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Re-Evaluation of the Reported Experimental Values of the Heat of Vaporization of N-Methylacetamide

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Abstract: The accuracy of empirical force fields is inherently related to the quality of the target data used for optimization of the model. With the heat of vaporization (ΔH_{vap}) of N-methylacetamide (NMA), a range of values has been reported as target data for optimization of the nonbond parameters associated with the peptide bond in proteins. In the present work, the original experimental data and Antoine constants used for the determination of the ΔH_{vap} of NMA are reanalyzed. Based on this analysis, the wide range of ΔH_{vap} values reported in the literature is shown to be due to incorrect reporting of the temperatures at which the original values were extracted and limitations in the quality of experimental vapor pressure-temperature data over a wide range of temperatures. Taking these problems into account, a consistent ΔH_{vap} value is extracted from three studies for which experimental data are available. This analysis suggests that the most reliable value for ΔH_{vap} is 13.0 ± 0.1 at 410 K for use in force field optimization studies. The present results also indicate that similar analyses, including analysis of Antoine constants alone, may be of utility when reported ΔH_{vap} values are not consistent for a given neat liquid.

Introduction

Structure−function studies of peptides and proteins, including protein folding studies,[1] consume a significant volume of intellectual and financial resources. Of the many approaches used to study such systems empirical force field based calculations represent an effective and ever increasingly used methodology from which atomic details of structure−function relationships may be obtained.[2,3] In addition, force fields have the potential to be predictive allowing, for example, the impact of chemical modification of inhibitors on protein binding or the impact of mutations on protein activity to be made. Of the protein based predictions, accurate prediction of protein structure based on sequence alone,[4] the so-called protein folding problem, represents a grail of empirical force fields and, accordingly, a significant number of studies have and continue to be performed toward solving this problem.

Central to the success of empirical force field based methods is the accuracy of the force fields themselves. Simply put, the force field must correctly represent the change in energy of the system as a function of conformation and environment in order to effectively reproduce the experimental regimen.[5] Accordingly, significant effort has been and is still being made toward the optimization of empirical force fields for proteins as well as other biomolecules. While much of this effort is based on the reproduction of high-level quantum mechanical data, the most important data with respect to the condensed phase are experimental data, including thermodynamic data on small compounds representative of chemical moieties in macromolecules.[2,6] For example, the availability of condensed phase data, including the heat of vaporization (ΔH_{vap}) and free energy of solvation, of N-methylacetamide (NMA) is key for the optimization of the force field parameters associated with the nonbond interactions of the peptide bond with the environment. Careful optimization of the nonbond force field parameters for NMA (e.g., the Lennard-Jones 6−12 and electrostatic parameters) to reproduce such condensed phase data lays the groundwork for a protein force field that accurately models energetic differences associated with changes in the environment, such as moving of the peptide

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Table 1. Enthalpies of Vaporization, kcal/mol, of NMA from Various Sources and Methods of Analysis[d,e]

temperature	Aucejo et al., 1993[15]	Manczinger and Krotüm, 1975[17]	Kortüm and Biedersee, 1970[13]	averages
		1) From Reported Antoine Constants[a]		
373 K	14.6	13.3	12.8[c]	np
410 K	13.0	12.9	12.8[c]	np
		2) From Antoine Constants Refit to Full Experimental Range[a,b]		
373 K	14.6, 14.5, 13.9	13.3, 13.3, 13.3	12.3, 12.3, 12.3	np
410 K	13.0, 13.0, 13.7	13.0, 13.0, 13.0	12.5, 12.5, 12.5	np
		3) From Original Experimental Data via Eq 2 (Temperature Range)		
	13.8 (353−428K)	13.2 (333−443K)	12.6 (353−479)	np
		4) From Original Experimental Data via Eq 2 from 390 to 430 K		
	13.1	12.9	13.0	13.0 ± 0.1
		5) From Antoine Constants Fit to 390 to 430 K[a,b]		
373 K	14.7, 13.6, 13.2	14.3, 13.4, 13.0	14.3, 13.4, 13.0	13.7 ± 0.6
410 K	13.1, 13.1, 13.1	12.9, 12.9, 12.9	12.9, 13.0, 13.0	13.0 ± 0.1

[a] Calculated from eq 4 at the reported temperatures. [b] The three individual values for each data set are from the Antoine constants from the three refits of each of the data sets as shown in Table 3. [c] Constant C set to zero in Antoine equation leading to no temperature dependence in the calculated ΔH_{vap}. [d] Statistical analysis performed for the data in the first 3 columns of the final two rows. np indicates that the calculation was not performed and errors are standard deviations. [e] NMA: bp: 479, mp: 303.7 K.

backbone from an aqueous environment to the protein interior during protein folding.

Successful development of accurate empirical force fields, therefore, requires the availability of experimental thermodynamic data for small molecules that are both accurate and precise. Experimentally, the most accurate way of determining the heat of vaporization is through calorimetry performed at the boiling point of the neat liquid. An alternative is the use of vapor pressure-temperature (P-T) data, as has been performed for NMA. When available, P-T data may be used directly to fit empirical force field parameters as has been done in a number of cases where accurate data over a wide temperature range are available.[7-10] However, in the case of neat NMA, the corresponding data reported in the literature[11-16] are not sufficiently accurate at low temperatures, making them unsuitable for use as target data for force field optimization. Presented in row 1 of Table 1 are experimental ΔH_{vap} values for NMA based on the reported Antoine constants from a number of sources.[12,15,17-19] As may be seen the values range from 12.8 up to 14.6 kcal/mol when temperatures of both 373 and 410 K are considered. In addition, values of 14.2[11] and 16.5[12] kcal/mol have been reported. No Antoine constants were presented in the former case, while the latter value can readily be excluded if one examines the raw experimental data, as performed below. Consistent with the range of reported values are the different values that have been used as target data for the optimization of empirical force fields for NMA and, by extension, peptides and proteins. For example, the OPLS and AMBER force fields were optimized targeting a value of 13.3 kcal/mol at 373 K;[20] a value also used by Caldwell and Kollman,[21] Gao and co-workers,[22,23] and Kaminski et al.[24] for the development of polarizable force fields. CHARMM22[25] and GROMOS[26] targeted a value of 14.2 at 373 K as did work by Patel and Brooks in the development of a polarizable force field based on a fluctuating charge model.[27] In addition, a recent study of a polarizable force field based on a classical Drude oscillator cited four values: −12.7, −13.1, −14.2, and −14.8 kcal/mol.[28] Thus, it is evident that in order to develop

accurate force field parameters for the peptide backbone it is essential to determine the proper experimental ΔH_{vap} of NMA.

In the present report we reanalyze the original experimental data used to determine ΔH_{vap} of NMA, including available experimental vapor pressure-temperature (P-T) curves for the neat liquid. From this analysis the source of discrepancies in the original data is identified, allowing for an understanding of the source of the range of previously reported ΔH_{vap} values. This is followed by determination of a consensus value for ΔH_{vap} of NMA, a value which we suggest should be the target for future force field development efforts.

Computation of the Heat of Vaporization from Vapor Pressure−Temperature Data. Typically, calculation of the heat of vaporization from experimental data is based on the Clausius-Clapeyron equation

$$\frac{dP}{dT} = \frac{\Delta H_{vap}}{(V - V_{liq})T} \approx \frac{\Delta H_{vap}}{VT} = \frac{P\Delta H_{vap}}{RT^2} \quad (1)$$

where P is the vapor pressure of the liquid, T is the temperature, R is the universal gas constant, V is the molecular volume of the gas phase, and V_{liq} is the molecular volume of the liquid phase. Since we deal with a phase transition from liquid to gas phase, V_{liq} is many times smaller than the volume of the gas phase, V, which justifies the use of the approximate form of the Clausius-Clapeyron equation shown in the right-hand side of eq 1.

There are two approaches for determining the heat of vaporization from experimental liquid-vapor pressure data. Assuming that the heat of vaporization is constant over the selected temperature range, this equation can be integrated by separating the independent variables:

$$\frac{dP}{P} = \frac{\Delta H_{vap}}{R} \cdot \frac{dT}{T^2} \quad \text{yielding } \ln\frac{P_2}{P_1} = \frac{\Delta H_{vap}}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right)$$

$$(2)$$

This approach allows ΔH_{vap} to be readily determined from the slope of the vapor pressure-temperature (P-T) curve, though limited to a situation where the heat capacity, the
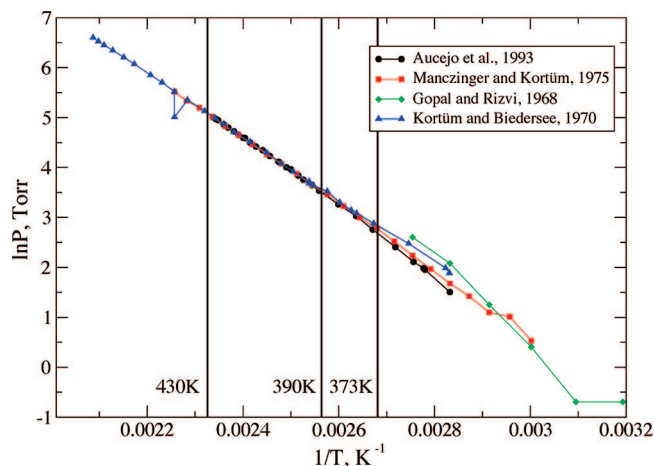
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Figure 1. Experimental inverse temperature versus the natural log of the vapor pressure (P-T) curves for N-methylacetamide from Aucejo et al.,[15] Manczinger and Kortüm,[17] Gopal and Rizvi,[12] and Kortüm and Biedersee.[13] Experimental data were converted to common units of ln*P* and Torr. Lines connecting the data points were included to facilitate visual inspection and do not represent fits of the data.

temperature dependence of the heat of vaporization, of the neat liquid is zero.

An alternative method for solving eq 1 assumes obtaining the derivative of the vapor pressure with respect to temperature. Different formulas have been suggested for this purpose. Among these, the Antoine equation is used extensively and has been found to be reliable except where the data are limited to very small temperature ranges or for low-boiling substances. The Antoine equation[29] is a simple 3-parameter fit to experimental vapor pressure measured over a given temperature range

$$\ln P = A - B\left(\frac{1}{(T+C)}\right) \qquad (3)$$

where *A*, *B*, and *C* are the fitted parameters. This function allows rearrangement of eq 1 in the following form:

$$\frac{dP}{PdT} = \frac{d(\ln P)}{dT} = \frac{\Delta H_{vap}}{RT^2} = \frac{B}{(T+C)^2} \quad \text{or } \Delta H_{vap} = RB\frac{T^2}{(T+C)^2}$$

$$(4)$$

This equation explicitly takes into consideration the temperature dependence of the heat of vaporization and should be valid for a wider range of temperatures than eq 2.

Analysis of Antoine Constants and Experimental Vapor Pressure-Temperature (P-T) for N-Methylacetamide. Step one of the analysis of the discrepancies in the ΔH_{vap} values of neat NMA was inspection of available experimental P-T data. Presented in Figure 1 are the P-T data in the form of $1/T$ versus ln*P* from four studies. Immediately evident is the oldest data set from Gopal and Rizvi.[12] Given the significant difference in this data set as compared to the remaining three sets along with the significant difference in ΔH_{vap} allows the value of 16.5 kcal/mol reported in that study to readily be discarded as can the experimental data. The remaining three data sets from Aucejo et al., Manczinger and Kortüm, and Kortüm and Biedersee appear to be in reasonable agreement, with all the curves

sampling a wide range of temperatures and including a large number of data points. However, inspection of Table 1 shows the ΔH_{vap} values at 373 K from the reported Antoine constants from those studies to differ by over 1 kcal/mol.

This difference suggested that the method of analysis of the original experimental data may be leading to the discrepancy. The original data were treated via the Antoine equation, eq 3 above. Presented in Table 2 are the Antoine equation constants as originally reported in the cited studies as well as following conversion to common units. The Dykyj constants are a refit of the experimental data from Manczinger and Kortüm; those values and the values from Gopal are included for completeness, though they will not be discussed further. As is evident, significant differences are present including the impact of constraining *C* to 0 (i.e., assuming the heat capacity = 0). Notable are the differences in the constants from Aucejo et al.,[15] Manczinger and Kortüm,[17] and Kortüm and Biederseede[13] despite the similarity of the curves shown in Figure 1. The impact of this difference is observed in the ΔH_{vap} at different temperatures (Table 1, row 1), including the lack of temperature dependence due to *C* being constrained to zero. The different values of ΔH_{vap} as a function of both the particular study and temperature along with analysis of the discussion of the reported ΔH_{vap} in the original publications indicate that the discrepancy of the values reported in the more recent force field development literature is due, in part, to a lack of clarity in the original publications on the temperature associated with the reported ΔH_{vap}. In addition, it appears that when available, the temperatures were often not correctly noted when citing the original ΔH_{vap}, further compounding the problem. However, the differences in the Antoine constants indicate that the data analysis and/or experimental data contribute to the discrepancies.

To check the previous data analysis the available experimental data were refit using a modified version of the FITCHARGE[30] module in CHARMM.[31] In all cases, each data set was fit three times using the original Antoine constants from the Aucejo et al., Manczinger and Kortüm, and Kortüm and Biedersee studies as initial guesses (Table 3). Fitting was initially performed over the full range of temperatures used in the respective experiments. Analysis of the Antoine constants for the three data sets (Table 3) reveals the impact of the initial guesses on the resulting constants. The fitting results are not surprising as the objective function is nonlinear and may have multiple local minima. In this case the parameter set showing the least RMSE represents the best fit. From the present fitting the lowest RMSE values were 0.0117, 0.0379, and 0.0926, for the Aucejo et al., Manczinger and Kortüm, and Kortüm and Biedersee data, respectively. Comparison of those values with the RMSE values from the original reported Antoine constants, 0.0118, 0.0383, and 0.0988 for the Aucejo et al., Manczinger and Kortüm, and Kortüm and Biedersee data, respectively, shows the refitting to yield only marginal improvement. These results suggest that the original fitting of the Antoine constants was satisfactory, and the noted differences in ΔH_{vap} originate from the inherent differences in the experimental data sets.

Table 2. Reported Antoine Constants for NMA[1]

reported[a]	A	B	C	eq
Aucejo, 1993[15]	12.49715	2658.377	−148.3473	$\ln P(\text{kPa}) = A\text{-}B(1/(T+C))$
Manczinger, 1975[17]	7.7377	2043.37	−60.75	$\log P(\text{Torr}) = A\text{-}B(1/(T+C))$
Kortüm, 1970[13]	7.8259	2793.3	0	$\log P \ (\text{kPa}) = A\text{-}B(1/(T+C))$
Gopal, 1968[12]	11.063	3606	0	$\log P(\text{Torr}) = A\text{-}B(1/(T+C))$
Dykyj, 1984[18b]	6.60575	1868.206	−75.963	$\log P(\text{kPa}) = A\text{-}B(1/(T+C))$
reported data converted to $\ln P$ and Torr				$\ln P(\text{Torr}) = A\text{-}B(1/(T+C))$
Aucejo, 1993	14.51214	2658.377	−148.3473	
Manczinger, 1975	17.81671	4705.0333	−60.75	
Kortüm, 1970	20.034786	6431.81094	0	
Gopal, 1968	25.473499	8303.121845	0	
Dykyj, 1984	17.225287	4301.70329	−75.963	

[a] Reported values are directly from the literature before and after conversion to common units. [b] Dykyj et al. Antoine constants represent a previously published refitting of the Manczinger and Kortüm data.

Table 3. Antoine Constants Following Refitting to the Original Experimental Data

fit over the full range of experimental data[a]	initial guess[b]	A	B	C	RMSE
Aucejo, 1993	i	14.5106	2658.4542	−148.3022	0.0118
	ii	14.5888	2696.4742	−146.5925	0.0117
	iii	20.2896	6183.4048	−22.2746	0.0304
Manczinger, 1975	i	18.4156	5107.5211	−47.0957	0.0379
	ii	18.4156	5107.5211	−47.0957	0.0379
	iii	18.4156	5107.5213	−47.0957	0.0379
Kortüm, 1970	i	20.7029	7157.6343	27.4688	0.0927
	ii	20.7080	7162.0838	27.6048	0.0927
	iii	20.8027	7245.8239	30.1571	0.0926

fit over 390 to 430 K	initial guess[b]	A	B	C	RMSE
Aucejo, 1993	i	14.6435	2703.0937	−147.3946	0.0071
	ii	17.9300	4698.0665	−64.1666	0.0075
	iii	20.2324	6422.3774	−5.8062	0.0084
Manczinger, 1975	i	14.9198	2887.2697	−136.9291	0.0077
	ii	17.8465	4706.7286	−61.4594	0.0066
	iii	20.1255	6430.2474	−2.6391	0.0067
Kortüm, 1970	i	15.0520	2956.6394	−133.4645	0.0117
	ii	17.8602	4704.1907	−61.7037	0.0110
	iii	20.1509	6428.3894	−3.1271	0.0112

[a] Refitted constants are over the full temperature ranges reported in the respective studies (353 to 428 K for Aucejo et al., 333 to 443 for Manczinger and Kortüm, and 353 to 479 for Kortüm and Biedersee) using eq 3. Units: pressure in Torr and temperature in K. [b] Initial guesses from the reported Antoine constants from i) Aucejo et al., ii) Manczinger and Kortüm, and iii) Kortüm and Biedersee as reported in Table 2.

To further verify that the original discrepancies in ΔH_{vap} values were associated with the experimental P-T data, ΔH_{vap} values were calculated from the P-T data based on the Clausius-Clapeyron equation,[29] eq 2, from the slopes of the $1/T$ versus $\ln P$ plots. It should be reiterated that this approach assumes that the heat capacity is zero (i.e., $C = 0$ in the Antoine equation). When this approach was applied to the data included in Figure 1, it yielded high quality fits ($R^2 > 0.99$ in all cases). Based on the resulting slopes ΔH_{vap} values of 13.8, 13.2, and 12.6 kcal/mol for the three data sets are obtained (Table 1, row 3). The level of agreement is similar to the ΔH_{vap} values obtained from the Antoine equation. Thus, the present analysis indicates that the discrepancy in the reported ΔH_{vap} values is dominated by contributions from limitations in the experimental data.

Inspection of the experimental data in Figure 1 shows the agreement to be good for the Aucejo et al., Manczinger and Kortüm, and Kortüm and Biedersee data sets at the higher temperatures. However, the data sets diverge at lower temperatures. The presence of such divergence is not

unexpected. Given that the pressures at these lower temperatures become quite small it may be assumed that the ability to measure them accurately becomes limiting. Indeed the extremely low temperatures of the Gopal experiments, to a point where the vapor pressures are a fraction of a Torr (Figure 1), is suggested to contribute to the significant problems with that data set. It is the divergence of the experimental data sets at the lower temperatures that leads to differences in the refit Antoine constants discussed above (Tables 2 and 3) and to the significant differences in ΔH_{vap} values.

Based on the limitations with the experimental data at lower temperatures, the experimental P-T data were reanalyzed over a higher, though limited, range of temperatures (390 to 430 K, Figure 1). This analysis included 1) calculation of the ΔH_{vap} values using eq 2 over the selected temperature range and 2) refitting the Antoine constants over the selected temperature range (390 to 430 K) following which ΔH_{vap} values were obtained from eq 4.

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Results from these analyses are included in Table 1 for the ΔH_{vap} values and in Table 3 for the Antoine constants. Based on the calculation of ΔH_{vap} using eq 2 values close to 13 kcal/mol were obtained for all three studies (Table 1, row 4), with an average and standard deviation of 13.0 ± 0.1 kcal/mol. Next, refitting of the three experimental data sets over the range 390 to 430 K leads to Antione constants that more accurately reproduce the experimental data as compared to fits of the full temperature ranges used in the experimental studies (Table 3, compare the RMSE values for the top and bottom sections), though the RMSE are similar for each of the subset Antoine constants. The corresponding ΔH_{vap} values using eq 4 for the three fits of the three data sets (Table 1, row 5) show the values to range over 1.7 kcal/mol at 373 K, while all the values are in excellent agreement at 410 K. Averaging over these values yields a mean ΔH_{vap} value of 13.0 ± 0.1 kcal/mol at 410 K, which is in ideal agreement with that obtained via eq 2 over the same data range. Thus, it is evident that limitations in the experimental data at low temperatures contribute to the discrepancies in the ΔH_{vap} values of NMA reported in the literature. Moreover, the present data analysis indicates that a ΔH_{vap} value at 13.0 ± 0.1 kcal/mol at 410 K is reliable and should be used as the target value (and temperature) for the development of theoretical models of NMA.

As discussed in the Introduction a number of force field development efforts have been based on calculation of the heat of vaporization at 373 K. Accordingly, the Antoine constants fit to 390−430 K data were used to predict ΔH_{vap} at 373 K. The results in row 5 of Table 1 show the derived values to range over 1.7 kcal/mol with an average and standard deviation of 13.7 ± 0.6 kcal/mol. Thus, it is not possible to determine a sufficiently accurate value of the heat of vaporization at 373 K for use in force field development due to the inherent limitations in the available experimental P-T data sets.

With many liquids it may be difficult to obtain the original experimental data to perform the analysis presented above; however, two or more sets of Antoine constants may be available in many cases. To test the possible utility of the Antoine constants alone, the reported constants for NMA (Table 2) were used to generate P-T data, with the results presented in Figure 2. Inspection of the curves shows them to agree well in the range of 390 to 430 K, with significant divergence at lower temperatures, consistent with the original experimental data. Such behavior is not unexpected as the Antoine constants are simply fit to the original data, but the behavior does indicate that if discrepancies exist in ΔH_{vap} values for a liquid, inspection of the P-T curves calculated from the Antoine constants may be of utility to select a temperature range where significant agreement between the different experiments occur, from which more reliable ΔH_{vap} values may be obtained. Applying this type of analysis in the present case using eq 2 applied to the calculated P-T data in Figure 2 yields ΔH_{vap} values of 13.0, 12.9, 12.9, and 12.8, respectively, for the four data sets in Figure 2, yielding an average of 12.9 ± 0.1 kcal/mol. This is within experimental error of that calculated from the original experimental data (Table 1, rows 4 and 5).
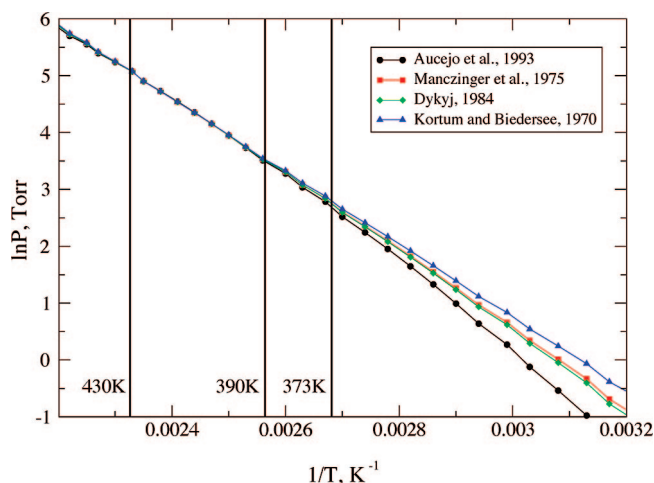

Figure 2. Calculated inverse temperature versus the natural log of the vapor pressure (P-T) curves for N-methylacetamide from the reported Antoine constants of Aucejo et al.,[15] Manczinger and Kortüm,[17] Dykyj,[19] and Kortüm and Biedersee.[13] Lines connecting the data points were included to facilitate visual inspection and do not represent fits of the data.

In summary, the wide range of ΔH_{vap} values reported in the literature for liquid NMA is shown to be due to 1) inaccuracies in reporting the temperatures at which the experiments were performed and 2) limitations in the experimental P-T data associated with decreased accuracy in the data obtained at lower temperatures due to the low vapor pressures of NMA. Taking these problems into account allows for the extraction of consistent ΔH_{vap} values from the data for the three studies for which experimental data are available. This analysis suggests that the most reliable value for ΔH_{vap} is 13.0 ± 0.1 at 410 K, the value and temperature recommended for use in force field optimization studies. The present results also indicate that similar analysis may be appropriate for other neat liquids for which reported ΔH_{vap} are used for empirical force field development.

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