Standard Thermodynamic Functions of Tripeptides N-Formyl-L-methionyl-L-leucyl-L-phenylalaninol and N-Formyl-L-methionyl-L-leucyl-L-phenylalanine Methyl Ester

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ABSTRACT: The heat capacities of tripeptides N-formyl-L-methionyl-L-leucyl-L-phenylalaninol (N-f-MLF-OH) and N-formyl-L-methionyl-L-leucyl-L-phenylalanine methyl ester (N-f-MLF-OMe) were measured by precision adiabatic vacuum calorimetry over the temperature range from \( T = 6 \) to 350 K. The tripeptides were stable over this temperature range, and no phase change, transformation, association, or thermal decomposition was observed. The standard thermodynamic functions: molar heat capacity \( C_p \), enthalpy \( H \), entropy \( S \), and Gibbs energy \( G \) of peptides were calculated over the range from \( T = 0 \) to 350 K. The low-temperature (\( T \leq 50 \) K) heat capacities dependencies were analyzed using the Debye’s and the multifractal theories. The standard entropies of formation of peptides at \( T = 298.15 \) K were calculated.

INTRODUCTION

The investigation of physicochemical properties of amino acids and peptides attracts much attention, since these systems can be used as molecular materials, drugs, and biomimetics.1 Furthermore, certain peptides are used as model systems to design and test experiments for protein studies.2,3 For example, tripeptides N-formyl-L-methionyl-L-leucyl-L-phenylalaninol (N-f-MLF-OH) and N-formyl-L-methionyl-L-leucyl-L-phenylalanine methyl ester (N-f-MLF-OMe) have been used in solid state NMR spectroscopy for developing and testing NMR experiments.4-6 These tripeptides have also been used as models for structural studies.7

There are no data on heat capacities and thermodynamic properties of these tripeptides found in the literature. Those are, however, necessary as the fundamental data for peptides and proteins and to calculate thermophysical properties for the model system. Therefore, the purpose of the present study was to measure heat capacities of tripeptides N-f-MLF-OH and N-f-MLF-OMe over the temperature range from \( T = 6 \) to 350 K, to calculate the standard (\( p = 0.1 \) MPa) thermodynamic functions \( C_p, H(0) \), \( S(T) \), and \( G(T) \) of peptides, to determine the characteristic temperatures and fractal dimensions \( D \), and to calculate the standard entropies of formation of N-f-MLF-OH (cr) and N-f-MLF-OMe (cr) at \( T = 298.15 \) K.

EXPERIMENTAL SECTION

Synthesis and Characterization of Tripeptides. Tripeptides N-formyl-L-Met-L-Leu-L-Phe-OH (lot 2500845) and N-formyl-L-Met-L-Leu-L-Phe-OMe (lot 1016424) were obtained from Bachem (King of Prussia, PA). Solid state NMR structure and X-ray structure of N-f-MLF-OH and N-f-MLF-OMe were described previously.7,8 Structural models of the studied samples are presented in Figure 1. The molecular formulas \( C_{19}H_{20}N_{3}O_{5}S \) for N-f-MLF-OH and \( C_{22}H_{34}N_{3}O_{5}S \) for N-f-MLF-OMe were confirmed by elemental analysis. In accordance with elemental analysis, high-performance liquid chromatography (HPLC), and thin layer chromatography (TLC) data, the content of the main compounds in the studied samples was at least 0.99 molar fraction. The information for the studied tripeptides is listed in Table 1.

Adiabatic Calorimetry. A precision automatic adiabatic calorimeter (Block Calorimetric Thermophysical, BCT-3) was used to measure heat capacities over the temperature range from \( T = 6 \) to 350 K. The design and operation of an adiabatic calorimeter are described in detail elsewhere.9,10 A calorimetric cell is a thin-walled cylindrical vessel made from titanium with a volume of \( 1.5 \times 10^{-6} \) m\(^3\). Its mass is \( 1.626 \pm 0.005 \) g. A miniature iron–rhodium resistance thermometer (nominal resistance 100 \( \Omega \)), was calibrated on ITS-90 standard by the Russian Metrology Research Institute, Moscow region, Russia) was used to measure the temperature of the sample. The temperature difference between the ampule and an...
The experimental values of $C_{p,m}$ (157 and 185 points for N-f-MLF-OH and N-f-MLF-OMe, respectively) were collected using liquid nitrogen as a cryogen in the intervals from $T = (6$ to $88$) K/$(6$ to $91$) K (Series 1) and using liquid nitrogen in the intervals from $T = (84$ to $349$) K/$(91$ to $343$) K (Series 2) for N-f-MLF-OH and N-f-MLF-OMe, respectively.

Heat capacities of the samples were between (55 to 83)% of the overall heat capacity of the calorimetric ampule. The molar masses were calculated from the IUPAC table of atomic weights. 

## RESULTS AND DISCUSSION

### Heat Capacities

Experimental data for the molar heat capacities of N-f-MLF-OH and N-f-MLF-OMe over the temperature range from $T = (6$ to $350$) K are given in Tables 2 and 3 and presented in Figure 2. Heat capacities of the samples rise gradually with temperature increasing. The tripeptides were stable over the studied temperature range, and no phase change, transformation, association, or thermal decomposition was observed.

The experimental data were smoothed using least-squares polynomial fits as follows:

$$C_{p,m} = \begin{cases} \sum_{i=0}^{6} A_i \ln \left( \frac{T}{30} \right), & 6 \text{ K} \leq T \leq 40 \text{ K} \\ \sum_{i=0}^{6} B_i \ln \left( \frac{T}{30} \right), & 40 \text{ K} \leq T \leq 350 \text{ K} \end{cases}$$

where $A_i$ and $B_i$ are polynomial coefficients. Relative standard uncertainty for the heat capacities $u(C_{p,m}) = 0.006$ in the temperature range from $T = (6$ to $40$) K and $u(C_{p,m}) = 0.003$ between $T = (40$ to $350$) K. The relative deviations of experimental data from the smoothing functions were listed in Figure 3.

The temperature dependencies of heat capacities of the two tripeptides are similar below 50 K. This tendency can be expected, since skeletal vibrations provide the main contribution to heat capacities in this range.

Low-temperature heat capacities data were also analyzed using the Debye theory and the multifractal theory of heat capacity. 

According to the fractal theory,

$$C(T, D) = 3D(D + 1)Nkr \left[ \frac{T}{\Theta} \right]^D \int_0^{\Theta/T} \frac{x^D \exp(x) - 1}{\exp(\Theta/T) - 1} dx$$

Equation 1 can be written as eq 2:

$$C_v = 3D(D + 1)kN\gamma(D + 1)\xi(D + 1)(T/\Theta_{max})^D$$

## Table 1. Sample Information

| chemical name | source                      | state     | mole fraction purity | purification method | analysis method |
|---------------|-----------------------------|-----------|----------------------|---------------------|-----------------|
| N-f-MLF-OH    | Bachem (King of Prussia, PA) | powder    | 0.99                 | HPLC, TLC          | TLC             |
| N-f-MLF-OMe   | Bachem (King of Prussia, PA) | powder    | 0.99                 | HPLC, TLC          | TLC             |

"N-f-MLF-OH = N-formyl-1-Met-1-Leu-1-Phe-OH. bN-f-MLF-OMe = N-formyl-1-Met-1-Leu-1-Phe-OMe. cHigh-performance liquid chromatography. dThin layer chromatography."
where $D$ is the fractal dimension, $N$ is the number of atoms in a molecular unit, $k$ is the Boltzmann constant, $\gamma(D + 1)$ is the $\gamma$-function, $\zeta(D + 1)$ is the Riemann $\zeta$-function, and $\Theta_{\text{max}}$ is the characteristic temperature. For a particular solid $3D(D + 1)$

### Table 2. Experimental Molar Heat Capacities of Crystalline N-f-MLF-OH ($M = 437.56$ g mol$^{-1}$)$^a$

| $T$/K | $C_{p,m}$/J K$^{-1}$ mol$^{-1}$ | $T$/K | $C_{p,m}$/J K$^{-1}$ mol$^{-1}$ | $T$/K | $C_{p,m}$/J K$^{-1}$ mol$^{-1}$ |
|-------|-------------------------------|-------|-------------------------------|-------|-------------------------------|
|       |                               |       |                               |       |                               |
|       |                               |       |                               |       |                               |
| Series 1 |                               |       |                               |       |                               |
| 6.07  | 3.03                          | 11.08 | 11.8                          | 32.83 | 82.65                          |
| 6.20  | 3.36                          | 11.52 | 12.5                          | 35.21 | 90.33                          |
| 6.39  | 3.61                          | 11.95 | 13.4                          | 37.62 | 97.96                          |
| 6.58  | 3.95                          | 12.39 | 14.6                          | 40.05 | 105.2                          |
| 6.77  | 4.19                          | 12.85 | 15.8                          | 42.50 | 112.5                          |
| 6.95  | 4.46                          | 13.31 | 17.0                          | 44.97 | 118.8                          |
| 7.13  | 4.64                          | 13.78 | 18.1                          | 47.45 | 124.6                          |
| 7.31  | 5.02                          | 14.29 | 19.5                          | 49.34 | 130.5                          |
| 7.66  | 5.64                          | 14.76 | 21.3                          | 50.80 | 134.7                          |
| 7.84  | 5.84                          | 15.24 | 23.4                          | 52.40 | 139.5                          |
| 8.02  | 6.22                          | 15.73 | 24.77                         | 56.90 | 149.6                          |
| 8.19  | 6.56                          | 16.23 | 26.48                         | 59.00 | 154.9                          |
| 8.37  | 6.65                          | 16.73 | 28.13                         | 61.10 | 159.7                          |
| 8.55  | 7.15                          | 17.24 | 29.68                         | 64.20 | 167.0                          |
| 8.72  | 7.42                          | 17.76 | 31.41                         | 67.25 | 174.4                          |
| 8.92  | 7.88                          | 18.29 | 32.48                         | 69.89 | 180.6                          |
| 9.10  | 8.16                          | 18.81 | 34.25                         | 72.43 | 186.4                          |
| 9.27  | 8.57                          | 19.34 | 36.24                         | 75.35 | 193.1                          |
| 9.44  | 8.94                          | 19.87 | 38.47                         | 77.93 | 197.9                          |
| 9.62  | 9.38                          | 21.37 | 44.16                         | 80.00 | 202.2                          |
| 9.80  | 9.59                          | 23.57 | 51.73                         | 83.20 | 207.8                          |
| 9.98  | 10.0                          | 25.84 | 59.41                         | 85.77 | 213.1                          |
| 10.26 | 10.5                          | 28.14 | 67.29                         | 87.50 | 216.0                          |
| 10.67 | 11.0                          | 30.47 | 75.15                         |       |                                |

| Series 2 |                               |       |                               |       |                               |
| 83.90  | 210.0                         | 179.11| 375.4                         | 267.60| 507.4                          |
| 86.84  | 215.7                         | 181.51| 379.4                         | 270.95| 513.7                          |
| 90.20  | 221.9                         | 182.44| 381.6                         | 273.80| 518.1                          |
| 93.70  | 228.4                         | 185.90| 386.5                         | 277.59| 524.9                          |
| 96.85  | 234.0                         | 188.64| 391.0                         | 280.88| 532.5                          |
| 100.96 | 241.6                         | 192.20| 397.2                         | 282.23| 537.3                          |
| 104.77 | 248.7                         | 195.77| 402.6                         | 285.29| 542.7                          |
| 110.00 | 259.0                         | 199.33| 408.1                         | 288.58| 549.3                          |
| 114.57 | 267.0                         | 200.73| 410.2                         | 293.30| 557.4                          |
| 118.10 | 273.3                         | 204.09| 414.5                         | 297.80| 563.3                          |
| 121.64 | 279.0                         | 207.65| 420.2                         | 301.54| 573.1                          |
| 125.17 | 285.5                         | 211.20| 423.3                         | 304.73| 582.3                          |
| 128.71 | 291.7                         | 214.75| 429.4                         | 307.89| 588.5                          |
| 132.24 | 297.1                         | 218.30| 433.6                         | 311.05| 593.5                          |
| 135.78 | 303.1                         | 220.18| 436.8                         | 313.20| 599.5                          |
| 139.31 | 309.8                         | 223.47| 441.4                         | 316.00| 602.2                          |
| 142.85 | 315.6                         | 226.98| 445.4                         | 318.33| 605.8                          |
| 146.39 | 321.0                         | 230.48| 451.2                         | 321.40| 610.8                          |
| 149.76 | 327.1                         | 234.30| 456.4                         | 323.50| 615.2                          |
| 153.11 | 331.8                         | 238.80| 462.3                         | 326.18| 619.5                          |
| 156.66 | 336.9                         | 242.45| 469.1                         | 329.70| 626.6                          |
| 158.99 | 341.8                         | 244.90| 472.6                         | 331.99| 630.9                          |
| 162.34 | 347.3                         | 246.30| 474.8                         | 334.86| 638.4                          |
| 165.75 | 352.2                         | 247.70| 474.8                         | 337.66| 643.6                          |
| 169.10 | 358.5                         | 250.00| 478.6                         | 340.47| 648.2                          |
| 171.03 | 363.2                         | 253.99| 484.7                         | 342.70| 653.7                          |
| 174.39 | 366.7                         | 257.43| 489.4                         | 346.02| 662.6                          |
| 176.01 | 369.0                         | 260.84| 494.6                         | 348.70| 668.4                          |
| 177.95 | 374.1                         | 264.24| 501.0                         |       |                                |

$^a$Standard uncertainty for temperature $u(T) = 0.01$ K and relative standard uncertainty for the heat capacities $u_r(C_{p,m}) = 0.02$ in the temperature range from $T = (6$ to $15)$ K, $u_r(C_{p,m}) = 0.005$ between $T = (15$ to $40)$ K, and $u_r(C_{p,m}) = 0.002$ in the temperature range from $T = (40$ to $349)$ K.
Table 3. Experimental Molar Heat Capacities of Crystalline N-f-MLF-OMe ($M = 451.59$ g·mol$^{-1}$)$^a$

| $T/K$ | $C_{p,m}/$J·K$^{-1}$·mol$^{-1}$ | $T/K$ | $C_{p,m}/$J·K$^{-1}$·mol$^{-1}$ | $T/K$ | $C_{p,m}/$J·K$^{-1}$·mol$^{-1}$ |
|-------|--------------------------------|-------|--------------------------------|-------|--------------------------------|
|       | Series 1                       |       |                                |       |                                |
| 6.02  | 2.60                           | 10.27 | 13.2                           | 32.65 | 88.71                          |
| 6.13  | 2.71                           | 10.63 | 14.1                           | 35.04 | 96.64                          |
| 6.28  | 2.91                           | 11.04 | 15.0                           | 37.44 | 105.0                          |
| 6.43  | 3.21                           | 11.45 | 16.0                           | 39.87 | 112.9                          |
| 6.59  | 3.52                           | 11.88 | 17.1                           | 42.32 | 120.6                          |
| 6.73  | 3.88                           | 12.29 | 18.0                           | 44.78 | 127.7                          |
| 6.88  | 4.29                           | 12.79 | 19.2                           | 47.26 | 134.1                          |
| 7.04  | 4.66                           | 13.24 | 20.4                           | 49.75 | 139.9                          |
| 7.19  | 4.97                           | 13.71 | 21.7                           | 52.01 | 145.9                          |
| 7.35  | 5.42                           | 14.18 | 22.7                           | 54.78 | 153.1                          |
| 7.52  | 5.83                           | 14.65 | 24.1                           | 57.30 | 160.1                          |
| 7.66  | 6.28                           | 15.12 | 25.3                           | 59.87 | 167.1                          |
| 7.84  | 6.73                           | 15.60 | 26.8                           | 62.41 | 174.1                          |
| 7.98  | 7.23                           | 15.99 | 28.0                           | 64.96 | 181.3                          |
| 8.17  | 7.72                           | 16.64 | 29.8                           | 66.90 | 186.5                          |
| 8.33  | 8.13                           | 17.10 | 31.5                           | 70.06 | 194.1                          |
| 8.50  | 8.58                           | 17.62 | 33.2                           | 72.60 | 201.0                          |
| 8.70  | 9.08                           | 18.10 | 34.7                           | 75.15 | 206.0                          |
| 8.84  | 9.48                           | 18.78 | 37.2                           | 77.73 | 212.1                          |
| 8.98  | 9.89                           | 19.22 | 38.7                           | 80.10 | 216.1                          |
| 9.13  | 10.3                           | 19.72 | 40.5                           | 82.93 | 221.7                          |
| 9.30  | 10.7                           | 21.41 | 47.3                           | 85.50 | 227.0                          |
| 9.45  | 11.0                           | 23.40 | 55.2                           | 88.20 | 232.3                          |
| 9.62  | 11.5                           | 25.67 | 63.4                           | 90.85 | 237.1                          |
| 9.78  | 11.8                           | 27.96 | 71.9                           |       |                                |
| 9.95  | 12.3                           | 30.29 | 80.5                           |       |                                |
| 10.60 | 176.09                         | 381.5 | 254.83                         | 514.5 |                                |
| 93.51 | 179.50                         | 385.9 | 257.07                         | 518.7 |                                |
| 96.19 | 182.11                         | 390.6 | 259.30                         | 523.3 |                                |
| 98.88 | 184.71                         | 394.8 | 261.50                         | 528.0 |                                |
| 101.58| 187.31                         | 398.3 | 263.68                         | 532.6 |                                |
| 104.28| 189.90                         | 402.2 | 265.84                         | 535.2 |                                |
| 106.98| 192.49                         | 407.4 | 267.99                         | 539.2 |                                |
| 109.69| 195.07                         | 411.8 | 270.16                         | 543.2 |                                |
| 112.38| 197.64                         | 416.1 | 272.34                         | 547.3 |                                |
| 115.08| 200.20                         | 420.0 | 274.50                         | 551.2 |                                |
| 117.78| 202.74                         | 423.8 | 276.67                         | 554.9 |                                |
| 120.47| 205.27                         | 428.2 | 277.10                         | 557.8 |                                |
| 123.16| 207.77                         | 433.6 | 279.97                         | 561.2 |                                |
| 125.85| 210.28                         | 436.5 | 282.11                         | 564.9 |                                |
| 128.53| 212.77                         | 442.5 | 284.23                         | 568.8 |                                |
| 131.22| 215.23                         | 446.4 | 286.34                         | 571.5 |                                |
| 133.99| 217.60                         | 450.8 | 288.80                         | 578.0 |                                |
| 136.67| 220.02                         | 455.6 | 290.49                         | 581.0 |                                |
| 139.35| 222.40                         | 459.1 | 292.53                         | 584.6 |                                |
| 142.02| 224.71                         | 463.1 | 294.54                         | 587.8 |                                |
| 144.68| 227.02                         | 467.1 | 296.39                         | 591.6 |                                |
| 147.35| 229.33                         | 471.1 | 298.40                         | 596.2 |                                |
| 150.01| 231.66                         | 475.2 | 300.24                         | 601.4 |                                |
| 152.68| 234.00                         | 478.4 | 302.09                         | 606.6 |                                |
| 155.33| 236.36                         | 484.2 | 304.77                         | 614.7 |                                |
| 157.99| 238.72                         | 488.0 | 307.42                         | 619.1 |                                |
| 160.64| 241.09                         | 490.9 | 309.83                         | 624.8 |                                |
| 163.28| 243.46                         | 493.2 | 312.19                         | 631.0 |                                |
| 165.92| 245.83                         | 498.9 | 314.41                         | 635.0 |                                |
| 168.56| 248.18                         | 503.0 | 316.68                         | 638.7 |                                |
| 171.19| 250.50                         | 507.1 | 318.91                         | 645.4 |                                |
| 174.60| 252.78                         | 509.6 | 321.09                         | 652.2 |                                |
| 176.24| 254.97                         | 512.2 | 323.22                         | 659.0 |                                |

$^a$
The Debye theory was used to fit the experimental data in the range from \( T = (6 \text{ to } 12) \text{ K} \) and extrapolate it to 0 K.\(^4\)

\[ C_{p,m} = nD(\Theta/\Theta_{max}) \]

where \( n \) is a constant value, and eq 2 can be rewritten as follows:

\[ \ln C_p = \ln A + D \ln T \] (3)

which can be used to obtain \( D \) and \( \Theta_{max} \).

Since below \( T = 50 \text{ K} \) the experimental values of \( C_{p,m} \) are equal to \( C_p \). Thus, experimental data in the range from \( T = (20 \text{ to } 50) \) K were used and yielded \( D = 1.6, \Theta_{max} = 202.8 \text{ K} \) for N-f-MLF-OH, and \( D = 1.8, \Theta_{max} = 183.0 \text{ K} \) for N-f-MLF-OMe. The relative standard uncertainty for the characteristic temperatures is \( u_r(\Theta_{max}) = 0.007 \).

According to the multifractal model of the theory of heat capacity of solids,\(^5\) \( D = 1 \) corresponds to solids with a chain structure, \( D = 2 \) corresponds to ones with a layered structure, and \( D = 3 \) corresponds to ones with a spatial structure, characterized by comparable interactions in all three dimensions. The obtained values of \( D \) point to the chain-layered structure for both tripeptides.

The Debye theory was used to fit the experimental data in the range from \( T = (6 \text{ to } 12) \text{ K} \) and extrapolate it to 0 K.\(^4\)
The obtained values fit the equations:

$$21C_{1} + 31/2H_{2} + 3/2N_{2} + 5/2O_{2} + S(cr) \rightarrow C_{2}H_{4}N_{2}O_{2}S(cr)$$

$$22C_{1} + 33/2H_{2} + 3/2N_{2} + 5/2O_{2} + S(cr) \rightarrow C_{2}H_{3}N_{2}O_{2}S(cr)$$

where cr, gr, and g are crystal, graphite, and gas, respectively.

**CONCLUSIONS**

This work reports heat capacities of crystalline tripeptides N-formyl-l-Met-l-Leu-l-Phe-OH and N-formyl-l-Met-l-Leu-l-Phe-OMe measured over the range from $T = (6$ to $350)$ K by precise adiabatic vacuum calorimetry. The standard thermodynamic functions of N-f-MLF-OH and N-f-MLF-OMe over the range from $T = (0$ to $350)$ K and the standard entropies of formation at $T = 298.15$ K were calculated. The low-temperature ($T \leq 50$ K) dependencies of heat capacities were analyzed using the Debye's and the multifractal theories, and a chain-layered structures topology was established.

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The authors declare no competing financial interest.

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