through the *ortho* and *para* positions. Analogs that are *meta*-substituted should allow for the analysis of electron density distribution by inductive means. To differentiate steric interactions at the amide N moiety in the DEET motif, *meta*- and *ortho*-substituted analogs were paired with the following amine substitutions: diethylamine, pyrrolidine, piperidine, morpholine, and 1-methyl piperazine (Figure 1). The amine substitution(s) varied in size and electronic properties where a

cyclic amine substitution reduced intramolecular steric effects (Figure 1).

2.2. Synthesis. All DEET analogs synthesized in this work follow this experimental procedure except for amino compounds (m-NH$_2$ and o-NH$_2$ series), and longer reaction times were taken for all *ortho* compounds: 1-methyl-4-(3-methyl benzoyl) piperazine (m-CH$_3$-E): a dry 25 mL round bottom flask was charged with 10 mL of distilled thionyl chloride (d 1.635 g/mL) and m-toluic acid (0.4995 g, 3.667 mmol). The mixture was refluxed for 2.5 h while stirring. Thionyl chloride was removed under reduced pressure.

Then, CH$_2$Cl$_2$ (10 mL) was added and stirred at room temperature for 5 min. N-methyl piperazine (0.5579 g, 5.570 mmol, 1.5 eq) was added dropwise over 5 min and stirred at room temperature for 5 h with a condenser; the addition of the amine produced a white gaseous hydrochloride cloud of the amine.[26] The organic layer was washed with two portions of 1 M NaOH (10 mL), deionized water (10 mL), and brine solution (10 mL) and dried over anhydrous MgSO$_4$. Evaporation of the solvent under reduced pressure yielded a light brown viscous oil (0.6579 g, 82.15% yield) of 1-methyl-4-(3-methyl benzoyl)piperazine (m-CH$_3$-E). The reaction was monitored by thin-layer chromatography and characterized using NMR.

For amino-based compounds, m-NH$_2$-B−E and o-NH$_2$-B−E, the nitrobenzoic analog was first synthesized using the experimental procedure described above followed by a hydrogenation reaction. The generalized reduction reaction scheme is as follows: to a dry 25 mL round bottom flask, the nitro-substituted analog (approximately 2 mmol) was added followed by reagent-grade methanol (12 mL). A double oblique stopcock was then connected to the charged flask with one outlet to a vacuum pump and the other to a high-quality rubber balloon filled with hydrogen gas. The air in the system was purged with nitrogen followed by hydrogen, and the process was repeated three times. The resulting reaction mixture was subjected to continue to stir with hydrogen gas overnight. The reaction was monitored using thin-layer chromatography to verify the completion of the reaction. Methanol was removed under reduced pressure by rotary evaporation, and the target compound was purified using standard chromatography methods.[25]

2.3. NMR Spectroscopy. All proton NMR experiments were performed in a 400 MHz (^{1}H resonance frequency) VNMRS spectrometer (Varian-Agilent). Each analog was dissolved in CDCl$_3$ for a total volume of 0.60 mL and 75 mM in concentration. Each NMR sample was glass-sealed using a freeze−thaw method where the dissolved air was removed under controlled reduced pressure after immersing it in liquid nitrogen, applying vacuum, thawing with vacuum closed, and sealed using a butane torch (freeze−thaw cycles were repeated 2−3 times to ensure complete removal of dissolved air). The temperature was calibrated using MeOH.[27] Variable-temperature NMR experiments ranged from 5 to 55 °C (in steps of 5 °C) with the corresponding calibrated temperatures: 278.15, 282.89, 288.27, 293.65, 299.03, 304.42, 309.80, 315.18, 320.56, 325.95, and 331.33 K. One-dimensional, variable-temperature experiments were performed using 32 transients over 16k complex points after calibrating the 90° pulse width at 30 °C. Samples were equilibrated for 15 min at each temperature, and a relaxation delay of 4 s was used with an Ernst angle (∼70° pulse). NMR spectra were processed and saved under a NUTS format, and the program WINDNMR

was used to estimate the exchange rates (k_{ex}, s^{-1}).[24] A two-site exchange simulation was used to estimate the exchange rate (k_{ex}, s^{-1}) for methylene peak resonances (N−CH$_2$−) of variable-temperature NMR spectra with special attention to line width for exchanging peaks.

An Eyring plot was used to approximate the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ of the transition state for 54 analogs using a linear fit between k_{ex} (s^{-1}) (logarithmic scale) versus $1000/T$ using a linear model as described previously.[24] The standard deviation in each of the measured values and the error propagation were determined using a Monte Carlo method based on the generation of a large number of sampling with reference to the mean and standard deviation of the individual variables. All the data analysis was performed using a combination of Microsoft Excel and using the R statistical environment.[28]

3. RESULTS

3.1. On the Existence of EEC in Partial Amide Bond Rotation. For an equilibrium process

$$\Delta H^{\ddagger} = \Delta G^{\ddagger} + T\Delta S^{\ddagger} \tag{1}$$

In the manuscript, the authors choose to use the thermodynamic parameters with a "‡" superscript (e.g., $\Delta H^{\ddagger}$ instead of ΔH) as we follow the theory $\Delta H^{\ddagger} = \Delta G^{\ddagger} + T\Delta S^{\ddagger}$ of activated complexes from transition state theory.

The enthalpy−entropy compensation (EEC) phenomenon has been empirically observed for many physical processes, both similar and nonsimilar. It favorably applies to similar systems and restrictedly to nonsimilar systems.[4] EEC is not an apparent thermodynamic phenomenon, even described as being neither thermodynamic nor non-thermodynamic (also known as extra thermodynamic), but is only observed under mathematically defined equilibrium conditions. Simply stated, eq 2 describes a linear plot between the change in enthalpy and entropy described by

$$\Delta H^{\ddagger} = \alpha + \beta \Delta S^{\ddagger} \tag{2}$$

where α and β are constants. Following the entropy-based interpretation of Hammett's relationship by Leffler[29,30] and review by Pan et al.,[4] the EEC in the case of partial amide bond rotational motions can be justified as follows.

It is assumed that the substitutional effects to the DEET moiety would alter the activation energy barrier for partial amide bond rotation as evidenced by the differential effect on the measured k_{ex} values in the series of DEET analogs. Then, the change in Gibbs energy for the process of partial amide bond rotation in the substituted DEET molecule can be written as

$$\Delta(\Delta G^{\ddagger})(s) = \beta\ \Delta(\Delta G^{\ddagger})(c) \tag{3}$$

where s represents the DEET with the altered substitution with reference to the control c DEET with β as the proportionality constant. For experiments at two different temperatures, T_i and T_j, and further assuming that the enthalpy and entropy of the system are independent of temperature

$$\Delta(\Delta G_i^{\ddagger})(s) = \Delta(\Delta H^{\ddagger})(s) - T_i\Delta(\Delta S^{\ddagger})(s)$$

$$\Delta(\Delta G_j^{\ddagger})(s) = \Delta(\Delta H^{\ddagger})(s) - T_j\Delta(\Delta S^{\ddagger})(s) \tag{4}$$

By taking the difference in the Gibbs energy between the two temperatures

$$\Delta(\Delta S^{\ddagger})(s) = [\Delta(\Delta G_i^{\ddagger})(s) - \Delta(\Delta G_j^{\ddagger})(s)]/(T_j - T_i) \quad (5)$$

Now, combining with eq 3 to relate with that of the control molecule

$$\Delta(\Delta S^{\ddagger})(s) = \left(\frac{\beta_i - \beta_j}{T_j - T_i}\right)\Delta(\Delta G^{\ddagger})(c) \quad (6)$$

By defining $\delta_{ij} = (\beta_i - \beta_j)/(T_j - T_i)$ and for non-zero δ_{ij}, eq 6 becomes

$$\Delta(\Delta G^{\ddagger})(s) = \beta\,\Delta(\Delta G^{\ddagger})(c) = \left(\frac{\beta}{\delta_{ij}}\right)\Delta(\Delta S^{\ddagger})(s) \quad (7)$$

Rewriting eq 7 in terms of a transition state enthalpy and entropy with $T_i \leq T \leq T_j$

$$\Delta(\Delta H^{\ddagger} - T\Delta S^{\ddagger})(s) = \left(\frac{\beta}{\delta_{ij}}\right)\Delta(\Delta S^{\ddagger})(s) \quad (8)$$

or

$$\Delta(\Delta H^{\ddagger})(s) = \left(\frac{\beta}{\delta_{ij}} + T\right)\Delta(\Delta S^{\ddagger})(s) \quad (9)$$

Equation 9 proves the existence of a linear relationship between enthalpy and entropy given in the form of a linear equation (eq 2).

In this work, transition state theory was used to study the kinetics affecting the dynamic processes behind the chemical exchange; the following relations are stated here:

$$K^{\ddagger} = e^{-(\Delta G^{\ddagger}/RT)} \quad (10)$$

$$k_{ex} = \kappa \frac{k_B T}{\hbar} e^{-(\Delta G^{\ddagger}/RT)} \quad (11)$$

Equation 10 is the expression for the transition state equilibrium constant $K^{\ddagger}$ between the transition state and the ground state. Equation 11 is the conventional form of the absolute rate equation based on transition state theory for first-order mechanisms where k_{ex} is the exchange rate, R is the gas constant, k_B is the Boltzmann constant, $\hbar$ is Planck's constant $(h/2\pi)$, and κ is the transmission coefficient. The pre-exponential frequency factor, $k_B T/\hbar$, has its meaning in collision theory.[31] Therefore, the well-known Eyring equation is

$$\ln\left(\frac{\kappa}{T}\right) = \left\{-\frac{\Delta H^{\ddagger}}{R}\right\}\frac{1}{T} + \left\{\ln\left(\frac{k_B}{\hbar}\right) + \frac{\Delta S^{\ddagger}}{R}\right\} \quad (12)$$

where $\Delta H^{\ddagger}$ is the activation enthalpy of the transition state and $\Delta S^{\ddagger}$ is the activation entropy of the transition state. Thus, transition state theory is a description of the equilibrium state between the ground state and transition state relative to the exchange constant (k_{ex}) of the process. Further, $\Delta S^{\ddagger}$ is the activation entropy required to reach the transition state from the ground state and specifically reflects the molecularity or randomness of the molecule as the transition state, which is approached from the ground state.[32] The transition-state enthalpy and entropy are determined using the Eyring analysis (eq 12) and then used to verify EEC given by eq 2.

3.2. NMR Spectroscopy. The physical process analyzed here in variable-temperature NMR spectra was the chemical exchange of the methyl group protons (N−CH$_2$−) about the amide bond in a series of analogs. Case examples of variable-temperature NMR data are summarized previously in similar samples.[22,23] Generally, most analogs showed temperature dependence corresponding to a classic two-site chemical exchange process for both methylene group protons (N−CH$_2$−), characteristic to DEET in the chemical shift range of 3.1−3.8 ppm. Figure 2 shows examples of the temperature-
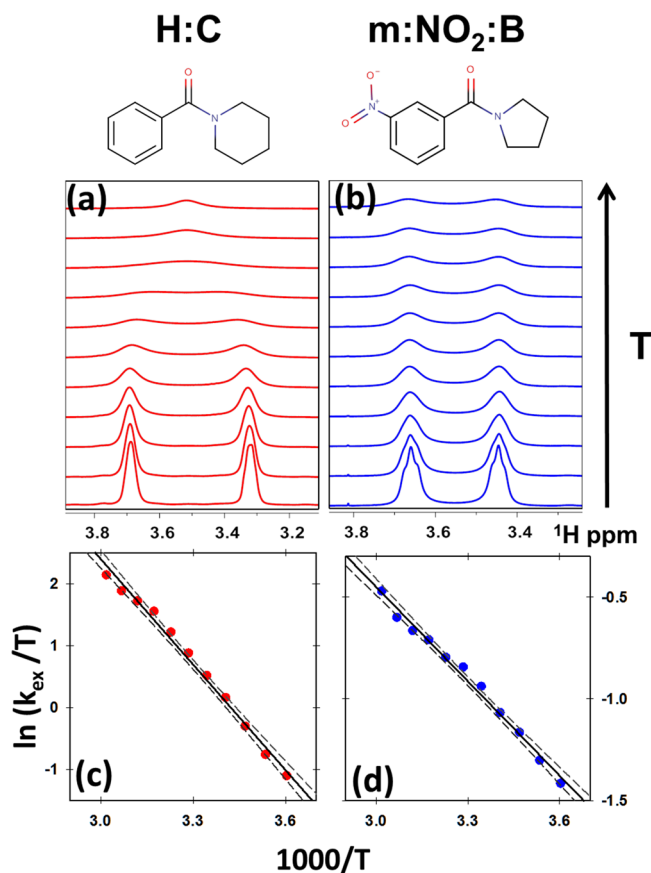

Figure 2. Two-site chemical exchange by NMR. Temperature-dependent changes in the line shape of a two-site exchange: (a) H−C and (b) m-NO$_2$-B. The exchange rates (k_{ex}, s^{-1}) were estimated using line-shape analysis of the spectra for the Eyring plots of (c) H−C and (d) m-NO$_2$-B. Experimental values are given in symbols with the linear fit in continuous lines and 95% confidence intervals in dashed lines. The ^{1}H spectra were acquired at 400 MHz from 278 to 331 K in steps of 5 K.

dependent spectral changes in the case of molecules H−C (Figure 2a) and m-NO$_2$-B (Figure 2b). The NMR spectra of all the molecules analyzed here follow the characteristic two-site chemical exchange phenomenon.

An Eyring plot (ln k_{ex}/T versus 1000/T) was used to estimate the activation enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) of the exchange process for each analog ($\Delta H^{\ddagger}$ (kJ/mol) = −slope × R and $\Delta S^{\ddagger}$ (J/(mol K)) = y-intercept − ln($k_B/\hbar$) × R) where R, k_B, and $\hbar$ are the gas, Boltzmann, and Planks' constants, respectively, in SI units. The Eyring plots for the representative molecules, H−C and m-NO$_2$-B, are shown in Figure 2c,d, respectively. For H−C, the change in the enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) values estimated using the Eyring analysis are 46.72 ± 2.12 kJ/mol, and −33.73 ± 6.99 J/(mol K), respectively. The corresponding $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for

m-NO$_2$-B are 13.59 ± 0.72 kJ/mol, and −156.57 ± 2.37 J/(mol K), respectively. A table summarizing the variable-temperature data (temperature and k_{ex} values for all the molecules) is given in the Supporting Information (Table S1). A criticism of using an Eyring plot to obtain $\Delta S^{\ddagger}$ is that the y-intercept is a large extrapolation from the experimental data to high temperatures. The Eyring plot R^2 values of the linear fit were good (>0.98 for most analogs), leading to reliable estimates of $\Delta S^{\ddagger}$, and are also a proven method.[33] The enthalpy and entropy derived from the Eyring plot for all the molecules are given in the Supporting Information (Table S2). Overall, a wide range of activation enthalpy, 3.46 to 78.65 kJ/mol, with an average value of 38.74 ± 19.96 kJ/mol, was observed in our analog series. A wide range of activation entropy, −193.20 to 63.54 J/(mol K) with an average of −71.56 J/(mol K), was observed.

3.3. Enthalpy−Entropy Compensation. A linear trend was observed between enthalpy and entropy of the transition state. It was noted that, whenever activation enthalpy was low, activation entropy was increasingly negative. Whenever activation enthalpy was high, activation entropy tends to increase in a positive direction as well. This relationship follows the well-known laws of statistical thermodynamics.[5] In Figure 3, activation entropy is plotted against activation
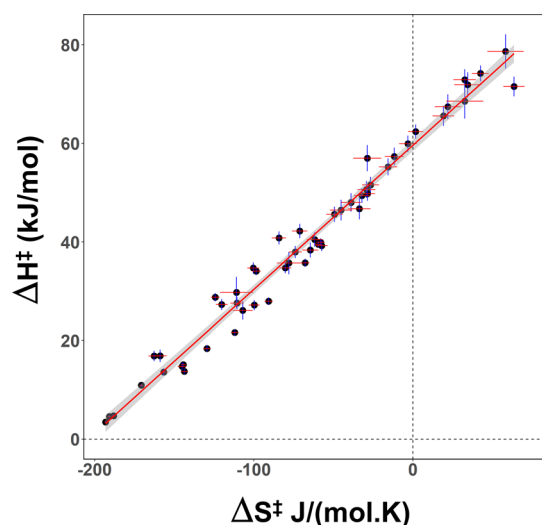

Figure 3. The enthalpy−entropy compensation (EEC) phenomenon in DEET analogs in CDCl$_3$ follows the relation: $\Delta H^{\ddagger} = \alpha + T_{\beta} \Delta S^{\ddagger}$. From the EEC plot, the correlation between enthalpy and entropy of activation is $T_{\beta} = 292.20 \pm 5.81$. The error bars are estimated from the fit to the Eyring equation. The continuous red line represents the best fit, and the gray bar shows 95% confidence. The R^2 value of the linear fit is 0.98.

enthalpy and shows a linear correlation. The trend is statistically significant because the data points all fall within a 95% confidence interval, and the error in enthalpy and entropy also fall within this confidence interval ($R^2 = 0.98$). The list of estimated $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for all the molecules are listed in the Supporting Information (Table S2). The trend in the data suggests that there exists an intrinsic EEC mechanism for the physical process of chemical exchange for partial amide bond rotation in analogs of DEET. In other words, EEC herein is a kinetic compensation effect. This means that, when activation enthalpy is perturbed, the entropy of activation dependently changes as well. From the EEC plot, the

correlation follows the relation: $\Delta H^{\ddagger} = \alpha + \beta \Delta S^{\ddagger}$ (eq 2) where the proportionality constant β is defined as the temperature compensation factor (T_{β}). A linear fit of the experimental to eq 2 results in a T_{β} of 292.20 K, 95% CI [290.664, 293.736].

The EEC plot (Figure 3) demonstrates that amide bond resonance in analogs of *DEET* follows an enthalpy−entropy compensation (EEC) mechanism and is limited to a relatively small window of Gibbs energy of the transition state $\Delta G^{\ddagger} = 65.70 \pm 0.67$ kJ/mol at room temperature (293 K). However, no patterns or groupings of analogs based on substituents, their location, or class of amine could be found in the trend. Figure S1a,b shows the EEC plot in reference to cyclic amine substitutions and aromatic substitutions, respectively. This suggests that the EEC phenomenon here is independent of changes in the system in terms of substituents or the class of amine.

In the EEC plot, the molecule m-CH$_3$-A (DEET) has the highest activation enthalpy (78.65 ± 3.46 kJ/mol) and entropy (58.21 ± 11.37 J/(mol K)), while on the other extreme, the molecule o-F-C (1-(2-fluorobenzoyl)piperidine) has the lowest activation enthalpy (3.46 ± 0.20 kJ/mol) and entropy (−193.20 ± 0.66 J/(mol K)). However, both these molecules have very similar activation Gibbs energies, 61.29 ± 4.85 kJ/(mol K) (m-CH$_3$-A) and 61.06 ± 0.28 kJ/(mol K) (o-F-C) at 298 K (Table S2).

4. DISCUSSION

What follows from EEC herein is that there is an inherent kinetic compensation effect mechanism behind the physical process of chemical exchange. From the EEC plot (Figure 3), $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are known for any single analog; then from eq 2, the Gibbs energy of the transition state ($\Delta G^{\ddagger}$) remains nearly constant and is synonymous with α, particularly at temperatures in the vicinity of T_{β} (eqs 1 and 2).[4] It is assumed that activation enthalpy is a direct result of bond breaking. Therefore, a low activation enthalpy means a lesser degree of resonance or amide partial double-bond character. Entropy is something different in that the molecularity of the transition state is described by degrees of freedom or polarizability. Entropy decreases toward the activated complex. Therefore, the more negative the entropic contribution is, the fewer possible microstates there are to distribute internal energy. Following the definition of Gibbs energy (eq 1), an analog having ($\Delta S^{\ddagger} \rightarrow -\infty$) would have a greater potential energy barrier in terms of $\Delta G^{\ddagger}$.

EEC implies that $\Delta G^{\ddagger}$ should remain constant based on constant α (eq 2) and that $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ do not singly reflect the energy barrier. Therefore, EEC may be used as a model to describe chemical exchange behavior in variable-temperature NMR spectra in terms of an energy barrier and exchanging methylene (N−CH$_2$−) protons. A narrow range of $\Delta G^{\ddagger}$ overall for the series of 54 analogs of DEET was observed at each experimental temperature deviating by ±3 kJ/(mol K) from the respective average $\Delta G^{\ddagger}$ values. Thus, EEC herein possesses a limited $\Delta G^{\ddagger}$ window, and the compensation between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ becomes a mathematically rational concept. A narrow range of the experimentally measured $\Delta G^{\ddagger}$ values was proposed as a potential reason against the EEC.[34−36] Nonetheless, a realistic model is proposed here to account for the thermodynamics of chemical exchange of N−CH$_2$− protons concerned with solvent properties and solute−solvent interactions. Following the formulation by Hepler[37,38]

and later reiterated by Pan et al.,[4] the concept of EEC is still valid by dividing the enthalpic and entropic contributions into external and internal components, the assumptions are as follows:

$$\Delta H^{\ddagger}_{sub} = \Delta H^{\ddagger}_{int} + \Delta H^{\ddagger}_{ext} \tag{13}$$

$$\Delta S^{\ddagger}_{sub} = \Delta S^{\ddagger}_{int} + \Delta S^{\ddagger}_{ext} \tag{14}$$

The parameters $\Delta H^{\ddagger}_{sub}$ and $\Delta S^{\ddagger}_{sub}$ are the activation enthalpy and entropy of the substitution, respectively. External contributions to enthalpy and entropy arise due to solute–solvent interactions. Internal contributions arise from differences in enthalpy and entropy within the molecule itself relative to substitutions and their resonance and inductive effects. It is safe to assume that, when a substitution is made

$$\Delta S^{\ddagger}_{int} = 0 \tag{15}$$

This notion here is justified from solute–solvent studies using the same analogs in different solvents where $\Delta S^{\ddagger}$ is extrapolated in an EEC plot and an area of convergence is apparent for the different trends possessing different values for β (see eq 2).[39] Thus, the difference in entropy of activation in the series is due to differences in solute–solvent interactions, and we write

$$\Delta S^{\ddagger}_{sub} = \Delta S^{\ddagger}_{ext} \tag{16}$$

If $\Delta H^{\ddagger}_{sub}$ and $\Delta S^{\ddagger}_{sub}$ are proportional and justified based on the derivation of eq 9, we write

$$\Delta H^{\ddagger}_{ext} = \beta \, \Delta S^{\ddagger}_{ext} = \beta \, \Delta S^{\ddagger}_{sub} \tag{17}$$

The proportionality constant β is unique to a single solvent phase (CDCl$_3$ in this work). Combining eqs 13 and 17, we write

$$\Delta H^{\ddagger}_{sub} = \Delta H^{\ddagger}_{int} + \beta \Delta S^{\ddagger}_{sub} \tag{18}$$

Following Hepler's formulation,[37,38] when we apply eq 18 to a series of n-substituted molecules, we get n equations like eq 18, n unknown $\Delta H^{\ddagger}_{int}$ values, and the additional unknown β that is common to all equations. In this work, $\beta = T_{\beta} = 292.20 \pm 5.81$ K, which is unique to the solvent CDCl$_3$, and the parameters $\Delta H^{\ddagger}_{sub}$ and $\Delta S^{\ddagger}_{sub}$ are known for each molecule (see Table S2). Thus, arguments concerning the resonance and inductive effects of a substituent on the stabilization of the amide bond should focus on $\Delta H^{\ddagger}_{int}$, and, from this parameter, the external contributions have been considered.

Concerning the change in Gibbs energy of activation, differentiating substitutional effects with enthalpic and entropic contributions into external and internal components, we write

$$\Delta(\Delta G^{\ddagger}) = \Delta(\Delta H^{\ddagger}) - T\Delta(\Delta S^{\ddagger})$$
$$= \Delta(\Delta H^{\ddagger}_{int}) + \Delta(\Delta H^{\ddagger}_{ext}) - T\Delta(\Delta S^{\ddagger}_{int})$$
$$- T\Delta(\Delta S^{\ddagger}_{ext}) \tag{19}$$

As molecules differ from each other by a change of one substitution with reference, it is safe to assume that the change in $\Delta H^{\ddagger}_{int}$ comes from the substitution effects leading to

$$\Delta(\Delta S^{\ddagger}_{int}) = 0 \tag{20}$$

Moreover, as the external components arise from the solute–solvent effects in the same solution phase (same solvent), this leads to

$$\Delta(\Delta H^{\ddagger}_{ext}) = \beta \Delta(\Delta S^{\ddagger}_{ext}) \tag{21}$$

Equation 21 is similar to eq 9. If one considers that the β is approximately equal to the experimental temperature (T_{expt}), one can write

$$\Delta(\Delta G^{\ddagger}) = \Delta(\Delta H^{\ddagger}_{int}) \tag{22}$$

The validity of eq 21, in particular, the influence of external factors such as solvent on β, could be tested further by performing experiments on the same molecule but with different solvents.[39] Based on eq 19 and similar to eq 18, we could assume that changing the solvent leads to

$$\Delta(\Delta H^{\ddagger}_{sub}) = \Delta(\Delta H^{\ddagger}_{int}) + \beta_{sol} \Delta(\Delta S^{\ddagger}_{sub}) \tag{23}$$

where β_{sol} represents a proportionality constant intrinsic to a solvent and the changes to the thermodynamic parameters are due to solvent–solute interactions. Thus, a single analog will not possess the same $\Delta H^{\ddagger}_{sub}$ and $\Delta S^{\ddagger}_{sub}$ from one solvent to another.[39] $\Delta H^{\ddagger}_{int}$ will be solvent-dependent too, which is logical if one considers the impact of solvent polarity on the magnitude of resonance and inductive effects of substituents. This notion could be justified by the random placement of the molecules in the EEC plot (see Figure S1).

Careful consideration of how the EEC herein is assessed by rewriting eqs 1 and 2 as

$$\Delta H^{\ddagger} = \alpha + T_{\beta}\Delta S^{\ddagger} \tag{24}$$

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \tag{25}$$

and combining eqs 24 and 25

$$\Delta G^{\ddagger} = \alpha + (T_{\beta} - T)\Delta S^{\ddagger} \tag{26}$$

Equation 26 shows that $\alpha = \Delta G^{\ddagger} = \Delta H^{\ddagger}_{int}$ when $T_{\beta} = T$ and is the case herein within experimental error. This assumes that there is only one single constant for one physical process or related processes (partial amide bond rotation here). Thus, eq 24 shows that the constant α describes the overall $\Delta H^{\ddagger}_{int}$ as limited by the $\Delta G^{\ddagger}$ value at each temperature for the analog series.

The narrow range of $\Delta G^{\ddagger}$ and the interdependence of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in the same system strongly suggest a kinetic compensation effect. The EEC for the partial amide bond rotation presented here and the deviations from the slope in the EEC plot are inherent properties belonging to the analog and solute–solvent interactions and unlikely caused by experimental error given the statistical methods used and large sample pool. Although analogs lower in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ did show to have slightly more uncertainty in $\Delta S^{\ddagger}$ and slower exchange rates, they are viewed as being simply less flexible. Interestingly, if the constant α and T_{β} (or β) were intrinsic properties to classes of carboxamides in particular solvents, then their thermodynamic properties would fit the same EEC plot, and such is the case for the pyridine carboxamides nicotinamide ($\Delta H^{\ddagger} = 54.0 \pm 1.3$ kJ/mol and $\Delta S^{\ddagger} = -32.2 \pm 4.1$ J/(mol K)) and picolinamide ($\Delta H^{\ddagger} = 76.6 \pm 1.7$ kJ/mol and $\Delta S^{\ddagger} = 5.4 \pm 4.2$ J/(mol K)) in CDCl$_3$.[40] It is apparent that the proportionality constant T_{β} becomes a theory of solute–solvent interaction and remains constant within a single solution phase.

With knowledge of the three-dimensional structure of the biomolecular target and its type of fluid environment, EEC plots can be used to measure the impact on the rate of intramolecular conversion with respect to the functional group though they appear to be random. The impact on either activation or inhibition of the target site, if molecular rigidity was an issue, maybe deduced; the amide group would act as a gate for larger drug molecules. In other words, based on small changes to the drug's basic structure, the correct shape or structure can be maintained over time. The plot simultaneously would identify which compounds show similar molecular dynamics and also the limitations of the desired functional groups. With the aid of computer-based simulations and an amide as a key functional group, more control over molecular dynamics is feasible. From the EEC plot, there is a general trend in the rate of interconversion with very few exceptions.

Possible future studies related to EEC and partial amide bond rotation might involve pressure, solvent polarity, computational analysis, molecular rotors, pharmacological activities, and generally molecular design with emphasis on amide bond modulation.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c00332.

> Figure S1: EEC plot for the subgroups, Figure S2: NMR (^{1}H and ^{13}C) spectra of all the molecules, Table S1: experimental data, temperature vs k_{ex}, and Table S2: estimated activation enthalpy and entropy of all the molecules (PDF)

AUTHOR INFORMATION

Corresponding Authors

Viswanathan V. Krishnan − *Department of Chemistry, California State University, Fresno, California 93740, United States; Department of Pathology & Laboratory Medicine, University of California Davis, Davis, California 95616, United States;* ⓘ orcid.org/0000-0002-0726-950X; Email: krish@csufresno.edu

Santanu Maitra − *Department of Chemistry, California State University, Fresno, California 93740, United States;* Email: smaitra@csufresno.edu

Authors

Jacob Guerra − *Department of Chemistry, California State University, Fresno, California 93740, United States*

Bhvandip Bajwa − *Department of Chemistry, California State University, Fresno, California 93740, United States*

Prarthana Kumar − *Department of Chemistry, California State University, Fresno, California 93740, United States*

Salvador Vazquez − *Department of Chemistry, California State University, Fresno, California 93740, United States*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acsomega.0c00332

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

REFERENCES

(1) Constable, F. H. The mechanism of catalytic decomposition. *Proc. R. Soc. London, Ser. A* **1925**, *108*, 355−378.

(2) Fox, J. M.; Zhao, M.; Fink, M. J.; Kang, K.; Whitesides, G. M. The Molecular Origin of Enthalpy/Entropy Compensation in Biomolecular Recognition. *Annu. Rev. Biophys.* **2018**, *47*, 223−250.

(3) Liu, L.; Guo, Q.-X. Isokinetic relationship, isoequilibrium relationship, and enthalpy-entropy compensation. *Chem. Rev.* **2001**, *101*, 673−696.

(4) Pan, A.; Biswas, T.; Rakshit, A. K.; Moulik, S. P. Enthalpy-Entropy Compensation (EEC) Effect: A Revisit. *J. Phys. Chem. B* **2015**, *119*, 15876−15884.

(5) Sharp, K. Entropy-enthalpy compensation: fact or artifact? *Protein Sci.* **2001**, *10*, 661−667.

(6) Gehrig, J. C.; Penedo, M.; Parschau, M.; Schwenk, J.; Marioni, M. A.; Hudson, E. W.; Hug, H. J. Surface single-molecule dynamics controlled by entropy at low temperatures. *Nat. Commun.* **2017**, *8*, 14404.

(7) Allerhand, A.; Gutowsky, H. S. Spin-Echo NMR Studies of Chemical Exchange. IV. Intramolecular Exchange of a Coupled AB System. *J. Chem. Phys.* **1965**, *42*, 4203−4212.

(8) Bain, A. D. Chemical exchange in NMR. *Prog. Nucl. Magn. Reson. Spectrosc.* **2003**, *43*, 63−103.

(9) Palmer, A. G. Chemical Exchange Effects in Biological Macromolecules. In *Encyclopedia of nuclear magnetic resonance, Advances in NMR*, Grant, D. M., Harris, R. K., Ed. Wiley: Chichester, 2002; Vol. 9, pp 344−353.

(10) Stewart, W. E.; Siddall, T. H. Nuclear magnetic resonance studies of amides. *Chem. Rev.* **1970**, *70*, 517−551.

(11) Drakenberg, T.; Forsen, S. Barrier to internal rotation of amides. I. Formamide. *J. Phys. Chem.* **1970**, *74*, 1−7.

(12) Forsén, S.; Hoffman, R. A. Study of moderately rapid chemical exchange reactions by means of nuclear magnetic double resonance. *J. Chem. Phys.* **1963**, *39*, 2892−2901.

(13) Gutowsky, H. S.; Vold, R. L.; Wells, E. J. Theory of Chemical Exchange Effects in Magnetic Resonance. *J. Chem. Phys.* **1965**, *43*, 4107−4125.

(14) Wiberg, K. B.; Rablen, P. R.; Rush, D. J.; Keith, T. A. Amides. 3. Experimental and Theoretical-Studies of the Effect of the Medium on the Rotational Barriers for N,N-Dimethylformamide and N,N-Dimethylacetamide. *J. Am. Chem. Soc.* **1995**, *117*, 4261−4270.

(15) Jensen, B. L.; Fort, R. C., Jr. Molecular mechanics and variable-temperature 1H NMR studies on N,N-diethyl-m-toluamide. An undergraduate NMR and molecular modeling experiment. *J. Chem. Educ.* **2001**, *78*, 538−540.

(16) Bain, A. D. Chemical exchange. In *Annual Reports on Nmr Spectroscopy*; Vol 63, Webb, G. A., Ed. Academic Press: 2008; Vol. 63, pp 23−48.

(17) Bain, A. D. Dynamic NMR. In *Modern NMR Techniques for Synthetic Chemistry*; Fisher, J., Ed. CRC Press: 2014, p 15−61.

(18) Ōki, M. *Applications of dynamic NMR spectroscopy to organic chemistry*; VCH Publishers: Deerfield Beach, FL, 1985; p xii, 423 p.

(19) Perrin, C. L.; Dwyer, T. J. Application of two-Dimensional NMR to Kinetics of Chemical Exchange. *Chem. Rev.* **1990**, *90*, 935−967.

(20) Pons, M.; Millet, O. Dynamic NMR studies of supramolecular complexes. *Prog. Nucl. Magn. Reson. Spectrosc.* **2001**, *38*, 267−324.

(21) Umemoto, K.; Ouchi, K. Hindered Internal-Rotation and Intermolecular Interactions. *Proc. - Indian Acad. Sci., Chem. Sci.* **1985**, *94*, 1−119.

(22) Krishnan, V. V.; Vazquez, S.; Maitra, K.; Maitra, S. Restricted amide rotation with steric hindrance induced multiple conformations. *Chem. Phys. Lett.* **2017**, *689*, 148−151.

(23) Krishnan, V. V.; Thompson, W. B.; Goto, J. J.; Maitra, K.; Maitra, S. Modulations in restricted amide rotation by steric induced conformational trapping. *Chem. Phys. Lett.* **2012**, *523*, 124−127.

(24) Krishnan, V. V. Molecular Thermodynamics Using Nuclear Magnetic Resonance (NMR) Spectroscopy. *Inventions* **2019**, *4*, 13.

(25) Guerra, J. *Amide Bond Modulation: Partial Amide Bond Rotation in Cyclic Amines of DEET Analogs Follow an Enthalpy-Entropy Compensation (EEC)*. California State University Fresno, Fresno, 2018.

(26) Pavia, D. L.; Lampman, G. M.; Kriz, G. S.; Engel, R. G. *Introduction to organic laboratory techniques: a small scale approach*. Cengage Learning: 2005.

(27) Van Geet, A. L. Calibration of methanol nuclear magnetic resonance thermometer at low temperature. *Anal. Chem.* **1970**, *42*, 679−680.

(28) R Core Team *R: A language and environment for statistical computing*; R Foundation for Statistical Computing: Vienna, Austria, 2014, 2014.

(29) Leffler, J. E. Errata: Entropy requirements of the Hammett relationship. *J. Chem. Phys.* **1957**, *27*, 981−982.

(30) Leffler, J. E. Entropy Requirements of the Hammett Relationship. *J. Chem. Phys.* **1955**, *23*, 2199−2200.

(31) Eyring, H. The Activated Complex in Chemical Reactions. *J. Chem. Phys.* **1935**, *3*, 107−115.

(32) McNaught, A. D.; McNaught, A. D. *Compendium of chemical terminology*; Blackwell Science: Oxford, 1997; Vol. *1669*.

(33) Lente, G.; Fábián, I.; Poë, A. J. A common misconception about the Eyring equation. *New J. Chem.* **2005**, *29*, 759−760.

(34) Karunakaran, C.; Palanisamy, P. N. Lack of linear free energy relationship: Tungsten(VI) catalyzed perborate oxidation of anilines. *Int. J. Chem. Kinet.* **1999**, *31*, 571−575.

(35) Exner, O. The validity of linear free energy relationships at various temperatures. *Collect. Czech. Chem. Commun.* **1974**, *39*, 515−527.

(36) Cornish-Bowden, A. Enthalpy-entropy compensation: a phantom phenomenon. *J. Biosci.* **2002**, *27*, 121−126.

(37) Hepler, L. G. Thermodynamic Analysis of the Hammett Equation, the Temperature Dependence of ρ, and the Isoequilibrium (Isokinetic) Relationship. *Can. J. Chem.* **1971**, *49*, 2803−2807.

(38) Hepler, L. G. Effects of Substituents on Acidities of Organic Acids in Water: Thermodynamic Theory of the Hammett Equation. *J. Am. Chem. Soc.* **1963**, *85*, 3089−3092.

(39) Morrelli, D. *Solvent Effect and Electronic Modulation of Amide Bond Resonance in DEET Analogs*; California State University Fresno: Fresno State Digital Repository, 2019.

(40) Olsen, R. A.; Liu, L.; Ghaderi, N.; Johns, A.; Hatcher, M. E.; Mueller, L. J. The amide rotational barriers in picolinamide and nicotinamide: NMR and ab initio studies. *J. Am. Chem. Soc.* **2003**, *125*, 10125−10132.