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MNDO Study of Tautomerism in 3-Acetyltetramic Acid

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The tautomerism of 3-acetyltetramic acid was investigated by using the semiempirical MNDO method. Calculations predict that the exo-enol tautomers (B and D) are more stable than the endo-enol forms (A and C). The estimated ΔH_f's are —473.7, —475.2, —457.5 and —453.4 kjoule mol^{-1}, respectively. Lactim tautomers A′ and B′ are found to be by ca. 22 kjoule mol^{-1} less stable than the corresponding lactam tautomers A and B. The origin of relative stabilities of tautomers is elucidated by the energy partitioning technique.

INTRODUCTION

The chemistry of 3-acetyltetramic acid* (*1*) has been the subject of numerous recent studies, prompted to a large extent by its close analogy to the naturally occurring tenuazonic acid[1–4], whose derivatives exhibit significant antitumor activity.[4] The structurally related 3-dienoyltetramic acid appears as a constituent of antibiotics streptolydigin[5–6] and tirandamycin[5–7] which have also stimulated considerable interest because of their modes of action, especially their inhibition of RNA polymerase.[8,9] An outstanding property of these compounds, which has been discussed from both experimental and theoretical points of view, is their tautomeric behaviour[10–13]. As a representative of the cyclic α,α-tricarbonyl compounds they can exist in four tautomeric forms[14,15] (Scheme I). In addition, lactam ⇌ lactim tautomerization (A ⇌ A′, B ⇌ B′) can also occur.

The interconversion of the "external" tautomers (A, B ⇌ C, D) is a slow process which was observed by NMR spectroscopy[10–12], whereas the "internal" tautomers (A ⇌ B, C ⇌ D) are generally rapidly interconverted. The ^{1}H and ^{13}C NMR studies of *1* have shown pronounced variation in the tautomeric equilibria with solvent polarity.[12] In apolar aprotic solvents like $CDCl_3$ a greater population of A ⇌ B tautomeric pair** was observed, while in strongly polar media only the presence of the C ⇌ D tautomeric pair was observed. In DMSO-d_6 3-acetyltetramic acid exists as a mixture of tautomers A and B and their lactim forms A′ and B′, respectively, presumably due to

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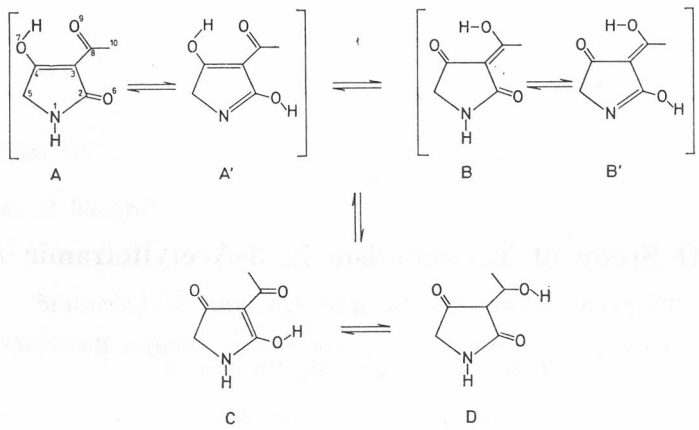
* IUPAC name: 3-acetyl-2,4-azolidinedione.

** see, however, ref. 7, in which ^{1}H NMR spectrum of *1* was assigned to the tautomer B exclusively.



Scheme I

the strong solvation effect of DMSO which drives tautomeric equilibria toward the lactim tautomers, thus preventing formation of C ⇌ D tautomeric pair.[12] Calculations[13] of the total energies using the CNDO/2 method[16] predicted higher stability of the A ⇌ B tautomeric pair for ca. 17 kjoule mol^{-1}.

As a part of our interest in structural properties of the naturally occurring tetronic acids[17] and their structural analogons[18,19], we undertook a systematic investigation of the tautomerization of *1* by use of the semiempirical MNDO method.[20] Calculations were carried out on all possible tautomers of *1* and most salient features of their molecular and electronic structures are reported here. Previous calculations were limited only to keto-enol tautomers.[13] MNDO method was chosen because of its good performance in estimating differences in molecular size, shape and energetics for structurally related compounds.[18,21] Since experimental structures are not usually available for all tautomers, it is of utmost importance to apply a method which optimizes all independent geometric parameters when studying tautomeric equilibria. Very recent application[22] of the MNDO approach to the monocyclic and bicyclic lactams has shown that calculated bond distances and angles are in reasonable agreement with the experimentally determined data. The MNDO approach was also proved to be sufficiently reliable for relative tautomerization energy calculations.[23]

RESULTS AND DISCUSSION

The calculated molecular structures for all tautomers are summarized, together with the corresponding heats of formations and dipole moments, in Table I, with the atoms labelled as in Scheme I.

Geometries

Inspection of the calculated geometrical parameters given in Table I reveals several interesting features. We will discuss only a few characteristic properties in terms of hybridization parameters, as calculated from the MNDO bond order matrix[24,25] and π-bond orders. This approach proved

TABLE I

The Structural Parameters, Heats of Formation and Dipole Moments of 3-acetyltetramic Acid Tautomers as Calculated by the MNDO Method

Bond	Tautomer A	B	C	D	A′	B′	I	II
	Bond distances/Å							
N_1C_2	1.413	1.406	1.385	1.402	1.323	1.317	1.422	1.373
C_2C_3	1.502	1.498	1.412	1.497	1.490	1.489	1.477	1.442
C_3C_4	1.388	1.495	1.484	1.497	1.398	1.507	1.432	1.467
C_4C_5	1.540	1.543	1.556	1.546	1.542	1.545	1.529	1.565
C_5N_1	1.452	1.450	1.463	1.451	1.461	1.459	1.457	1.471
C_2O_6	1.223	1.226	1.333	1.229	1.340	1.343	1.223	1.271
C_4O_7	1.330	1.224	1.222	1.222	1.326	1.223	1.269	1.222
C_3C_8	1.487	1.382	1.473	1.382	1.483	1.379	1.439	1.440
C_8O_9	1.234	1.342	1.237	1.341	1.236	1.346	1.297	1.302
C_8C_{10}	1.526	1.524	1.527	1.525	1.527	1.525	1.518	1.520
O_6H			0.951		0.952	0.951	1.225	1.225
O_7H	0.950				0.950		1.225	
O_9H		0.947		0.948		0.947		1.225
N_1H	0.995	0.995	0.996	0.995			0.995	0.995
C_5H	1.116	1.117	1.114	1.117	1.117	1.115	1.116	1.114
$C_{10}H$	1.109	1.109	1.109	1.109	1.108	1.108	1.108	1.108
	Bond angles deg							
$C_2C_3C_4$	106.9	105.9	106.5	105.9	102.9	101.6	107.9	107.2
$C_3C_4C_5$	111.8	108.9	107.5	108.5	110.0	107.4	110.8	106.5
$N_1C_5C_4$	101.0	102.7	102.4	103.0	104.0	105.5	100.7	103.7
$O_6C_2C_3$	132.5	131.4	133.8	130.5	124.8	123.9	121.3	
$O_7C_4C_3$	132.2	127.3	129.9	128.1	132.8	127.4		130.1
$C_8C_3C_4$	127.8	128.7	127.5	126.9	127.1	128.3	125.7	136.3
$O_9C_8C_3$	119.1	124.3	119.6	124.4	118.2	123.6		119.5
$C_{10}C_8C_3$	121.4	125.2	121.3	125.1	124.4	128.1	125.7	125.1
HO_6C_3			115.6		113.7	113.6		
HO_7C_4	116.3				116.4			
HO_9C_8		117.5		117.5		117.6		
HN_1C_5	121.5	121.2	123.0	121.4			120.8	125.5
HC_5C_4	112.1	111.7	112.3	111.7	111.9	111.6	112.1	112.7
$HC_{10}C_8$	111.0	111.1	111.0	111.1	109.7	110.3	110.1	110.2
ΔH_f / kjoule mol^{-1}	—457.5	—473.7	—453.4	—475.2	—435.5	—450.0	—312.0	—317.3
D. M. / Debye	2.94	0.89	3.97	0.57	0.47	2.23	1.73	2.07

to be very useful in describing the structural features of molecules in our previous studies.[17–19,26,27]

In all keto-enol tautomers the σ-hybrid orbital directed from C_2 to C_3 exhibits a substantially higher s-character relative to the others. This is a consequence of rehybridization at the C_2 centre dictated by a shift of p-character[28] toward more electronegative oxygen and nitrogen atoms, respectively. Similarly, the s-characters of hybrids pointing from C_4 to O_7 and C_8 to O_9,

respectively, are significantly lower than the canonical sp^2 value. Concomitantly, s-characters of hybrids directed toward the neighbouring carbon atoms are increased relative to the sp^2-value. Tautomers B and D possess almost identical ring structures. The $C_4=O_7$ bond length appears to be slightly shorter than the $C_2=O_6$ bond distance in both forms in accordance with its higher π-bond order and a lower average s-character (Table II). Slight elongation of C_4O_7 bond on going from D to B is most probably a consequence of hydrogen bonding. Rotation of hydrogen around the C_8O_9 bond by 180° leads to a shortening of this bond by ca. 0.003 Å. The same effect is responsible for elongation of $C_2=O_6$ bond in tautomer D.

TABLE II

The s-characters of the Local Hybrid Orbitals and π-Bond Orders in 3-acetyltetramic Acid Tautomers as Calculated by the MNDO Method

Bond	Tautomer A	B	C	D	A′	B′
			s-character			
N_1C_2	27.3—29.7	27.4—30.3	26.5—29.0	27.3—30.3	13.8—33.3	14.1—33.8
C_2C_3	41.4—29.9	40.9—30.3	44.4—31.3	40.7—30.1	38.3—30.0	38.1—30.2
C_3C_4	33.2—39.6	30.6—35.4	31.2—37.4	30.8—35.6	32.5—38.7	30.0—34.2
C_4C_5	33.2—23.5	35.0—23.8	33.3—24.5	34.8—24.0	33.4—22.7	35.6—23.3
C_2O_6	29.6—10.6	29.7—10.6	27.0—12.9	29.7—10.6	27.1—12.6	27.2—12.5
N_1C_5	25.1—20.1	25.7—19.8	27.4—18.6	25.8—19.7	12.5—20.5	13.0—20.2
C_4O_7	25.2—13.1	27.7—11.4	28.0—11.2	27.7—11.4	25.2—13.3	27.5—11.5
C_3C_8	34.7—35.1	36.9—39.7	35.4—35.7	36.9—39.7	35.2—35.5	37.5—39.9
C_8O_9	26.3—11.4	23.2—13.3	26.3—11.4	22.1—13.2	26.1—11.5	22.8—13.1
C_8C_{10}	32.7—23.1	35.5—22.7	36.7—23.2	35.5—22.8	37.1—23.4	35.6—23.0
O_6H			15.1		13.7	13.7
O_7H	14.5				14.4	
O_9H		14.5		14.5		14.4
N_1H	28.5	28.3	29.7	28.3		
C_5H	28.4	27.9	28.0	27.9	28.1	27.6
$C_{10}H$	24.9	25.3	24.8	24.5	24.4	24.8
			π-Bond Orders			
N_1C_2	0.415	0.429	0.500	0.443	0.856	0.874
C_2C_3	0.226	0.226	0.678	0.233	0.270	0.236
C_3C_4	0.831	0.268	0.310	0.259	0.807	0.254
C_4C_5	0.142	0.131	0.124	0.128	0.153	0.135
C_2O_6	0.836	0.829	0.417	0.818	0.370	0.360
C_4O_7	0.431	0.904	0.896	0.911	0.444	0.907
C_3C_8	0.261	0.816	0.307	0.816	0.270	0.825
C_8O_9	0.900	0.436	0.884	0.438	0.899	0.427

The calculated structural parameters for tautomers A and C differ considerably, as expected on the basis of dissimilar molecular environment of enolized oxygen. Bond lengths indicate a more pronounced localization in tautomer C, as confirmed by calculated π-bond orders (Table II). Similarly, like in tautomers B and D, the bond length of the carbonyl group participating in hydrogen bonding is elongated by ca. 0.004 Å relative to the carbonyl which is not involved in hydrogen bonding.

The formation of lactim tautomers A′ and B′ is accompanied by a pronounced rehybridization of nitrogen (Table II). Due to the change of σ-bonding orbital to σ-lone pair, this orbital loses its p-character to a large extent. As a consequence, the other two hybrids involved in N_1C_2 and N_1C_5 bonds gain in p-character.

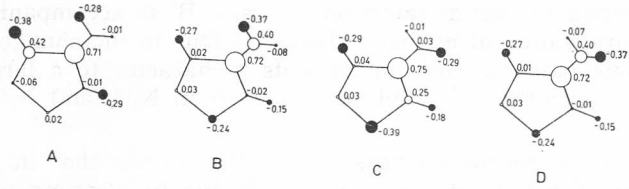
Analysis of the formal charges (Table III) reveals that in all tautomers nitrogen carries the highest negative charge due to a strong polarization of σ density toward this atom. Nitrogen acts, however, as π-electron donor in all keto-enol tautomers. In lactim tautomers nitrogen behaves as a π-electron acceptor. Among ring carbon atoms C_2, C_4 and C_5 are positively charged, the C_2 being the most positive in all tautomers. In contrast, C_3 atom is negatively charged. Carbonyl oxygens are negatively charged by ca. 0.35 | e |, while enolized oxygens carry a smaller fraction of negative charge by ca. 50%.

TABLE III

Formal Atomic Charges and π-Electron Densities (in parentheses) of 3-acetyltetramic Acid Tautomers as Calculated by the MNDO Method

Atom	Tautomer A	B	C	D	A′	B′
N_1	—0.464 (1.832)	—0.447 (1.822)	—0.379 (1.774)	—0.438 (1.813)	—0.370 (1.325)	—0.352 (1.294)
C_2	0.421 (0.744)	0.426 (0.743)	0.412 (0.767)	0.421 (0.739)	0.247 (0.841)	0.247 (0.852)
C_3	—0.328 (1.267)	—0.373 (1.305)	—0.456 (1.424)	—0.374 (1.306)	—0.306 (1.287)	—0.333 (1.290)
C_4	0.194 (0.819)	0.280 (0.727)	0.292 (0.745)	0.283 (0.735)	0.177 (0.803)	0.256 (0.725)
C_5	0.197 (0.941)	0.143 (0.938)	0.115 (0.945)	0.136 (0.938)	0.106 (0.957)	0.061 (0.955)
C_6	—0.345 (1.437)	—0.363 (1.446)	—0.240 (1.858)	—0.387 (1.463)	—0.237 (1.881)	—0.252 (1.886)
O_7	—0.219 (1.842)	—0.318 (1.346)	—0.302 (1.351)	—0.296 (1.331)	—0.210 (1.834)	—0.314 (1.342)
C_8	0.301 (0.719)	0.268 (0.776)	0.320 (0.712)	0.260 (0.778)	0.305 (0.718)	0.252 (0.793)
O_9	—0.351 (1.349)	—0.241 (1.843)	—0.384 (1.381)	—0.241 (1.842)	—0.359 (1.354)	—0.248 (1.849)
C_{10}	0.008	0.049	0.011	0.050	0.007	0.050
H_{11}	0.211	0.218	0.223	0.209	0.223	0.222
H_{12}	0.240	0.233	0.256	0.240	0.238	0.233
H_{CH_2}	0.031	0.026	0.038	0.026	0.060	0.046
H_{CH_3}	0.018	0.022	0.014	0.023	0.026	0.034

In view of recent interest[5–7] in the reactivity of 3-acetyltetramic acid it is of some interest to consider the composition of the frontier orbitals of the keto-enol tautomers. According to MNDO, the highest occupied orbital in all tautomers should be a π orbital. Its composition for A—D is given bellow:

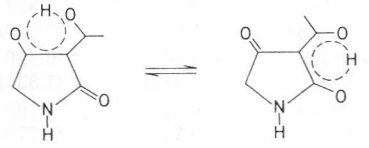


It appears that HOMO is predominantly localized at C_3 site. Thus, a frontier controlled electrophylic attack will be favoured at that position.[29,30] In contrast, composition of LUMO varies considerably from one tautomer to another. In tautomers B and D LUMO is predominantly localized at C_8, while in A and C forms LUMO shows its maxima at C_4 and C_2 positions, respectively. This indicates that the course of a frontier orbital controlled nucleophylic reaction will depend on the nature of the tautomer in question. Since tautomeric population is influenced by solvent polarity[12], the outcome of the frontier orbital controlled nucleophylic reactions might be strongly dependent on the solvent.

Energies

Calculations predict similar stabilities for all keto-enol tautomers depicted in Scheme I, with tautomer C being the least and tautomer D the most stable (see Table I). Rotation of the —OH group by 180° leads to a decrease in stability of all forms by ca. 20 kjoule mol^{-1}. Hence, the intramolecular hydrogen bonding is qualitatively well described by the standard MNDO method. This conjecture is supported by our extensive MNDO studies of intramolecular hydrogen bonded systems.[31] One should not confuse intramolecular with extramolecular hydrogen bonding. The latter is poorly reproduced by the MNDO procedure.[32]

»Symmetrical« tautomers (I and II) which can be considered as transition states for the interconversion of internal tautomers (A ⇌ B, C ⇌ D)



I II

have been also examined. It was found that they are significantly less stable than the unsymmetrical tautomers A — D (Table I). The calculated barrier height (~12 000 cm^{-1}) suggests that the »internal« interconversion would be a rather slow process in the gas phase. Among two equilibria mentioned above the process A → I → B is predicted to be slightly less favourable (by ca. 9 kjoule mol^{-1}) than its counterpart. In this connection it should be pointed out that the MNDO scheme overestimates the activation energy of the tautomeric process.[20,31] NMR studies seem to indicate that internal interconversions are rather fast because they were not* observed by the NMR measurements[10,13].

* See, however, ref. 12.

Lactim tautomers A' and B' are also considerable less stable (ca 22 kjoule mol^{-1}) than their lactam counterparts A and B, respectively.

Energetic properties are best discussed by the energy partitioning technique. It was pointed out first by Pople[33] that within the ZDO approximation the total energy can be decomposed in two contributions corresponding to monocentric and bicentric terms:

$$E_t = \sum_A E_A + \sum_{A<B} E_{AB} \quad (1)$$

We found it useful to decouple the two-centre term into bonding and nonbonding interactions. Hence, the formula (1) takes the form:

$$E_t = E_1 + E_2 + E_3' \quad (2)$$

where $E_1 = \sum_A E_A$, $E_2 = \sum_{A<B} E_{AB}$ and $E_3' = (1/2) \sum_A E_A^{nb}$. Here the second sum is extended over all directly bonded atoms, whereas the last term describes nonbonded repulsions, conveniently written as a sum over all atoms. For our purpose it will be useful to single out the energy of the intramolecular hydrogen bond(s), which would formally belong to the E_3 term, otherwise:

$$E_t = E_1 + E_2 + E_3 + E(O \ldots H) + E(N \ldots H) \quad (3)$$

Thermodynamic stabilities of tautomers are given by molecular heats of formation:

$$\Delta H_f^{mol} = E_t^{mol} - E_t^{pr} + \sum_A \Delta H_f^A \quad (4)$$

where $E_t^{pr} = \sum_A E_A^{fa}$ is a sum of electronic energies of free atoms. If one defines a promolecule as an ensemble of atoms brought to the equilibrium positions in such a way that all intraatomic interactions are neglected, then E_t^{pr} gives its total energy. The last term in eq. (4) represents heats of formation of free atoms. Since tautomers have the same number of constituent atoms, relative thermodynamic stabilities are determined by the differences in total energies. Perusal of the data displayed in Table IV shows that total

TABLE IV

Energy Decomposition in 3-acetyltetramic Acid Tautomers as Calculated by the MNDO Method

E / eV	Tautomer A	B	C	D	A'	B'
E_1	—1773.09	—1772.89	—1772.50	—1772.86	—1776.05	—1775.94
E_2	— 281.61	— 282.03	— 282.66	— 282.06	— 276.69	— 277.04
E_3	14.91	14.91	15.50	14.97	13.54	13.52
E_{OH}	—0.42	—0.35	—0.50	—0.44	—0.43	—0.34
E_{NH}	—	—	—	—	—0.34	—0.33
E_{tot}	—2040.21	—2040.37	—2040.16	—2040.39	—2039.97	—2040.12

energies are the result of an interplay of all terms and that relative differences are given by their delicate balance. In spite of the crudeness of the MNDO method, energy partitioning gives an interesting insight into energetic properties. For example, A′ and B′ forms are relatively unstable despite additional N...H hydrogen bond and a substantial decrease in one-centre energy and the nonbonded interactions. The reason is easily uncovered by considering the bicentric bonding term. It is dramatically increased mostly due to the relatively low $N_1 = C_2$ bond strength as compared to the $C_2 = O_6$ bond energy in A and B tautomers. It was mentioned earlier that π-bond orders indicate that delocalization is most pronounced in form C. This conjecture is substantiated by the analysis of the corresponding bicentric terms. More specifically, sums of two-centre bonding terms for N_1C_2, C_2C_3, C_3C_4, C_2O_6, C_4O_7, C_3C_8 and C_8C_9 bonds for A and C tautomers are —146.4 eV and —148.7 eV, respectively, indicating a better distribution of bond distances and increased delocalization energy in the latter compound. Nevertheless, tautomer A is more stable due to a decrease in E_1 and E_3 terms. Hence, MNDO energy partitioning is enlightening indeed in discussing molecular stabilities in simple and meaningful chemical terms.

Due to small differences in the calculated total energies between keto--enol tautomers of *1*, the solvent effect is expected to be extremely important in determining tautomers' population in solutions[34–37]. An estimate of the effect of solvent on the stability of tautomers may be attained by means of the continuum approach developed by Sinanoglu[35] and Rein[36]. According to this approach, the additional stability gained by the molecule in the environment of the solvent is given by:

$$E_{soln} = E_{gas} - 0.5\ f/(1 - f\,\alpha).\mu^2 \tag{5}$$

where E_{gas}, f, α and μ represent the energy of the molecule in gaseous phase, reaction field factor, polarizability and dipole moment, respectively. Reaction field factor is given by:

$$f = [(2\,\varepsilon - 2)/(2\,\varepsilon + 1)]/(1/\hat{a}^3) \tag{6}$$

where ε is the dielectric constant of the solvent and $\hat{a}$ is the radius of the spherical cavity containing the molecule. It is reasonable to assume that the cavity radii and polarizabilities are roughly constant[35] for considered tautomers. Hence, the ordering of the calculated dipole moments should be decisive. The latter indicates that forms A and C will be more influenced by the solvent effect in condensed media than forms B and D, respectively. More specifically, in the interconversion A ⇌ B, one would expect structure B to predominate by virtue of its ΔH_f value, and this was found to be the case in reference 7. Also, in strongly polar solvents, one would expect structure C to be stabilized relative to A by virtue of its μ value and hence the process C ⇌ D would be favoured over A ⇌ B. As mentioned earlier, the importance of solvent effects in determining the tautomeric ratio of 3-acetyltetramic acid was suggested on the basis of NMR measurements[11,12].

Small differences in stabilities of keto-enol tautomers are in agreement with the previously published CNDO/2 results[13], but the relative ordering of tautomers is different. The MNDO approach predicts tautomer D as the most stable form. On the contrary the CNDO/2 scheme suggests that tautomer

B is the most stable one. Furthermore, MNDO gives higher differences in stabilities between »internal« than between »external« tautomers in contrast to the CNDO/2 results. Due to the lack of experimental evidence for gas-phase equilibria of 3-acetyltetramic acid it is difficult to assess the validity of these two sets of results. Numerous previous studies of the prototropic equilibria of heterocyclic species have indicated that MNDO is more reliable in determining relative tautomerization energies than the CNDO/2 approach.[23,38] Therefore, it is not unreasonable to assume that this is also the case here. Some caution is in place, however, in wiev of the approximate nature of the MNDO scheme. It is worthwhile repeating these calculations using high quality ab initio methods. In this connection one should keep in mind that even highly sophisticated ab initio computations have to be empirically adjusted if reliable ΔH_f are desired.[39,40]

Conclusions

The relative stabilities of keto-enol and lactam-lactim tautomers of 3-acetyltetramic acid have been calculated by means of the MNDO method. The most important features of the calculated structures are discussed in terms of hybridization parameters and π-bond orders. Estimated heats of formation indicate that among keto-enol tautomers the exo-enol tautomeric pair B ⇌ D is by ca. 20 kjoule mol^{-1} more stable than the corresponding endo-enol tautomers. Lactim tautomers A′ and B′ appear to be less stable by ca. 22 kjoule mol^{-1} than their lactam counterparts. Differences in intrinsic stabilities of tautomers have been elucidated by the energy partioning technique. Importance of the solvent effects on tautomeric population has been stressed in earlier spectroscopic studies by other investigators. The calculated dipole moments indicate that tautomers A and C are more liable to stabilization through the interaction with solvent than the other tautomers.

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SAŽETAK

MNDO studij tautomerizacije 3-aciltetramske kiseline

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Primjenom MNDO metode izračunate su molekulske strukture i relativne stabilnosti keto-enol i laktam-laktim tautomera 3-aciltetramske kiseline. Izračunate topline stvaranja ukazuju da su u odsustvu otapala egzo-enol tautomeri (B i D) za cca. 20 kjoule mol^{-1} stabilniji od endo-enol tautomera (A i C). Isto tako laktam tautomeri su za 22 kjoule mol^{-1} stabilniji od odgovarajućih laktim tautomera. Razmatran je također i utjecaj solvatacijskih efekata na populaciju tautomera u otopini.