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Infrared study of some 2-substituted-6-hydroxy-4-pyrimidine carboxylic acids. Correlation with MO-calculations*

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The IR spectra of a series of 2-substituted-6-hydroxy-4-pyrimidine carboxylic acids (substituent = OH, SH, CH_3, CH_3S and NH_2) were studied from the aspect of the influence of the subsitutent on the polarizability of some bonds, keto-enol tautomerism and hydrogen bond formation. The spectra were taken using solids due to the low solubility of the acids. Theoretical calculations were done using the MNDO-AM1 semiempirical molecular-orbital method. The stabilities of various tautomers were calculated simulating the dielectric continuum using the COSMO facility of the MOPAC program package. Theoretical calculations were made for all the possible tautomers of the 2-substituted-6-hydroxy-4-pyrimidine carboxylic acids. For the most stable isomers, the vibrational spectra were calculated. For the majority of the compounds the most stable isomer was identified having the structure 2-Y-6-oxo-4-carboxy-3H-pyrimidine. Besides this structure, for the 2-amino-, and 2-methyl- derivatives the zwitterionic forms have very similar stability. The 2-hydroxy compound is most stable as the 2,6-dioxo-1H, 3H isomer. The calculated vibrations for the compounds with a single stable structure correlate very well with the experimental frequencies. For the 2-methyl- and 2-amino-compounds the correlation is considerably less satisfactory. The most probable reason for this deviation is the existence of two or more tautomets in equilibrium. The correlation of the measured frequencies and the pK_a values of the acids, indicate that the same tautomers exist in the solid state and in the solution.

Keywords: IR-spectra, pyrimidine-4-carboxylic acids, calculation of vibrational frequencies, AM1-MNDO.

INTRODUCTION

The interest in various pyrimidine carboxylic acids stems largely from their pharmacological action, byt little work has been done on their spectroscopic properties.[1] We undertook an investigation of the spectra of some 2-substituted-6-hydroxy-4-pyrimidine carboxylic acids (YHPC), especially in the COOH frequency region, which could offer an indication of the actual tautomeric form. The intention

* Dedicated to Professor Slobodan Ribnikar on the occasion of his 70th birthday

was to study the effects of substituents in position 2 of the pyrimidine nucleus on the spectral characteristics of YHPC and to correlate the IR frequencies with polar substituent constants. The obtained results could be useful for a better understanding of the reactivity of YHPC.

EXPERIMENTAL

The 2-substitutet-6-hydroxy-4-pyrimidine carboxylic acids (YHPC) (substituent Y =OH, SH, CH_3, CH_3S and NH_2) were synthesized by procedures reported in the literature[2,3] and their purity was checked by elemental analysis and m.p.s.

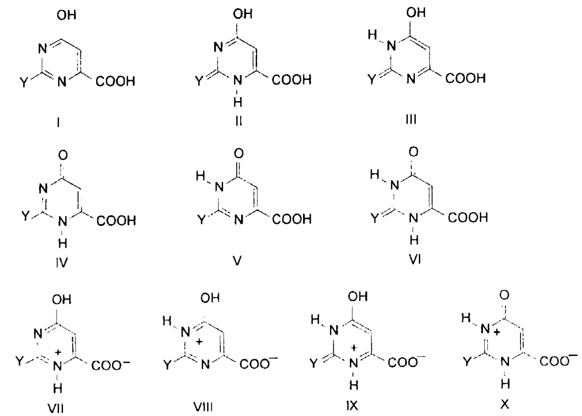
The IR spectra were taken on a Perkin-Elmer 983G spectrophotometer using the KBr pellets technique; about 150 mg of KBr per 1 mg of the sample. Only the solids were examined due to the low solubilities of the acids, hence comparisons with dilute solutions could not be made.

Method of calculation

In many previous studies,[4] the MNDO procedure has proven itself to be reliable for the study of molecular properties. The AM1 parameterization was used as a reliable method for atomic charges.[5,6] The MOPAC program package, Version 7.01 was used. The optimized geometries of all the molecules were obtained by the force field minima in vacuum, according to the AM1 method. The effect of a dielectric continuum with a corresponding dielectric constant was simulated using the COSMO model implemented in MOPAC.[7] For the most stable tautomers, the vibration spectra were also calculated.

RESULTS AND DISCUSSION

YHPC may exist in various tautomeric forms I-X (Scheme 1) and may form intra- and intermolecular hydrogen bonds of the type –NH···O=C– or –OH···O=C–. Therefore, the spectra of these compounds often are complex, and despite the structural similarity of the compounds, the spectra do not show any common pattern.



Scheme 1.

All the acids are highly associated in the solid state. The obtained bands in 4000–2500 cm^{-1} region have a complex structure, and, therefore, the attained bands were numerically resolved. The low frequency of the N–H band, as well as the very low frequency of the OH band, reflects the strong hydrogen bonding in the solid state (Table I). The hydrogen bond is the strongest in the cases of substituent Y=H or OH. In addition, the IR spectrum of Y=NH_2, in this region, is markedly different from the spectra of the other YHPC's, and the bands in the spectrum indicate very strong hydrogen bonding. In the IR spectrum a strong, broad band in the region 3700–2500 cm^{-1} is evident. Only the compound with Y=NH_2 has a strong band at 3321 cm^{-1}, which is assigned to $\nu(NH_2 \cdots OH)$. On the other hand, the CH_3 and CH_3S substituted acids have specific spectra with less pronounced hydrogen bonding. (Reduced tautomerism).

TABLE I. Characteristic IR frequencies (cm^{-1}) of 2-substituted-6-hydroxy-4-pyrimidine carboxylic acids in the 4000–3100 cm^{-1} region

Vibrational assignment	Substituents					
	SH	CH_3	CH_3S	OH	H	NH_2
ν(OH)	3560(*w*)	3533(*w*)	3529(*w*)	3512(*w*)		3520
ν(OH···O)	3430(*w*)	3423(*w*)	3419(*w*)	3417(*m*)	3441(*s*)	
ν(OH···O)					3330(*m*)	
ν(OH···O)	3200(*m*)	3250(*w*)	3212(*w*)	3233(*m*)	3247(*m*)	
$\nu(NH_2 \cdots H)$						3321(*s*)
H stretch	3107(*s*)	3100(*m*)	3113(*m*)	3159(*s*)		3120(*m*)
H stretch		3055(*m*)			3030(*s*)	
ν(OH···O)	2943(*s*)	2929(*s*)	2933(*m*)			2957(*s*)
ν(OH···O)			2843(*m*)	2809(*m*)	2799(*s*)	2780(*m*)
ν(OH···O)	2611(*m*)	2569(*w,b*)	2590(*m*)	2486(*m*)	2627(*s*)	2430(*b*)
ν(OH···O)			2486(*m*)			
ν(OH···O)	1906(*w*)	1982(*w,b*)		1850(*w,b*)	1912(*s*)	1960(*w,b*)

In the 1800–1400 cm^{-1} region, bands due to the stretching vibrations of C=O, COO^-, COOH groups, ring vibrations, as well as bending vibrations of the N–H bonds, are to be expected. The variation in the frequencies of the key bands with change of polar character of the bonds and various special interactions make the appearance of these bands large and well-structured, so different assignments are possible. Furthermore, the intensities of the ring vibrations depend on the equilibrium between different tautomeric structures. Therefore, the bands recorded in this region (1800–1500 cm^{-1}) have a complex structure. So, the attained bands are resolved and the Lorentz-Gaussian function was employed for deconvolution of the bands. An example is shown in Fig. 1. On the basis of the band areas, an estimation of the intensities of the bands was made. The frequencies and the intensities of the derived bands are listed in Table II. Beyond the basic assignments of the COOH, C=O and COO^- groups it is difficult to interpret further details of the complex infrared spectra.

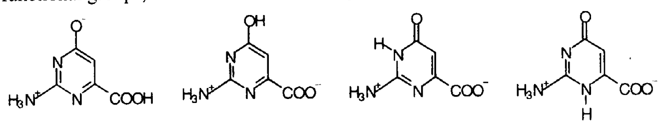
A marked similarity exists in the 1800–1400 cm^{-1} region of the spectra of the acids with Y=CH_3 and CH_3S. The bands at 1705 cm^{-1} and 1681 cm^{-1} (Y=CH_3 and CH_3S, respectively) are related to the stretching frequencies of the lactam C=O group. The lack of a band at about 1733 cm^{-1} and the presence of a strong band related to the carboxylate anion indicate that the carboxyl is to a high degree dissociated. Therefore, it is safe to assume that in the solid state these acids are predominantly in the tautomeric form X.

TABLE II. Characteristic IR frequencies (cm^{-1}) of 2-substituted-6-hydroxy-4-pyrimidine carboxylic acids in the 1750–1500 cm^{-1} region

Vibration assignment	Substituents					
	SH	CH_3	CH_3S	OH	H	NH_2
ν(C=O)	1733(*m*)	1746(*w*)	1735(*sh*)	1723(*m*)	1733(*s*)	1730(*sh*)
		1714(*w*)	1718(*sh*)	1703(*m*)	1712(*m*)	1725(*sh*)
ν(C=O) ring	1660(*m*)	1705(*vs*)	1681(*s*)	1680(*m*)	1686(*m*)	1681(*vs*)
ν(COO)*	1641(*s*)	1648(*m*)	1654(*m*)	1647(*s*)	1664(*s*)	
		1631(*m*)	1673(*s*)		1645(*m*)	1647(*w*)
					1628(*m*)	
ν(NH) ring vibrations	1601(*m*)	1606(*vs*)	1613(*w*)	1607(*m*)	1607(*m*)	
	1587(*w*)	1586(*w*)	1573(*w*)	1580(*w*)	1583(*m*)	
	1556(*s*)					

*Carboxylate vibrations could arise from zwitterionic forms. Otherwise, the splitting of the carbonyl vibrations results from the lattice effect in solid state

It should be noticed that the spectrum of YHPC with Y=NH_2 shows in this region a strong band. Due to the mentioned intermolecular interactions of the functional groups, the broad band in this region is symmetrical.



XI XII XIII XIV

Scheme 2.

The spectra of the acids with Y=H, OH or SH are more complex. This can be explained in the case Y=OH and SH by the fact that the OH and SH groups are capable of prototropic change enabling the possibility of more tautomeric structures, and giving rise to increased electron availability at the nitrogen atom, which facilitates tautomeric change. The strong band at about 1730 cm^{-1} of the carboxyl carbonyl, the presence of the lactam band, as well as the bands of the carboxylate anion, indicate an equilibrium between structures VI and X for Y=SH and OH, and equilibrium between structure V and X for Y=H.

For the explanation of the experimental data, quantum chemical calculations of the vibrational frequencies were performed. The possible tautomeric forms of 2-substituted-6-hydroxy-4-pyrimidine carboxylic acids are given in Scheme 1. The values of the enthalpies of formations calculated for the possible tautomers are given in Table III. Additional zwitterionic structures for the 2-amino derivative are given in Scheme 2.

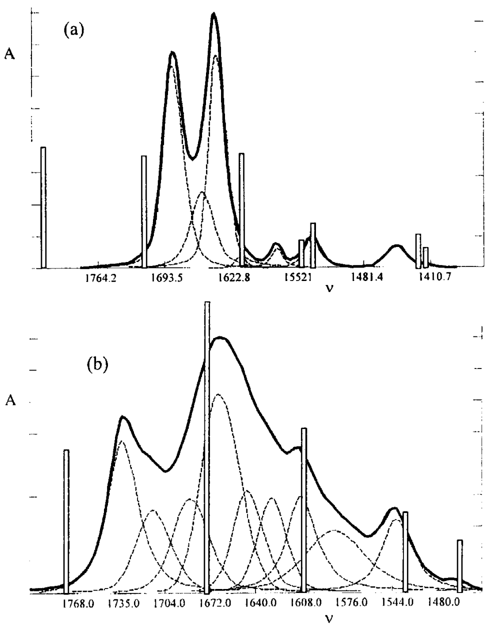


Fig. 1. Infrared spectra of YHPC in the 1800–1500 cm^{-1} range: a) Y=H, and b) Y=CH_3S. The vertical bars are (not scaled) theoretical values. Their height is proportional to the calculated transition dipole. The dashed lines are result of numerical deconvolution of the experimental curve.

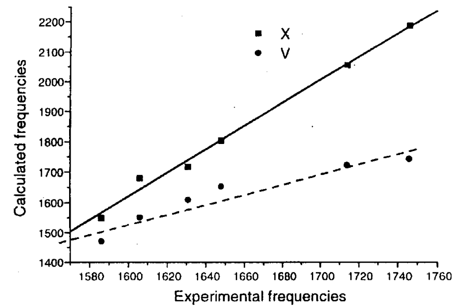


Fig. 2. Correlation of the experimental and the calculated frequencies of two tautomeric forms of 2-methyl-6-hydroxy-4-pyrimidine carboxylic acid.

The analysis of the calculation results leads to the same conclusion as those obtained from the analysis of the IR spectra. In the case of YHPC (Y=CH_3), very similar values of $\Delta_f H$ are obtained for structures V (r=0.953) and X (r=0.996). Compared with the spectral data, structure V is less probable due to the absence of the carboxyl carbonyl band in the spectrum.

The calculated data are also in agreement with the proposed structure on the basis of the analysis of their IR spectra for Y = CH_3S (r=0.984). Concerning the heat of formation of 6-hydroxy-4-pyrimidine carboxylic acid, the similar values for the structure V (r=0.966) and X (r=0.964) are in accordance with the equilibrium proposed on the basis of their IR spectra. For the acids with Y = SH or OH, the calculated values favor structure VI.

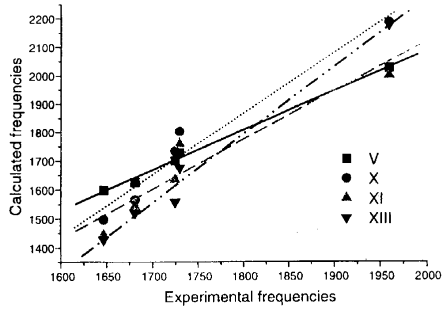


Fig. 3. Correlation of the experimental and the calculated frequencies of four tautomeric forms of 2-amino-6-hydroxy-4-pyrimidine carboxylic acid. V, r=0.998; X, r=0.978; XI, r=0.950; XIII, r=0.992.

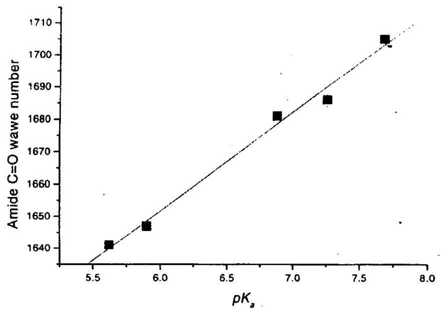


Fig. 4. Correlation of the experimental frequencies of the amide carbonyl group in 2-substituted-6-hydroxy-4-pyrimidine carboxylic acids and the pK_a values of the acids (r=0.995). The value for Y=NH_2 is lacking because of its poor solubility in water and DMSO.

TABLE III. Enthalpies of formation (kcal/mol) for the tautomers of 2-substituted-6-hydroxy-4-pyrimidine carboxylic acids in polar dielectric medium

Struct.	Substituent							
	SH	CH_3	CH_3S	OH	H	NH_2		
I	–100.020	–108.192	–105.538	–122.209	–102.893	–101.538		
II	–96.628			–148.571		–88.109		
III	–96.585			–150.462		–88.726		
IV	–105.573	–99.792	–105.939	–144.760	–105.334	–106.676		
V	–95.235	–108.387	–110.751	–151.580	–112.408	–112.004		
VI	–111.908			–162.207		–101.084	*Struct.*	
VII	–88.445	–103.349	–95.723	–139.557	–96.661	–95.324	XI	–105.031
VIII	–85.307	–96.955	–94.834	–141.064	–94.727	–97.533	XII	–98.770
IX	–86.969			–150.540		–83.494	XIII	–108.382
X	–91.631	–111.087	–101.263	–141.205	–109.466	–108.658	XIV	–96.101

There is many reports that the calculated vibrational spectra are fairly close to the experimental ones, after inclusion of a scaling factor.[8] A comparison of the experimental spectra and the theoretically calculated vibrations (without scaling) is given in Fig. 1. For the acids which have a single stable structure (Y= SH, OH, CH_3S and H) there is very good correlation between their calculated and measured IR spectra. For acid with Y= CH_3 the correlation of the calculated spectra for the forms V and X are shown in Fig 2. The much better correlation for the X form indicates the dominance of the zwitterionic structure. A similar correlation for 2-amino-6-hydroxy-4-pyrimidine carboxylic acid (Fig. 3), is in accord with the assumption that forms V (r = 0.998), X (r = 0.978) and XIII (r = 0.992) exist in equilibrium.

For the bands of the C=O lactam group, a linear correlation (Fig. 4) of band frequencies and pK_a values of the acids[10] has been found, too:

$$\nu = 1467.8 + 30.6\, pK_a \quad r = 0.995$$

CONCLUSION

On the basis of the theoretical calculations and the analysis of the IR spectra of 2-substituted-6-hydroxy-4-pyrimidine carboxylic acids, the most probable tautomeric forms of the acids in the solid state have been proposed. The good correlation of the calculated and experimental IR frequencies of the three bands of the carboxylic groups, as well as of the experimental frequencies and pK_a values of the acids, indicate that the relative stability of the tautomers in solutions is the same as in the solid state. Moreover, the comparison of the experimental and the calculated vibrational spectra enables a reliable prediction of the structure of the investigated molecules.

ИЗВОД

ИНФРАЦРВЕНИ СПЕКТРИ НЕКИХ 2-СУПСТИТУИСАНИХ 6-ХИДРОКСИ-4-ПИРИМИДИН КАРБОКСИЛНИХ КИСЕЛИНА. КОРЕЛАЦИЈА СА МО-ИЗРАЧУНАВАЊИМА

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IC спектри серије 2-супституисаних 6-хидрокси-4-пиримидин карбоксилних киселина (супституент = OH, SH, CH_3, CH_3S и NH_2) проучавани су са аспекта утицаја супституената на поларизабилност неких веза, кето-енолну таутомерију и формирање водоничних веза. Снимљени су спектри чврстих узорака због мале растворљивости киселина. Теоријска израчунавања урађена су применом MNDO-AM1 семиемпиријске молекулско-орбиталне методе. Стабилност различитих таутомера израчуната је симулацијом диелектричног континуума коришћењем COSMO процедуре у MOPAC програмском пакету. Теоријска израчунавања су извршена за све могуће таутомере 2-супституисаних 6-хидрокси-4-пиримидин карбоксилних киселина. За најстабилније изомере израчунати су вибрациони спектри. За већину једињења идентификован је само један најстабилнији изомер, онај који има структуру 2-Y-6-оксо-4-карбокси-3H-пиримидина. Поред ове структуре, за 2-амино-, и 2-метил- деривате цвитерјонски облици имају сличну стабилност. Једињење 2-хидрокси- је најстабилније као 2,6-диоксо-1H, 3H изомер. Израчунате вибрације за једињења са једном стабилном структуром корелишу веома добро са експерименталним фреквенцама. За 2-метил- и 2-амино- једињења корелација је знатно мање задовољавајућа. Највероватнији разлог за ово одступање је постојање два или више таутомера у равнотежи. Корелација измерених фреквенци и pK_a вредности киселина показује да су исти таутомери присутни у чврстом стању и у раствору.

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