

Theoretical Study of the Tautomeric Preference and Self Association Processes of 2-Pyrrolidinone

Ahmed M. El Defrawy*, Maii S. Mashaly, Mamdouh S. Soliman

Department of Chemistry, Faculty of Science, Mansoura University, Mansoura, 35516, Egypt.

*ameldefrawy@mans.edu.eg

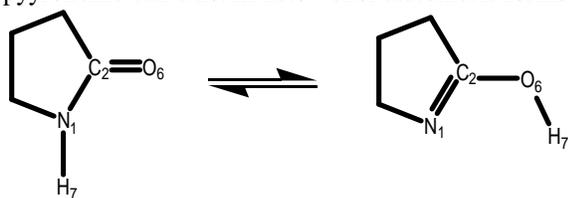
Abstract: Relative tautomerization energies, dipole moments for the tautomers of 2-pyrrolidinone was studied by quantum-chemical calculations, using the B3LYP level of calculation with the 6-311G(d,p) basis set in the gas phase with full geometry optimization. Entropies, enthalpies and Gibbs free energies for the tautomerization process of 2-pyrrolidinone was obtained using the RHF/6-31G(d) level of computation. The calculations showed that, the Keto form is the most stable form in the gas phase. The entropy effect on the Gibbs free energy change of the tautomerization process 2-pyrrolidinone is found to be very small, and has practically no significance for the tautomeric equilibria of the 2-pyrrolidinone. The enthalpic term is dominant in the determination of the equilibrium constant. The ability to form dimer, trimer and tetramer was investigated concerning the energetical changes; dipole moments using the RHF/6-31Gd level of computation. The thermodynamic parameters at different temperatures were studied using the PM3 semiempirical method. The results showed that, there is a high interconversion process between the cyclic and open dimer. Also, the probability to form higher association forms is presumably rare. At room temperature 2- pyrrolidinone only could exist in a dimer form in equilibrium with the monomer. The results are in good agreement with the available experimental data.

[Ahmed M. El Defrawy, Maii S. Mashaly, Mamdouh S. Soliman. **Theoretical Study of the Tautomeric Preference and Self Association Processes of 2-Pyrrolidinone.** Journal of American Science 2011;7(6):1163-1172]. (ISSN: 1545-1003). <http://www.americanscience.org>.

Key words: 2-pyrrolidinone, tautomerization, self association, thermodynamic Parameters, theoretical calculations.

1. Introduction

The experimental studies on tautomerism still a challenging task, because most of the tautomers are not observed in the experimental studies due to their low concentration. So, the theoretical investigation of tautomers is meaningful. 2-pyrrolidinone (2-py), is a saturated cyclic five membered ring molecule, which has the peptide moiety HN-C=O containing an acidic NH proton and a basic C=O group, that can act as a hydrogen bond donor and hydrogen bond acceptor with the expected hydrogen bonding interactions. The protropic tautomerism of these 2-pyrrolidinone, results from the migration of liable hydrogen from the ring nitrogen or oxygen atom, hence the 2-pyrrolidinone can exist in keto - enol tautomeric forms.



Knowing the relative stabilities of the various tautomeric forms of a molecule is not only important for chemical research but also the fundamental for biological research [1-2].

The proton attached to the Nitrogen atom (N1) in the 2-py molecule, is responsible for its interaction with different molecules through hydrogen bonding.

Several experimental studies have been conducted on the self association of 2-pyrrolidinone molecule [3-7]. Although theoretical calculations were proved to give good results for thermodynamic properties [8-10], little attention has been paid to the influence of temperature on tautomerization process, and no theoretically thermodynamic studies at different temperatures were reported [11].

Hydrogen bonding and proton transfer have been studied in great detail both experimentally and theoretically [12-14]. Substantial progress has been achieved in the elucidation of the detailed mechanism of proton transfer in small molecules using high-level ab initio quantum mechanical theory [13, 15, 16]. However, the ab initio approach becomes prohibitively expensive in terms of computer resources and time when dealing with large organic molecules or molecular associations. Therefore, it is of considerable interest to study the applicability of semi empirical methods for the confident prediction of hydrogen bonding interactions. The semi empirical method, namely PM3, describes the energetics and topographies of hydrogen-bonded systems fairly accurate [17, 18]. Accordingly, we present here the results DFT and RHF calculations for the proton transfer process, as well as the RHF/6-31Gd and PM3 methods of calculations, for studying the ability to form dimer, trimer and tetramer, concerning the energetical changes and the thermodynamic

parameters at different temperatures, respectively, for depth comprehension of these formation processes.

2. Methods of Calculations

All of the calculations have been performed using the Hyperchem 8.0 program [19]. The molecular stability as well as a thermodynamic study of the keto- and enol- tautomeric forms, were theoretically investigated using the B3LYP and RHF level of computation using the 6-311G(d,p) and 6-31G(d) basis sets, respectively. For studying the self association process of 2- pyrrolidinone, the RHF /6-31G(d) method was used for the geometry optimization and for the dipole moment, the length of the hydrogen bond formed as well as the energies of the different associated forms without any geometrical constraints. The semi empirical PM3 method was used for the thermodynamic studies on the self associated forms of 2-pyrrolidinone molecule. The vibrational frequencies were calculated to confirm all stationary points. The thermodynamic parameters were calculated at (300-500) K temperature range.

3. Results and Discussion

3.1. Tautomerization of 2-pyrrolidinone

The complete transfer of the acidic hydrogen attached to nitrogen to the basic Oxygen atom of the ketonic group in the same molecule, lead to the formation of the 2-pyrrolidinone tautomeric form, and an equilibrium state between the keto and enol tautomers could be established.

Two possible conformations of 2-pyrrolidinone could be expected. A one-dimensional potential energy scans were performed to determine the most stable structure, where the torsion angle $N_1-C_2-O_6-H_7$ is changed in the range of -180 to 180° , starting with the O-H Cis conformation to the nitrogen atom ($\angle N_1-C_2-O_6-H_7 = 0^\circ$) and with 20° angle increment, applying the B3LYP/ 6-311G(d,p) method (Fig. 1). As seen in Fig. 1, the energy profile shows local minimum at about -180° and 180° and a global minimum at 0° , corresponding to the cis form which is more stable than the trans form by about 6.2 Kcal/mol.

The calculated optimum energies of the two tautomers and that of the transition state of 2-pyrrolidinone, and some geometrical parameters for the transition state are shown in Table 1 and Fig. 2, respectively.

As indicated in Table 1, the keto form is found to be more stable and has a lower binding energy by about 8.5 Kcal/mole than the enol form. The conversion process from keto to enol form requires an energy barrier of about 66.9 Kcal/mole. Also, from Table 1, one can see that the ring twisting angle

in the keto and enol forms are 25° and 17° , respectively. This gives an indication that the proton transfer process results in a decrease in the ring twist angle, and this explains the lower stability of the enol form. The dipole moment (μ), is an important tool which can be used to show the charge distribution in a molecule, and it is one of the properties often used to rationalize the structure of many chemical systems [20]. Thus, by comparing the calculated dipole moment values, 4.134 and 1.264 Debye, for the optimized structures of the keto and enol tautomers respectively, with the experimentally measured value for the monomeric 2-pyrrolidinone (3.96 Debye) [21], a strong evidence for the existence of the 2-pyrrolidinone molecule in the keto form rather than the enol form can be supported.

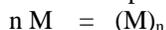
After the stationary points were located, vibration frequencies were calculated in order to ascertain that the structures found corresponds to minima on the potential energy surface. Based on the vibrational analysis, the changes of the thermodynamic properties: Change in free energy G , change in enthalpy H , change in entropy S , as well as the equilibrium constant(K) as a function of temperature for the keto-enol conversion process, were theoretically determined from the results of electronic, vibrational and electronic components using the RHF/6-31G(d) level of calculation, for the tautomerization process with the temperature ranging from 300 to 500 K (Table 2). Plot of the relations between equilibrium constant (K) and the absolute temperature (T) is shown in Fig.3.

With a correct application of the equation $G = -RT \ln K$, the value of the equilibrium constant K which represent the expected ratio of 2-pyrrolidinone to the 2-pyrrolidinone has been found to be of a value less than 1.45×10^{-7} at room temperatures (Table 2). This indicate the predominance of the keto form of 2-pyrrolidinone at room and lower temperatures. As observed in Fig. 3, the presence of the enol form increased by increasing temperature, but, even at 500°C the ratio enol to keto form is not expected to exceed 10^{-4} , which is relatively a very small ratio. In addition to that, the entropy effect on the Gibbs free energy change of the tautomerization process is very small (Table 2), and has practically no significance for the tautomeric equilibria. Thus, the enthalpic term is found to be dominant in the determination of the equilibrium constant.

3.2. Self-association of 2-pyrrolidinone and Temperature effect

The acidic NH proton and the basic C=O groups, in 2-pyrrolidinone molecule, permit the possible self-association via hydrogen bonding ($-C=O \dots H-N$) to be expected [22, 23]. Association

may take place between two or more molecules to form open linear dimers, cyclic dimers, open linear trimers, cyclic trimers and open and cyclic tetramers. However, higher degrees of association to form higher polymeric structures are also expected. Other type of association, which is described as a kind of side-association of two molecules to form side on dimer could be expected [24]. Such association can occur between the N-H group of one molecule and the N-H and the C=O groups of the other molecule, where the N-H hydrogen atom of the first molecule will be hydrogen-bonded with the N-H nitrogen atom of the second molecule, and the N-H nitrogen atom of the first molecule will be hydrogen bonded with the oxygen atom of the carbonyl group of the second molecule (Fig. 4). Accordingly, we can say that we are dealing with the reversible process:



Where M represents the molecule in the monomer state, and n is the degree of association. An equilibrium state between monomer state and self-associated state are established.

The electronic structure of the different expected self-associated structures were theoretically calculated and their geometry were optimized, representing a stationary point in the potential energy curve using the RHF /6-31Gd level of computation. The binding energies, hydrogen bond distance and the dipole moments of the different associated form of the 2-pyrrolidinone molecule are depicted in Table 3. On the other hand, geometry optimization of the side on self-association dimer (Fig 4) did not show any stationary point in the potential energy curve, and the structure is rapidly converted to cyclic dimer structure. This indicated that such kind of association does not represent a stable association form in case of 2-pyrrolidinone.

To the best of our knowledge, there is a lack in the study of the temperature dependence of the self association of 2-pyrrolidinone. Thus, the thermodynamic parameters of the conversion processes, H, G, and S as well as the equilibrium constant K as a function of temperature, were calculated from the results of quantum mechanical calculations of electronic, vibrational, rotational, and translational energy components, and the estimated entropy at different temperatures using the PM3 level of computation. The relation between the equilibrium constant K and temperature for the conversion between monomer and both expected cyclic and open dimeric, trimeric and tetrameric associated forms, are shown in Figs. 5, 6, 7.

From the results of this thermodynamic study, it can be seen that the conversion process of 2-pyrrolidinone in its cyclic trimer state to the open

linear trimer state, as well as the conversion for the cyclic tetramer state to the open linear tetramer state is highly increased as the temperature increase (Figs, 6 and 7). Moreover, by comparing the equilibrium constant values for the conversion process for these higher associations at room temperatures (less than 10^{-4} mol/l), one can predict that there is no existence of the higher polymeric structures such as trimers or tetramers in the association model.

From previous experimental studies [5-7], it was reported that, at low concentration of 2-pyrrolidinone, the dominant species will be the cyclic associated dimer (with zero dipole moment), in addition to the open dimer is present with small amounts. For the conversion process of 2-pyrrolidinone from the cyclic dimer to the open linear state, the K values is highly increased as the temperature increase (Fig.5-c). This indicated that as the temperature increase, this favors the conversion of 2-pyrrolidinone from the cyclic dimer to the open dimer. Since the dipole moment value is a very useful tool to deduce the structure of a molecule [20]. Thus, by comparing the experimentally determined dipole moment value (2.30 D) from the nonlinear dielectric spectroscopic study [21], with the calculated values for the cyclic and the open associated forms (Table 4), one can predict that, the higher measured value for dipole moment for the dimer (more than zero and lower than 4.13 D) indicates the very rapid inter conversion between cyclic and open associated structures.

Also, it worthy to notice that, the binding energies of the cyclic and open dimer, are 13.5 kcal/mol and 8.7kcal/mole, respectively. These values when compared with experimentally determined dissociation energies of the water dimer [25], which give an indication that, the hydrogen bonding interaction in 2-pyrrolidinone is moderate. Moreover, the G values for both dimers (Table 3) increase with the increase of the temperature, indicating that the interaction weaken as the temperature increase. From Table 5, it can be noticed that, the enthalpy change in the conversion process from the cyclic to open dimer is an endothermic process. In addition to that, the value of the equilibrium constant is high enough to raise the probability of the existence of the open dimer at room temperature, which support the idea of rapid their conversion [25].

As observed from the previous results, one can conclude that, the association process to form cyclic or open species must be considered not only a factor of energy, but also a factor of the thermodynamic parameters of the equilibrium process.

Table 1: Calculated energies and dipole moment of tautomers and its transition states using B3LYP 6-31G(d,p) calculations.

Conformation	Total Energy (K Cal/mol)	Dipole Moment (Debye)	Ring twist angle
Keto	-179802.82	4.134	25
Enol	-179794.29	1.264	17
Transition state	-179735.95	3.343	21

Table 2 : Theoretically calculated thermodynamic parameters of the conversion process of 2-pyrrolidinone to 2-pyrrolidinole .

Temp (Kelvin)	H (Kcal/mol)	G (Kcal/mol)	S (cal/mol/deg)	K
300	9.688	9.40	0.00096	1.45x10 ⁻⁷
320	9.690	9.38	0.00097	4.01x10 ⁻⁷
340	9.697	9.36	0.00099	9.83x10 ⁻⁷
360	9.704	9.34	0.00101	2.17x10 ⁻⁷
380	9.711	9.32	0.00103	4.44x10 ⁻⁶
400	9.716	9.30	0.00104	8.45x10 ⁻⁶
420	9.715	9.27	0.00106	1.51x10 ⁻⁵
440	9.731	9.26	0.00107	2.57x10 ⁻⁵
460	9.727	9.23	0.00108	4.16x10 ⁻⁵
480	9.738	9.21	0.00110	6.48x10 ⁻⁵
500	9.750	9.19	0.00112	9.75x10 ⁻⁵

Table 3: Calculated Dipole moment values and some characteristic data For self-associated molecules using the RHF/6-31G(d) calculations.

Compound	Dipole moment (Debye)	Total energy Kcal/mol	O...H distance A	Binding energies Kcal/mol
Monomer	4.28	-178764.760		
Cyclic Dimer	0.3636	-357542.98	1.98816	13.5
Open Dimer	2.094	-357538.25	2.02586	8.7
Cyclic Trimer	0.000	-536315.71	1.97713	21.4
Open Trimer	5.637	-536311.08	2.01237	16.8
Cyclic Tetramer	0.1120	-715076.94	2.02751	17.9
Open Tetramer	5.0309	-715073.67	2.00748	14.6

Table 4: Theoretically Calculated thermodynamic parameters of the conversion process of monomer 2-pyrrolidinone to cyclic and open dimmers.

Temp (K)	monomer to cyclic dimer				monomer to open dimer			
	H	G	S	K	H	G	S	K
300	-2.670	0.27	-0.0099	0.0036253	-0.560	1.74	-0.0038	0.1047
320	-2.408	0.59	-0.0094	0.0025962	-0.324	1.78	-0.0043	0.0935
340	-2.360	0.66	-0.0090	0.0019507	-0.268	1.93	-0.0048	0.0855
360	-2.196	0.99	-0.0086	0.0015251	-0.128	1.97	-0.0052	0.0797
380	-2.154	1.05	-0.0083	0.0012325	-0.028	2.10	-0.0056	0.0755
400	-2.860	1.36	-0.0079	0.0010241	-0.300	2.11	-0.0060	0.0725
420	-1.792	1.40	-0.0076	0.0008713	-0.388	2.30	-0.0064	0.0703
440	-1.668	1.47	-0.0072	0.0007565	-0.492	2.50	-0.0068	0.0688
460	-1.474	1.67	-0.0069	0.0006682	-0.766	2.51	-0.0071	0.0679
480	-1.468	1.77	-0.0066	0.0005992	-0.800	2.80	-0.0075	0.0675
500	-1.250	1.95	-0.0063	0.0005444	-1.004	2.896	-0.0078	0.0673

H, gas-phase (kcal /mol); S, gas-phase entropy (cal /mol / deg); G, gas-phase free energy (kcal /mol); K equilibrium constant.

Table 5 : Theoretically Calculated thermodynamic parameters of the conversion process of cyclic dimmer to open dimmer.

Temp o K	H	G	S	K
300	2.101	-2.00	0.01367	28.89
320	2.097	-2.29	0.01374	36
340	2.092	-2.59	0.01380	43.82
360	2.086	-2.79	0.01385	52.26
380	2.182	-3.18	0.01390	61.26
400	2.180	-3.38	0.01395	70.76
420	2.172	-3.67	0.01398	80.69
440	2.164	-3.86	0.01401	91.00
460	2.263	-4.26	0.01405	101.65
480	2.254	-4.55	0.01407	112.56
500	2.255	-4.76	0.01411	123.70

H, gas-phase (kcal /mol); S, gas-phase entropy (cal /mol / deg); G, gas-phase free energy (kcal /mol); K equilibrium constant.

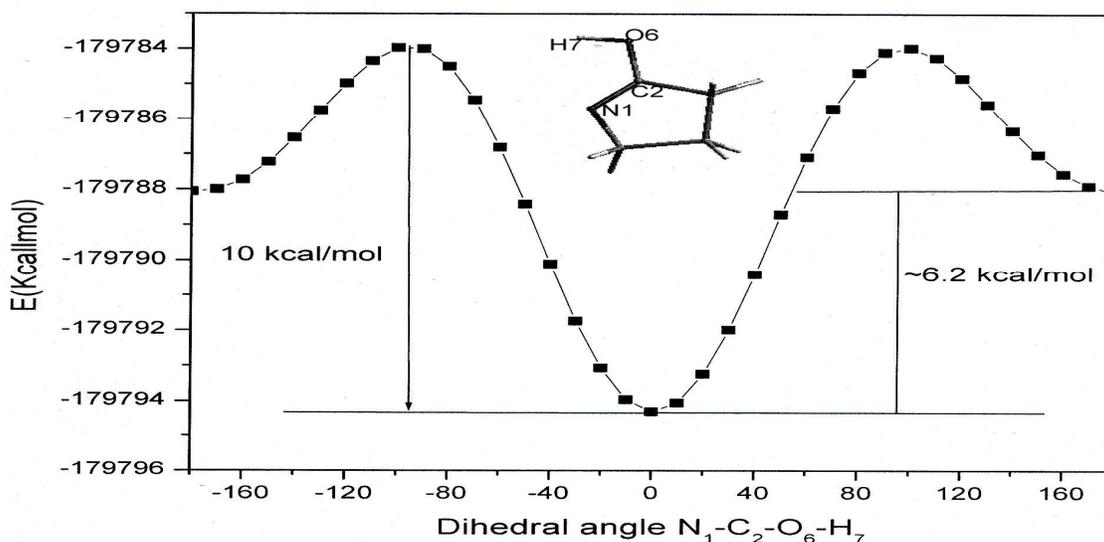


Fig.1: The energy profile for the rotation of the O-H group in 2-pyrrolidinol by B3LYP/6- 311G(d,p) basis set.

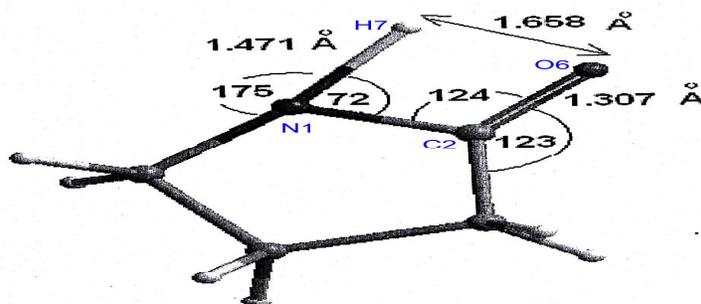


Fig.2: The characteristic structural parameters of the transition state of keto-enol conversion.

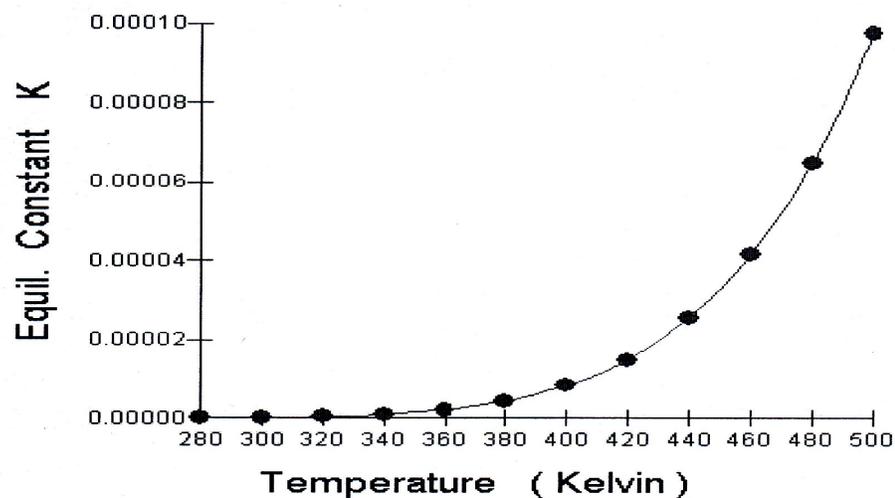


Fig.3: Variation of equilibrium Constant (K) with temperature for the keto - enol tautomerization calculated using RHF /6-31G(d) basis set.

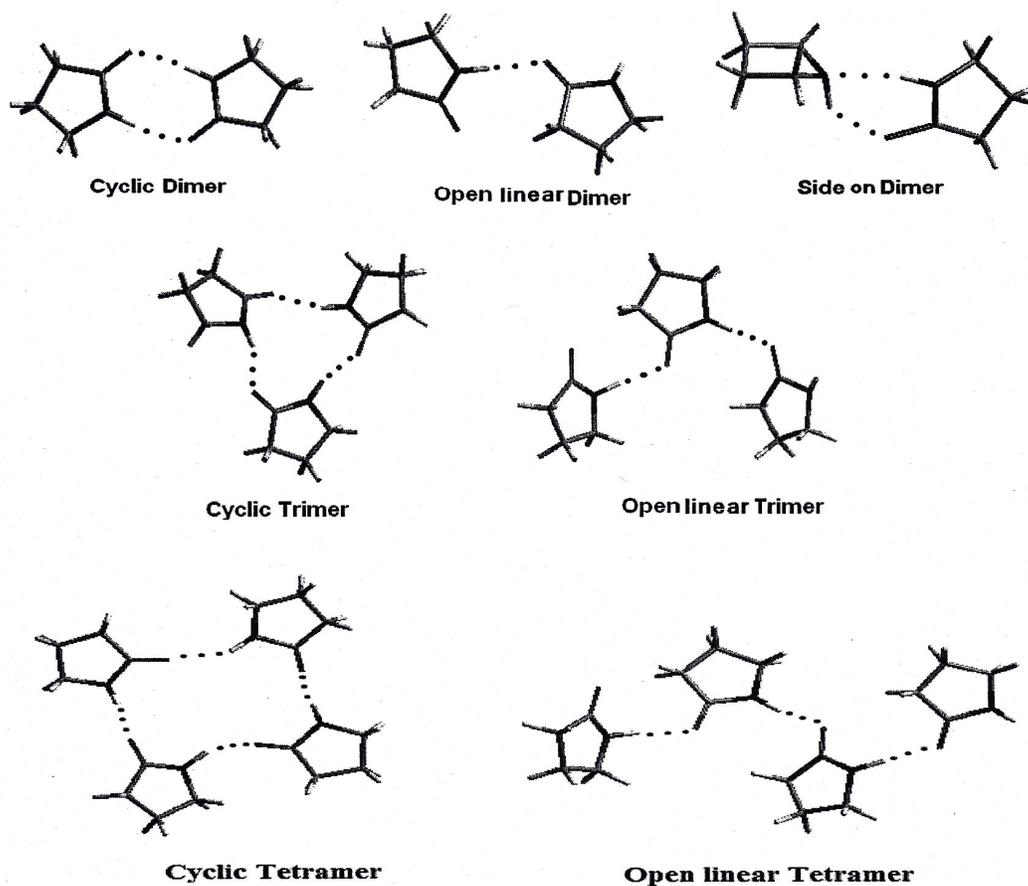


Fig.4: The expected self-association structural forms of 2-pyrrolidinone.

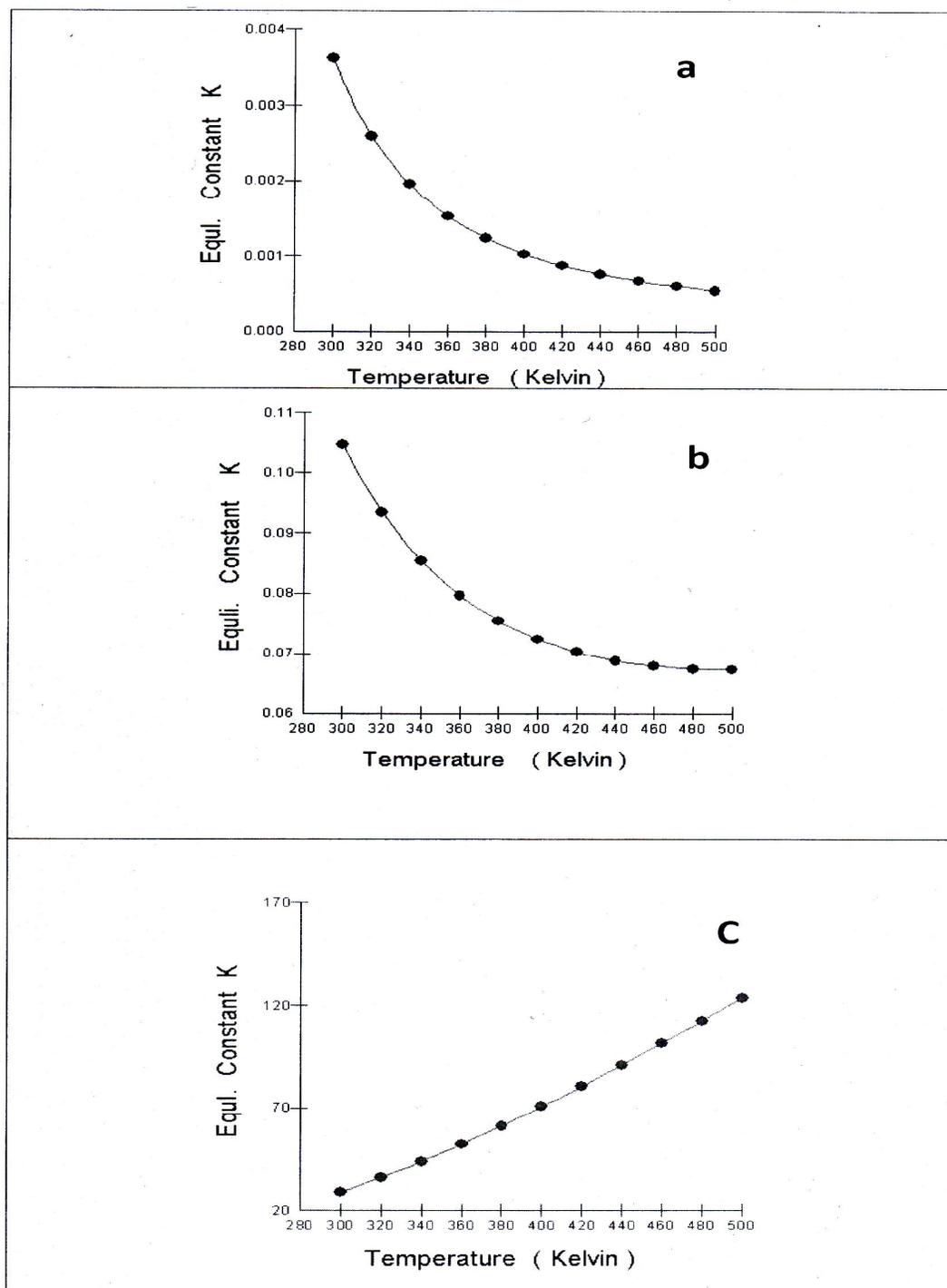


Fig.5: Variation of equilibrium Constant (K) with temperature for the conversion process of (a) monomer 2-pyrrolidinone to cyclic dimer; (b) monomer 2-pyrrolidinone to open dimer; (c) cyclic dimer to open dimer.

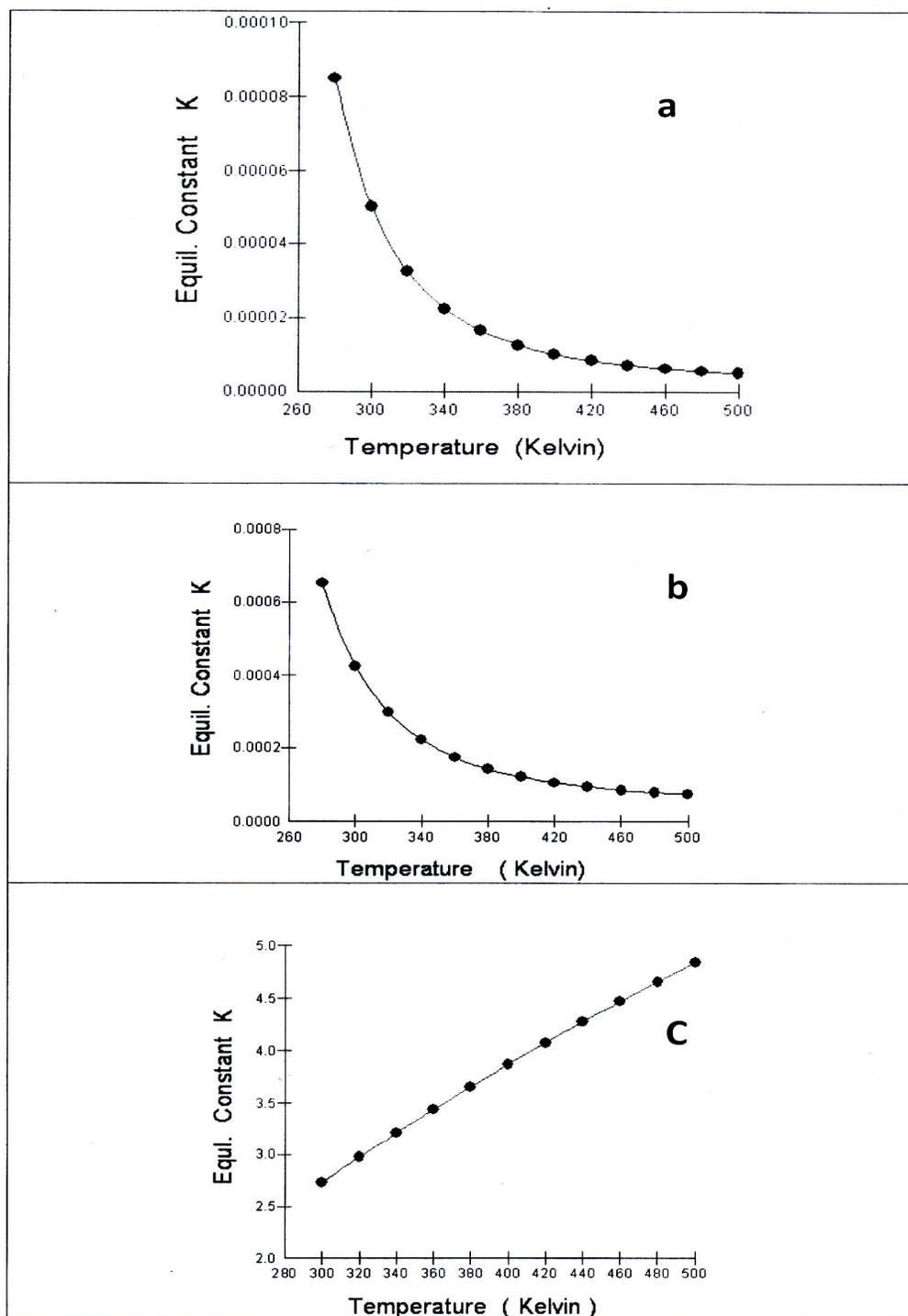


Fig.6: Variation of equilibrium Constant (K) with temperature for the conversion process of (a) monomer 2-pyrrolidinone to cyclic trimer; (b) monomer 2-pyrrolidinone to open trimer; (c) cyclic trimer to open trimer.

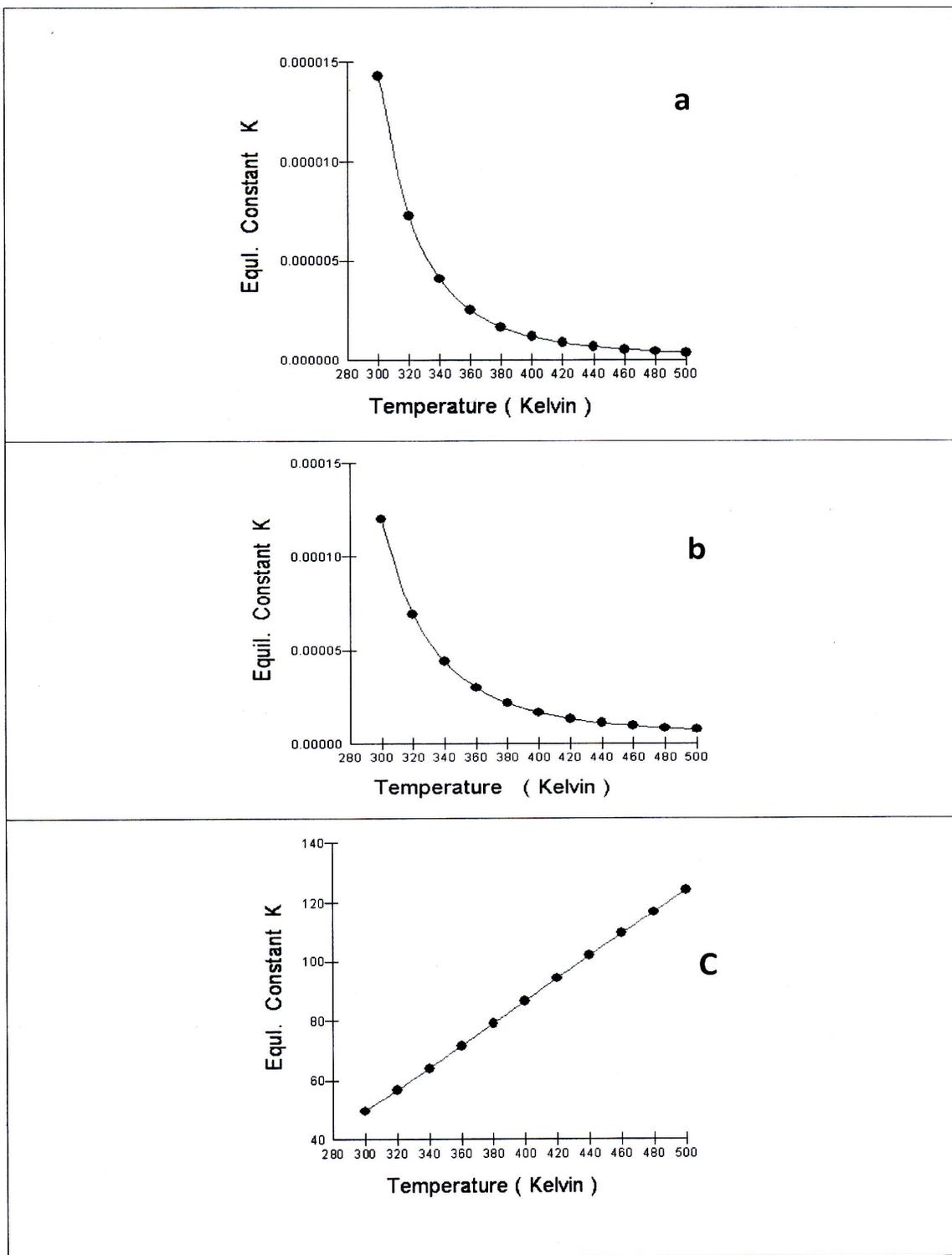


Fig.7: Variation of equilibrium Constant (K) with temperature for the conversion process of (a) monomer 2-pyrrolidinone to cyclic tetramer; (b) monomer 2-pyrrolidinone to open tetramer; (c) cyclic tetramer to open tetramer.

References

1. Levy D. H. (1988): Rev. Phys. Chem.; 31: 197.
2. Formosinho S. J., Arnaut G. L.(1993): Photochem J. Photobiol., A; 75: 21.
3. Walmsley J.A., Jacob E.J., Thompson H.P. (1976): J. Phys. Chem.; 80: 2745.
4. Walmsley J.A. (1978): J. Phys. Chem.; 82: 2031 .
5. Jadzyn J., Malecki J., Jadzyn C. (1978): J. Phys. Chem.;82: 2128 .
6. Hopman R., Bunsenges B. (1973): J. Phys. Chem.;77: 52 .
7. Mc Dermott D.P. (1986): J. Phys. Chem.;90: 2569 .
8. Popole J.A., Luke B.T., Frisch M.J., Binkely J.S. (1985): J.Phys.Chem.; 89:2198 .
9. Ju G.Z., Bian W.S. (1990):Thermo Chim. Acta;167: 37 .
10. Ju G.Z., Bian W.S. (1990):Thermo Chim. Acta;176: 259 .
11. Isin D.O., Yekler H. (2004): J. Mol. Struct: THEOCHEM; 685: 117 .
12. Gauduel Y., J.Rossky P. (1994): Eds.; Ultrafast Reaction Dynamics Solvent Effects, Part III; AIP: New York,.
13. Bountis T. (1992): Ed.; Proton Transfer in Hydrogen-Bonded Systems; Plenum: New York,.
14. Politzer P., Murray J. S. (1994): Eds.; Quantitative Treatments of Solute-Solvent Interactions; Elsevier:Amsterdam, .
15. Dannenberg J. J., Rios R. (1994): J. Phys. Chem.;98: 6714 .
16. Wu C. C., Lien M. H. (1996): J. Phys. Chem.;100: 594 .
17. Dewar M. J. S., Zoebisch E. G., Healy E. F., Stewart J. J. P. (1985): J. Am. Chem. Soc.;107: 3902.
18. Stewart J. J. P. (1989): J. Comput. Chem.;10: 209 .
19. Hyperchem 8, Hypercube, Inc.
20. Chatterjee A., Balaji T., Matsunaga H., Mizukami F.(2006): J.Mol. Graph Model;25: 208 .
21. De Smet K., Kedziora P ., Jadzyn J. , Hellemans L. (1996): J. Phys. Chem.;100: 7662 .
22. Malewski G. , Konig R. (1964): Spectrochim. Acta;20: 565 .
23. Konig R., Malewski G. (1968): Spectrochim. Acta; 24: 219.
24. Nakabayashi T., Sato H., Hirata F., and Nishi N. (2001): J. Phys. Chem. A; 105: 245.
25. Feyereisen M.W., Feller D., Dixon D.A. (1996): J. Phys. Chem.;100: 2993 .

5/26/2011