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IR, Raman and theoretical ab initio RHF study of aminoglutethimide — an anticancer drug

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Abstract

A comparative analysis of the IR and Raman spectra of aminoglutethimide (AG) dissolved in CCl_4, $CHCl_3$ and CH_3CN was performed. Most of the absorption bands were assigned to characteristic group vibrations with the use of the IR and Raman spectra of deuterated AG, glutethimide, *N*-methyl glutethimide and glutarimide. The AG samples very weakly interacting with the environment were studied with the use of the Ar matrix isolation IR spectra. For comparison, the IR and Raman spectra of the crystalline samples formed by hydrogen-bonded AG molecules were recorded. The spectra were analyzed also in terms of normal modes and the harmonic approximation with the use of the ab initio restricted Hartree-Fock theory. It was found that increasing the solute concentration in CCl_4 and $CHCl_3$ leads to formation of the autoassociates. In CH_3CN the solute–solvent AG–CH_3CN dimers occur. Possible structures of the associates were theoretically studied on the model systems: the centrosymmetric glutarimide dimer and the linear AG–CH_3CN dimer. By a comparison of the theoretical and experimental spectra we were able to identify several peaks originating from the solute–solvent interactions. © 1998 Elsevier Science B.V.

Keywords: IR spectroscopy; Raman spectroscopy; Ab initio calculations; Aminoglutethimide; Anticancer drugs

1. Introduction

Aminoglutethimide (AG, see Fig. 1), is used as an efficient agent for the treatment of advanced breast cancer in post menopausal women [1–4].

A close structural analog of AG, glutethimide (GT, see Fig. 1) exhibits sedative–hypnotic activity [4].

It is commonly believed that AG inhibits aromatase (a cytochrome P-450, EC 1.14.13), an enzymatic complex catalyzing biochemical transformation of androgens to estrogenic steroids, which in turn arrests cancer cell development [5–9]. It was suggested that at the initial stages of interaction with the enzymatic complex the AG phenylamine nitrogen lone pair electrons interact with the Fe^{3+} haem of the cytochrome P-450. Simultaneously, the AG imide moiety interacts via a hydrogen bond network with the carbonyl C=O region of the P-450 active site [10].

Basic physical and chemical properties of AG have been known since the early 1950s [11] but more detailed characteristics of AG, its molecular structure and its interactions with the surrounding molecules are still unknown. The present work attempts to extend the knowledge of AG by means of spectroscopic and theoretical studies.

AG appears in two enantiomeric forms, R(+) or

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D-form and S(−) or L-form. The dextrorotatory R(+) enantiomer is of pharmacological particular interest because it inhibits aromatase 2–3 times more strongly than the racemate and about 10–30 times more strongly than the levorotatory S(−) enantiomer [7,11].

AG is a polar molecule and has a dipole moment of 2.83 D (in dioxane at 30°C) [11]. It can interact with the surrounding molecules primarily via a moderate-strength hydrogen bond network. AG is virtually insoluble in water, but is freely soluble in chloroform, methanol and many organic solvents. It can be crystallized in two polymorphic forms [12]. In the elementary cell a pair of AG molecules forms a double centrosymmetric hydrogen bond.

An AG methanol–water solution has pH of 6.2–7.3 that may result from the simultaneous presence of a weakly acidic imide NH moiety and a basic phenylamino group. The latter group is probably responsible for the formation of a hydrochloride salt (CAS 31075-85-1).

The IR spectrum of AG in Nujol mull was tentatively assigned in 1961 [13]. The present work reveals that in high frequency spectral regions the assignment must be corrected owing to intermolecular interactions not considered carefully enough in the earlier studies.

In the present paper we focus on the vibrational spectra of AG immersed in a series of solvents of variable polarity and different proton donor–acceptor properties. The concentration-dependent spectra were studied with particular emphasis on the possible formation of hydrogen-bonded species. The results may shed more light on the details of the AG intermolecular interactions with the receptor site located on aromatase backbones.

2. Methods

2.1. Experimental

The AG samples were obtained from the production unit of the Pharmaceutical Research Institute Warsaw.

N-Methylglutethimide was obtained via the following condensation procedure. A mixture of GT (1 g, 0.0046 mol), finely powdered potassium hydroxide (0.55 g), potassium carbonate (1.90 g) and 18-crown-6 (20 mg) in toluene (25 ml) was stirred and refluxed for 15 min. Then a solution of iodomethane (0.718 g, 0.0051 mol) in toluene (10 ml) was added dropwise and the mixture was refluxed for 6 h. The inorganic precipitate was filtered off and the filtrate was evaporated. The oily residue was purified by SiO_2 chromatography ($CHCl_3$) and the product was crystallized from ethyl acetate. Yield: 0.107 g (10%).

The solutions of *N*-deuterated derivative of AG and GT were prepared by dissolving the appropriate amount of sample (AG or GT) in 5 ml of $CDCl_3$, adding 1 ml of D_2O and shaking for 1 h. Next, the $CDCl_3$ layer was dried by adding 1 g of anhydrous sodium sulfate and used directly for IR and Raman measurements.

The IR spectra were recorded on a Perkin-Elmer FT-IR 1725X spectrometer. Solid samples were measured in KBr pellets. The IR spectra of the solutions (in CCl_4, $CHCl_3$, $CDCl_3$, CH_3CN) were measured in KBr cuvettes with variable path length (0.044–0.91 mm) depending on the concentration of the sample. A spectral resolution of 4 cm^{-1} was used.

The Raman spectra were recorded on a Perkin-Elmer FT-IR 2000 system equipped with a Raman accessory using a diode-pumped Nd:YAG laser (1064 nm) as an excitation source. Solid samples and the solutions (in CCl_4, $CHCl_3$, $CDCl_3$, CH_3CN) were measured in capillary tube. For most diluted solutions a fluorescence cuvette was used for the measurements to maximize the Raman signal. A spectral resolution of 4 cm^{-1} was used.

The low temperature Ar matrices were prepared by depositing the sample and Ar gas on the cold tip of the cryostat [Displex closed cycle refrigerator (APD Cryogenics Inc.)] maintained at 12 K.

2.2. Theoretical chemistry

The ab initio restricted Hartree–Fock (RHF) method with the standard Gaussian basis sets (6-31G**, 6-31G*, 3-21G) implemented in the Gaussian 94 code [14] was used. The Berny algorithm was employed for the optimization of molecular geometry expressed in terms of the bond lengths, valence bond angles and tetrahedral angles. Standard convergence criteria were used to terminate the geometry optimization process. The normal modes of molecular vibrations were calculated with the use of the analytical second derivatives of the total molecular energy, with respect to the nuclear displacements, for the optimal

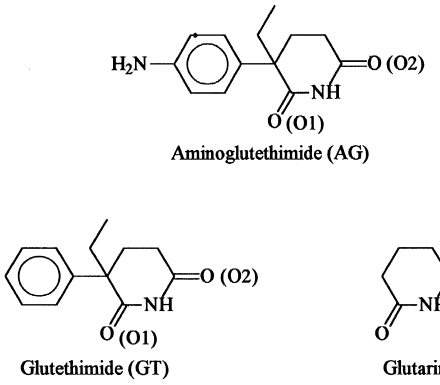

Fig. 1. Aminoglutethimide (AG), 3-(4-aminophenyl)-3-ethyl-2,6-piperidinedione, $C_{13}H_{16}N_2O_2$, CAS 125-84-8; glutethimide (GT), 3-ethyl-3-phenyl-2,6-piperidinedione, $C_{13}H_{15}NO_2$, CAS 77-21-4; glutarimide (G), 2,6-piperidinedione, $C_5H_4NO_2$, CAS 1121-89-7. Oxygen atom labelling in AG and GT is given in parentheses.

structure. A factor of 0.9 was used to scale down uniformly the calculated frequencies of the normal modes.

The solvent effect on the calculated vibrational spectra was estimated with the use of the Onsager continuum solvent model [15] implemented in the Gaussian 94 code. The theoretical calculations were performed on an IBM RISC 6000 workstation and CRAY YMP supercomputers.

3. Results and discussion

3.1. Experimental vibrational spectra

The IR and Raman spectra of AG can be analyzed in a few regions where a number of bands corresponding to characteristic vibrations related to group frequencies can be inspected in details. In the high

Table 1
Rac-aminoglutethimide (AG). The N–H stretching region

Environment	Solvent	Method	Frequencies (cm^{-1}) and relative intensities [a]				
			Conc. of AG (% m/v)				
Solutions	CCl_4	IR	0.1	3485(w),	3401(sh-w),	3380(m)	
	CH_3CN	IR	4	3463(m),	3376(m),	3269(m-bb)	
		Raman	4		3378(m)		
	$CHCl_3$	IR	0.2	3490(w),	3400(sh-w),	3370(m)	
			2	3490(w),	3400(sh-w),	3369(m),	3210(w-bb), 3102(w-bb)
	$CDCl_3$	IR	2	3486(w),	3400(sh-w),	3370(m),	3212(w-bb), 3100(w-bb)
	N-deuterated AG [b] $CDCl_3$	IR	2		not detected		
Crystals	polymorphic form I [b]	IR (KBr pellet)		3472(m),	3378(s),		3212(sh-m), 3181(m-bb), 3089(m-bb)
		Raman		3471(w),	3376(s),		3222(w)
	polymorphic form II [b]	IR (KBr pellet)		3433(m),	3356(s),		3227(s-bb), 3104(w-bb)
		Raman		3433(w),	3356(s),		3232(w-bb)
Ar matrix		IR		3505(w),	3385(w),	3399(m)	
Calculated [d] (ab initio RHF/6-31G**)		IR		3524(20),	3427(30)	3454(80)	
				$\nu^a(NH_2)$	$\nu^s(NH_2)$	ν(NH)	
		Raman		3524(70),	3427(170)	3454(80)	

[a] w, weak; m, medium; s, strong; sh, shoulder; bb, broad band.

[b] *N*-deuterated AG denotes the *N*-deuterated rac-aminoglutethimide dissolved in a given solvent.

[c] Rac-aminoglutethimide can be crystallized in two polymorphic forms, I and II, which exhibit different X-ray structures, IR spectra and DSC curves [12].

[d] ν, stretching; s, symmetric; a, antisymmetric.

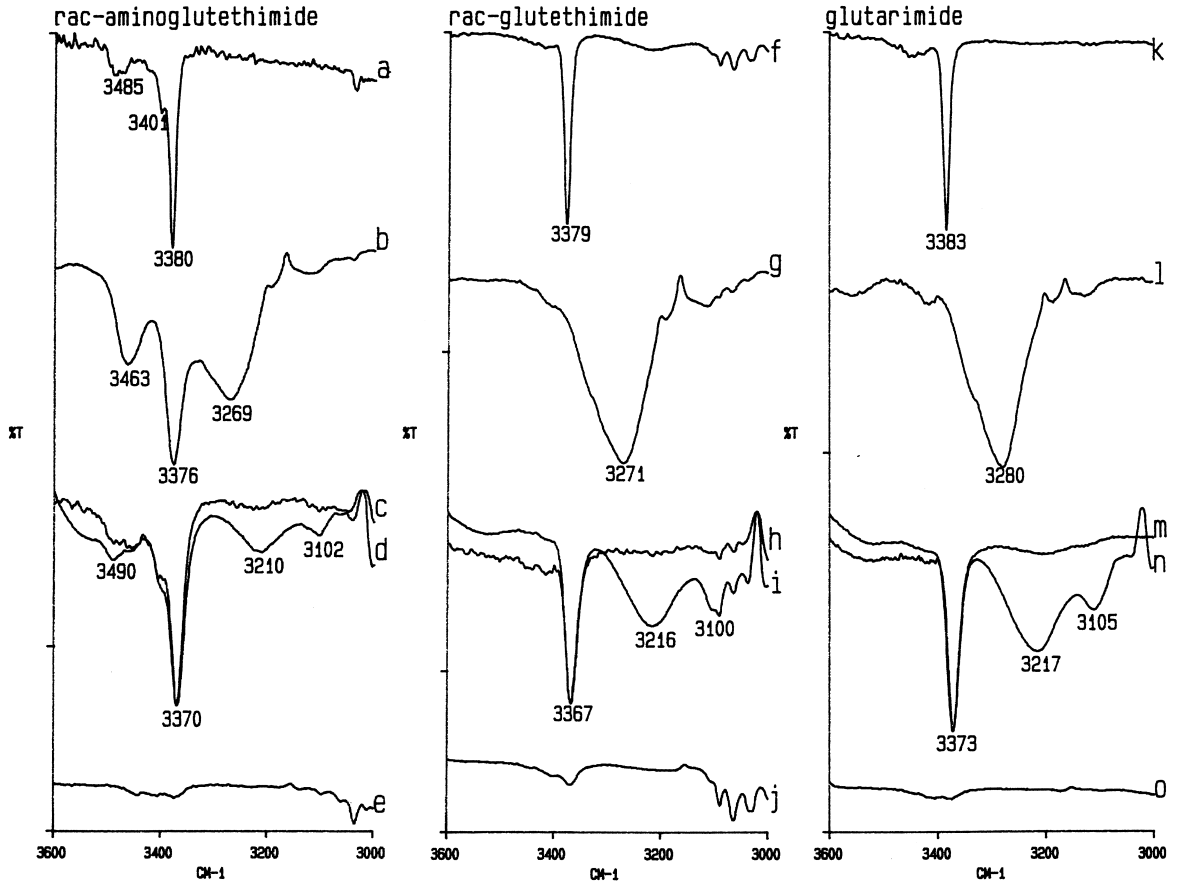

Fig. 2. The N–H region. IR spectra of: (a) < 0.1% (m/v) CCl_4 solution of rac-aminoglutethimide; (b) 1% (m/v) CH_3CN solution of rac-aminoglutethimide; (c) 0.2% (m/v) $CHCl_3$ solution of rac-aminoglutethimide; (d) 2% (m/v) $CHCl_3$ solution of rac-aminoglutethimide; (e) 2% (m/v) $CDCl_3$ solution of N-deuterated rac-aminoglutethimide; (f) 0.1% (m/v) CCl_4 solution of rac-glutethimide; (g) 1% (m/v) CH_3CN solution of rac-glutethimide; (h) 0.2% (m/v) $CHCl_3$ solution of rac-glutethimide; (i) 8% (m/v) $CHCl_3$ solution of rac-glutethimide; (j) 8% (m/v) $CDCl_3$ solution of N-deuterated rac-glutethimide; (k) < 0.1% (m/v) CCl_4 solution of glutarimide; (l) glutarimide 1% (m/v) CH_3CN solution of; (m) 0.2% (m/v) $CHCl_3$ solution of glutarimide; (n) 4% (m/v) $CHCl_3$ solution of glutarimide; (o) 4% (m/v) $CDCl_3$ solution of N-deuterated glutarimide.

frequency region, above 2900 cm^{-1}, N–H stretches, aliphatic and aromatic C–H stretches are present in the spectra. Another spectral region between 1800 and 1650 cm^{-1} contains information about carbonyl stretches of the imide moiety. Most of the bands in the IR and Raman spectra are present in the next spectral region between 1650 and 400 cm^{-1}. They originate from simultaneous vibrations of many different molecular fragments and can be assigned with the help of a theoretical quantum chemical treatment. The N–H and C=O stretching vibrations regions are most interesting because of their intrinsic sensitivity to intra- and inter-molecular interactions.

The IR spectra are more sensitive to hydrogen bonding and polar intermolecular interactions than the corresponding Raman spectra but a real insight into the nature and symmetry of some vibrational modes can be achieved only by application of both experimental methods supported by theoretical spectra.

3.1.1. The N–H stretching region

The IR spectra of AG in different solvents, in the N–H stretching region are shown in Fig. 2(a)–(e). For comparison, data concerning frequencies and intensities of the observed IR and Raman bands for AG, GT

Table 2
Rac-glutethimide (GT). The N–H stretching region

Environment		Method	Frequencies (cm^{-1}) and relative intensities [a]	
	Solvent		Concentration of GT (% m/v)	
Solutions	CCl_4	IR	0.1	3379(m)
		Raman	0.5	3378(w)
	CH_3CN	IR	4	3271(m)
	$CHCl_3$	IR	0.2	3368(m)
			8	3367(m), 3216(m-bb), ≈ 3100(m-bb)
		Raman	8	3369(m)
	$CDCl_3$	IR	8	3368(m), 3217(m-bb), ≈ 3100(m-bb)
		Raman	8	3369(w)
	N-deuterated GT[b] $CDCl_3$	IR	8	not detected
		Raman	8	not detected
	N-methylated GT[c] $CHCl_3$	IR	4	not detected
		Raman	4	not detected
Crystals		IR (KBr pellet)		3192(m-bb), 3141(m), 3090(m-bb)
		Raman		3194(w), 3160(w)
Ar matrix		IR		3402(m)
Calculated [d] (ab initio RHF/3-21G)		IR		3382(80) ν(NH)
		Raman		3382(90)

[a] w, weak; m, medium; s, strong; sh, shoulder; bb, broad band.
[b] *N*-deuterated GT denotes the *N*-deuterated rac-glutethimimide dissolved in a given solvent.
[c] *N*-methylated GT denotes the *N*-methyl-rac-glutethimide dissolved in a given solvent.
[d] ν, stretching.

and G in different solvents, solid state, in Ar matrices and those theoretically predicted by the ab initio calculations are gathered in Tables 1–3. Diluted solutions of AG in CCl_4 (Fig. 2(a)) reveal three bands at 3485, 3401 and 3380 cm^{-1}. They can be assigned to two N–H stretches of the amine group and one N–H stretch of the imide group with the help of the corresponding spectra of GT and G which play roles of model compounds not containing amino group. The GT and G spectra are shown in Fig. 2(f)–(j) and Fig. 2(k)–(o), respectively. Only one strong sharp band is present in the GT and G spectra at 3379 and 3383 cm^{-1}, respectively, which is readily assigned to the N–H stretching mode of the imide group in the model compounds. By analogy, the AG strong band at 3380 cm^{-1} placed at nearly the same frequency as in the GT and G spectra should correspond to the imide N–H stretching mode.

In CH_3CN solution, the band corresponding to the imide N–H stretch is shifted to lower frequencies by 111 cm^{-1} and it appears as a broad band centered at 3269 cm^{-1} (Fig. 2(b)). A similar shift of the imide N–H stretch is observed in the spectra of the GT and G (Fig. 2(g) and (l)) solutions in CH_3CN. The two other bands in the AG spectrum assigned to N–H stretches of the amino group are also shifted to lower frequencies by 22 and 25 cm^{-1} and they become broad and intense. Taking into account the significant shift and broadening of the imide N–H band in CH_3CN with respect to the CCl_4 solution spectrum, one can expect that the imide proton (slightly acidic) should be involved in presumably linear hydrogen bonding with the basic N atom of the solvent CH_3CN molecule. The AG amino group seems to be affected by CH_3CN solvent to a much smaller extent.

Because of the better solubility of AG in $CHCl_3$ than in CCl_4 an influence of the AG concentration on the IR spectra has been studied in $CHCl_3$ solution.

Table 3
Glutarimide (G). The N–H stretching region

Environment		Method	Frequencies (cm^{-1}) and relative intensities [a]	
	Solvent		Concentration of G (% m/v)	
Solutions	CCl_4	IR	0.05	3383(m)
	CH_3CN	IR	4	3280(m)
	$CHCl_3$	IR	0.05	3372(m)
			4	3373(m), 3216(m-bb), 3110(m-bb)
	$CDCl_3$	IR	0.05	3373(m)
			4	3373(m), 3217(m-bb), 3105(m-bb)
	N-deuterated G [b] $CDCl_3$	IR	4	not detected
	N-methylated G [c] $CHCl_3$	IR	4	not detected
Crystals		IR (KBr pellet)		3191(m-bb), 3106(sh-m), 3091(m-bb)
Ar matrix [d]		IR		3046(m)
Calculated [e] (ab initio RHF/6-31G**)		IR		3455(80) ν(NH)
		Raman		3455(70)

[a] w, weak; m, medium; s, strong; sh, shoulder; bb, broad band.
[b] *N*-deuterated G denotes the *N*-deuterated glutarimide dissolved in a given solvent.
[c] *N*-methylated G denotes the *N*-methyl-glutarimide dissolved in a given solvent.
[d] Table 3 in Ref. [16].
[e] ν, stretching.

The IR spectra of diluted CCl_4 and $CHCl_3$ solutions are very similar. However, when the concentration of AG is increased, new broad bands are observed at 3210 and 3102 cm^{-1} in $CHCl_3$ solution (Fig. 2(c) and (d)). They probably originate from autoassociates bound by hydrogen bonding. The presence of such bands is also noticed in the spectra of concentrated solutions of GT and G in $CHCl_3$ shown in Fig. 2(h) and (i) and Fig. 2(m) and (n), respectively. It is also important to emphasize that these autoassociates are observed neither in concentrated solutions of AG, GT and G in CH_3CN (where the N–H group interacts strongly with a single solvent molecule), nor in their *N*-methylated analogs (where the N–H moiety is absent). Therefore their origin is obviously associated with an N–H moiety involved in hydrogen bonding. After deuteration of the AG, the high frequency bands (characteristic for both the monomer and the autoassociates) disappear (Fig. 2(e), (j), (o)) and they are moved to a region close to 2500 cm^{-1}. The structure of possible autoassociates and the assignment of the corresponding IR spectra in the N–H region will be discussed in Section 3.2.

3.1.2. The C=O stretching region

The IR spectra of AG in different solvents are shown in Fig. 3(a)–(c). For comparison, data concerning frequencies and intensities of the observed IR and Raman bands in the C=O stretching region for AG, GT and G in different solvents, solid state, in Ar matrices and those theoretically predicted by the ab initio calculations are collected in Tables 4–6. In diluted solution of AG in CCl_4 (Fig. 3(a)) two bands are observed at 1731 and 1714 cm^{-1} which can be assigned to the C=O stretches. In CH_3CN solution these bands are downshifted to 1723 and 1707 cm^{-1} (Fig. 3(b)) and in $CHCl_3$ solution to 1724 and 1704 cm^{-1} (Fig. 3(c)). On the other hand, only one strong carbonyl band is observed in the Raman spectra of AG in CH_3CN and $CHCl_3$ solutions at 1723 and 1724 cm^{-1}, respectively. The lower frequency carbonyl band, more intense in the IR spectra, is much weaker in the Raman spectra. The shift to lower frequencies in CH_3CN solution can be interpreted as due to increased charge separation in the carbonyl group induced by polar solvent and specific interaction of CH_3CN with the imide proton. In $CHCl_3$ solution such

Table 4
Rac-aminoglutethimide (AG). The C=O stretching region

Environment	Solvent	Method	Frequencies (cm^{-1}) and relative intensities [a]	
			Concentration of AG (% m/v)	
Solutions	CCl_4	IR	< 0.1	1731(m), 1714(s)
	CH_3CN	IR	1	1723(sh-m), 1707(s)
			4	1723(sh-s), 1706(s)
		Raman	4	1722(s), 1707(sh-w)
	$CHCl_3$	IR	0.2	1724(sh-m), 1705(s)
			2	1724(sh-s), 1704(s)
		Raman	2	1724(s), 1713(m), 1703(sh-w)
Crystals	polymorphic form I [b]	IR (KBr pellet)		1726(sh-m), 1715(s), 1693(s), 1678(sh-s)
		Raman		1708(s), 1687(m), 1678(sh-m)
	polymorphic form II [b]	IR(KBr pellet)		1723(sh-m), 1714(s), 1704(s), 1669(s)
		Raman		1715(s), 1664(m)
Ar matrix		IR		1752(w), 1738(m), 1722(s), 1715(sh-s), 1703(sh-m)
Calculated [c,d] (ab initio RHF/6-31G**)		IR		1812(380) 1785(560)
				ν(C=O2) ν(C=O1) [e]
		Raman		1812(30), 1785(8)

[a] w, weak; m, medium; s, strong; sh, shoulder.
[b] Rac-aminoglutethimide (AG) can be crystallized in two polymorphic forms, I and II, which exhibit different X-ray structures, IR spectra and DSC curves [12].
[c] In the assignment only the internal coordinate with the highest contribution to the normal mode composition is used.
[d] ν, stretching.
[e] See O atoms numbering of the AG molecule (Fig. 1)

a shift can result from interaction of a carbonyl group with a solvent molecules via a solvent acidic hydrogen. In general, the spectral shifts generated by the environment in the carbonyl stretching region are smaller than shifts previously described for imide N–H stretching region.

Similar spectral shifts for carbonyl bands are observed in the spectra of GT solutions recorded in the series of solvents (Fig. 3(d)–(f)). It is interesting to note that in the spectrum of G solution in CCl_4 an additional band appears at 1729 cm^{-1}. Such a band can originate from Fermi resonance occasionally manifesting itself in cyclic imides.

3.1.3. The 1650–400 cm^{-1} region

The IR spectrum of AG in diluted CCl_4, CH_3CN and $CHCl_3$ solutions and the theoretically calculated spectrum of an isolated molecule over the entire spectral region are shown in Fig. 4(a)–(c). The data concerning frequencies and intensities of the observed IR and Raman bands for AG in different solvents, in the solid state, in Ar matrices and those theoretically predicted by the ab initio calculations are gathered in Table 7. Tentatively one can assume that a diluted solution of AG in CCl_4 (Fig. 4(a)) contains AG molecules surrounded by solvent molecules weakly interacting with AG. In order to confirm this assumption a low temperature Ar matrix of AG was prepared and its IR spectrum measured (Fig. 4(d)). It turns out that the IR spectra of AG in an Ar matrix and in diluted CCl_4 solution are very similar except for some narrow spectral ranges not available in the solvent spectra due to interferences with the solvent bands. The largest difference between the positions of bands in the spectra does not exceed 6 cm^{-1} and for most bands it is less than 3 cm^{-1}. The IR spectra of AG in CH_3CN and $CHCl_3$ solutions are shown in Fig. 4(b) and (c). The spectral pattern in this range is only slightly sensitive to solvent. The largest changes concern bands assigned to the N–H deformations in the $-NH_2$ and =NH groups and they can be deduced from *N*-deuterated and *N*-methylated AG spectral measurements and theoretical calculations.

Theoretical calculations of the IR spectrum of

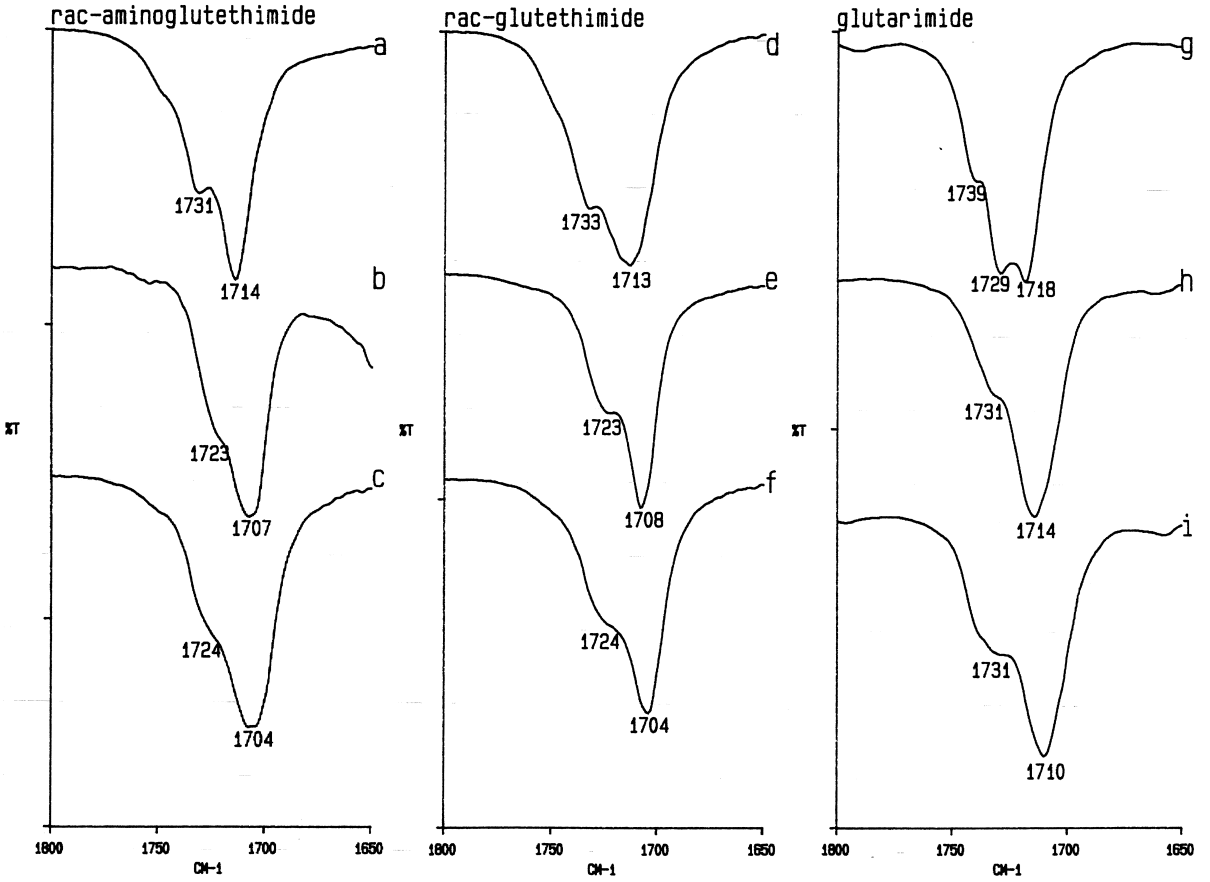

Fig. 3. The C=O region. IR spectra of: (a) < 0.1% (m/v) CCl_4 solution of rac-aminoglutethimide; (b) 1% (m/v) CH_3CN solution of rac-aminoglutethimide; (c) 0.2% (m/v) $CHCl_3$ solution of rac-aminoglutethimide; (d) 0.1% (m/v) CCl_4 solution of rac-glutethimide; (e) 1% (m/v) CH_3CN solution of rac-glutethimide; (f) 0.2% (m/v) $CHCl_3$ solution of rac-glutethimide; (g) < 0.1% (m/v) CCl_4 solution of glutarimide; (h) 1% (m/v) CH_3CN solution of glutarimide, 0.2% (m/v) $CHCl_3$ solution of glutarimide.

AG were made by the quantum chemical ab initio RHF method. The calculated frequencies, intensities and visualization of the vibrational modes were particularly useful for a reasonable assignment of the spectra. The IR spectra of the model compounds of GT and G were also helpful to distinguish the modes of NH_2 group, aromatic ring and glutarimide moiety.

The NH_2 in-plane bending occurs at 1624 cm^{-1} in CCl_4, $CHCl_3$ solutions and in an Ar matrix, and is shifted to 1633 cm^{-1} in CH_3CN solution (theoretical value is 1645 cm^{-1}). The next band whose frequency is sensitive to solvent occurs at 1384 cm^{-1} in CCl_4 solution and in an Ar matrix, and is shifted to 1395 cm^{-1} in $CHCl_3$ solution, is assigned to the N–H in-plane bending (theoretical value is 1426 cm^{-1}). The lowest prominent band occurs at 1182 cm^{-1} in CCl_4 solution and corresponds to a mixed mode composed from C–H bendings of glutarimide and aromatic moieties and N–H in-plane bending (theoretical value is equal to 1198 cm^{-1}). Below 1000 cm^{-1} the band corresponding to the N–H out-of-plane bending is expected in the spectra. Unfortunately, it is observed only in the Ar matrix spectrum at 750 cm^{-1} (theoretical value is 766 cm^{-1}) and is hidden by the solvent bands in the solution spectra. The rest of the bands were assigned based on the theoretical calculation, see Table 7.

Table 5
Rac-glutethimide (GT). The C=O stretching region

Environment		Method	Frequencies (cm^{-1}) and relative intensities [a]	
	Solvent		Concentration of GT (% m/v)	
Solutions	CCl_4	IR	0.1	1733(m), 1713(s)
		Raman	0.5	1732(s), 1728(sh-s), 1719(sh-m)
	CH_3CN	IR	1	1723(m), 1708(s)
			4	1723(s), 1708(s)
		Raman	4	1725(s), 1708(sh-w)
	$CHCl_3$	IR	0.2	1724(sh-m), 1704(s)
			2	1724(sh-m), 1703(s)
		Raman	2	1726(s), 1716(sh-m)
Crystals		IR(KBr pellet)		1719(s), 1698(s), 1687(sh-s)
		Raman		1715(s), 1678(s)
Ar matrix		IR		1754(w), 1742(m), 1729(s), 1723(s), 1716(sh-m)
Calculated [b,c] (ab initio RHF/3-21G)		IR		1746(340), 1719(360) ν(C=O2) ν(C=O1) [d]
		Raman		1746(20), 1719(11)

[a] w, weak; m, medium; s, strong; sh, shoulder.
[b] In the assignment only the internal coordinate with the highest contribution to the normal mode composition is used.
[c] ν, stretching.
[d] See O atom numbering of the GT molecule (Fig. 1).

3.2. Theoretical spectra of model dimers

The effect of hydrogen bond formation in cyclic imides was studied theoretically on two model systems: the centrosymmetric G–G glutarimide dimer and the CH_3CN–AG linear dimer. The RHF/6-31G* (5d) theoretical IR and Raman spectra of the G–G dimer, presented in Fig. 5, reveal two bands at 3370 cm^{-1} and 3358 cm^{-1} corresponding to the ''in-phase'' (Raman strong peak) and ''out-of-phase'' (IR strong peak) stretch vibrations of the N–H moiety. These bands are downshifted by about 70–80 cm^{-1} with respect to the 3441 cm^{-1} band for the free NH imide stretch, and, they can be roughly assigned to the

Table 6
Glutarimide (G). The C=O stretching region

Environment		Method	Frequencies (cm^{-1}) and relative intensities [a]	
	Solvent		Concentration of G [% m/v]	
Solutions	CCl_4	IR	< 0.1	1739(m),1729(s), 1718(s)
	CH_3CN	IR	1	1731(sh-m), 1714(s)
	$CHCl_3$	IR	0.2	1731(m), 1710(s)
Crystals		IR (KBr pellet)		1722(sh-s), 1703(s), 1667(s)
Ar matrix [b]		IR		1748(w), 1739(s), 1723(m)
Calculated [c,d] (ab initio RHF/31-6**)		IR		1818(200), 1801(790) ν^s(C=O) ν^a(C=O)

[a] w, weak; m, medium; s, strong; sh, shoulder.
[b] Table 3 in Ref. [16].
[c] In the assignment only the internal coordinate with the highest contribution to the normal mode composition is used.
[d] ν, stretching; s, symmetric; a, antisymmetric.

Table 7
Rac-aminoglutethimide (A6) The 1650–400 cm^{-1} region

Environment		Method	Frequencies (cm^{-1}) and relative intensities[a]							
	Solvent		Concentration of AG [% m/v]							
Solutions	CCl_4	IR	0.1%	1624(w),	1196(w),	1517(w), 1182(s)		1461(w),	1384(w),	1287(w),	1265(w),
	CH_3CN	IR	4%	1633(m),	1614(w), 1200(s),	1519(w), 1188(s),	832(m),			1290(w),	1267(m), 547(m)
		Raman	4%	1629(m),	1614(s), 1199(w),		839(s),	1462(w),		1287(w), 644(s)	1267(m),
	$CHCl_3$	IR	0.2%	1642(m),		1517(m), 1183(m),		1459(w),	1395(w),	1286(w),	1266(w), 542(w)
Crystals	polimorphic form I[b]	IR (KBr pellet)		1626(s), 1205(s),	1610(m), 1191(s),	1516(s), 1150(w),	885(m), 831(m),	1454(m),	1365(m), 701(m),	1290(m), 643(w),	1272(s), 546(m)
		Raman		1626(s), 1205(w),	1610(s), 1189(w),	1517(w), 1150(m),	885(m), 839(s),	1453(m), 829(m),	1442(m), 701(m),	1299(m), 655(s),	1270(w), 643(m), 546(w)
	polimorphic form II[b]	IR (KBr pellet)		1631(m), 1204(s),	1613(w), 1190(s),	1518(s),		1459(m), 826(m),	1356(m), 732(m),	1289(m), 558(m),	1265(m), 542(m)
		Raman		1631(m),	1613(s), 1190(w),	1518(w), 1162(m),	891(m), 838(s),	1459(m), 828(sh-m),		1289(m), 643(s),	1263(w), 498(m)
Ar matrix		IR		1624(m),	1198(m),	1520(s), 1184(s),	824(w),	1459(w),	750(m),	1294(w),	1266(w), 542(w)
Calculated[c,d] (ab initio RHF/6-31**)		IR		1645(170), $\beta(NH_2)$	1624(13), sciss(NH_2)	1522(110), β(CH Ar)	1473(10), sciss(CH_2)	1463(4), def(CH_3)	1426(95), β(NH)	1300(35), wag(CH_2)	1266(80), β(CH Ar)
				1264(87), wag(CH_2)	1183(77), mixed	1198(199), β(CH Ar)	842(74), γ(CH Ar)	811(1), mixed	766(109), γ(NH)	596(250), γ(NH_2)	553(85) mixed
		Raman		1645(85), 1264(11),	1624(9), 1183(7),	1522(1), 1198(5),	1473(17), 842(2),	1463(17), 811(20),	1426(2), 766(1),	1300(2), 596(7),	1266(9), 553(2)

[a] w, weak; m, medium; s, strong; sh, shoulder; bb, broad band. [b](R,S)-aminoglutethimide can be crystallized in two polymorphic forms, I and II, which exhibit different X-ray structures, IR spectra and DSC curves [12]. [c] In the assignment only the internal coordinate with the highest contribution to the normal mode composition is used. [d] β, in-plane bending; γ, out-of-plane bending; def, deformation; sciss, scissoring; wag, wagging.

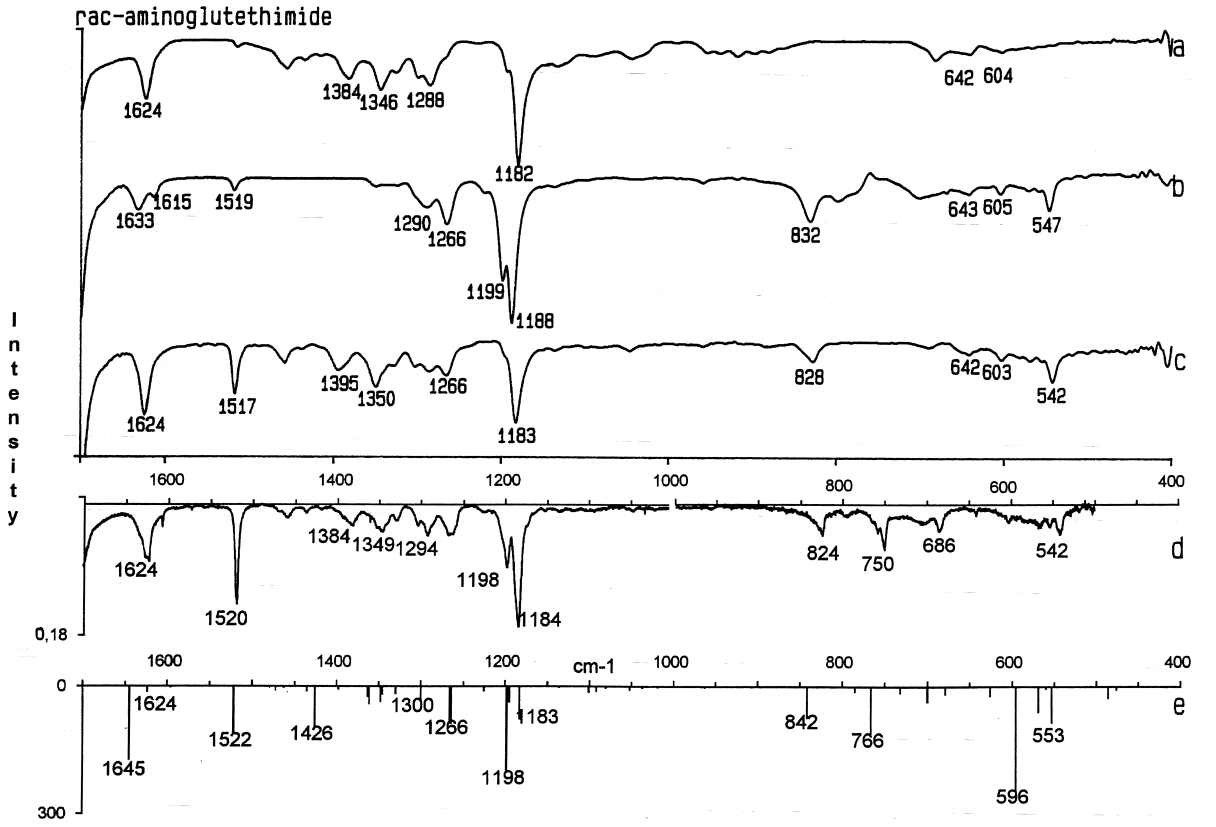

Fig. 4. The 1650–400 cm^{-1} region. IR spectra of: (a) $< 0.1\%$ (m/v) CCl_4 solution of rac-aminoglutethimide; (b) 1% (m/v) CH_3CN solution of rac-aminoglutethimide; (c) 0.2% (m/v) $CHCl_3$ solution of rac-aminoglutethimide; (d) Ar matrix of rac-aminoglutethimide; (e) theoretical spectrum of rac-aminoglutethimide (quantum mechanical ab initio RHF/6-31G**).

experimental 3200 cm^{-1} band. Surprisingly, another experimental band in the 3100 cm^{-1} region also originating from the autoassociates' formation (Fig. 2(n)) has no counterpart in the theoretical spectra. In order to shed some more light onto the problem it was tentatively assumed that in the cyclic G–G dimer the hydrogen atoms can migrate along the hydrogen bond leading to a tautomeric hydroxy–hydroxy dimer, Fig. 5. The theoretically predicted IR and Raman spectra (RHF/6-31G* 5(d)) of such a tautomeric G–G dimer indeed revealed a strong shift of the NH stretch bands towards 3152 and 3110 cm^{-1} suggesting that the shift in the high frequency region can originate from glutarimide tautomerization. There are two arguments, however, that contradict such a plausible explanation of the 3100 cm^{-1} band origin. The first is the extremely unfavorable total energy of the tautomeric dimer, about 48 kcal mol^{-1} above the normal (oxo–oxo) dimer. The second argument is the theoretically predicted vibrational spectrum of the tautomeric dimer in the carbonyl stretch region. The predicted strong IR bands at 1653 and 1591 cm^{-1}, and the Raman bands at 1666 and 1537 cm^{-1} have not been observed in any experimental spectra. Thus, the experimental 3100 cm^{-1} band cannot be reproduced by a theory based on the harmonic approximation to molecular vibrations of centrosymmetric dimers, such as the G–G dimer, a model of the AG–AG autoassociates. There exists a possibility that in cyclic dimers a significant coupling of intra- and intermolecular vibrations occurs that is not included in the harmonic theory. Such a possible coupling does not seem to affect the vibrational spectra of the CH_3CN–AG pair. The theoretical RHF/3-21G calculations reveal a

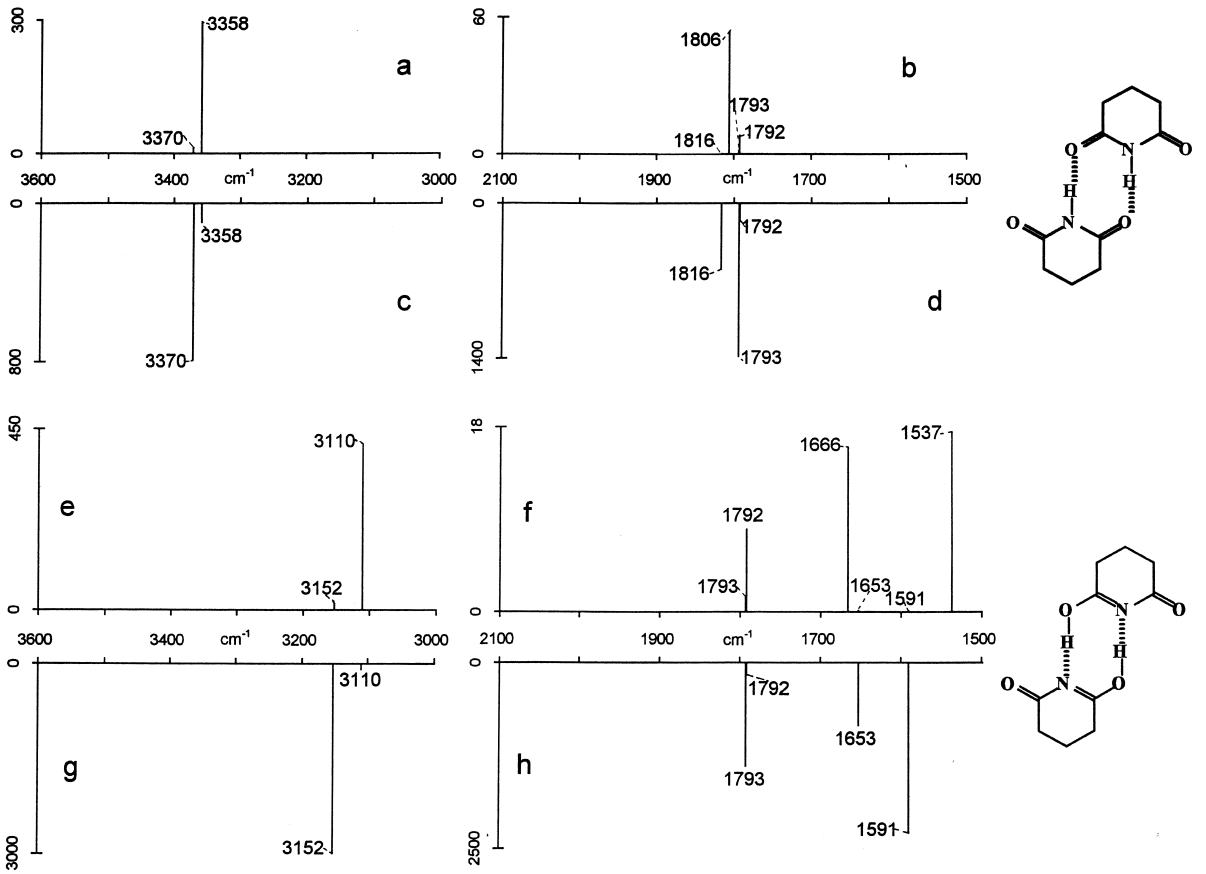

Fig. 5. The dimers. Quantum mechanical ab initio RHF/6-31G*(5d): (a), (b) Raman spectra of oxo-oxo dimer of glutarimide, c,(d) IR spectra of oxo-oxo dimer of glutarimide; (e), (f) Raman spectra of hydroxy-hydroxy dimer of glutarimide; (g), (h) IR spectra of hydroxy-hydroxy dimer of glutarimide.

strong band at 3262 cm^{-1} originating from vibrations of the NH moiety engaged in the linear hydrogen bond with a basic nitrogen atom of CH_3CN. This frequency is considerably downshifted with respect to the calculated 3382 cm^{-1} band for the free NH moiety. The overall pattern of the theoretical spectra fits the experimental counterpart reasonably well.

The solvent effect on the vibrational spectra was also studied with the use of the Onsager solvent reaction field model. It appeared that the theoretical spectra (RHF/3-21G for AG and for the CH_3CN–AG pair) are hardly affected by the medium. Such a result reflects the significance of specific nearest-neighbor intermolecular interactions between the solute molecule and the solvent molecules.

4. Conclusions

1. IR and Raman spectra of AG dissolved in CCl_4, $CHCl_3$, and CH_3CN were recorded and analyzed in order to understand the details of intermolecular solute–solvent interactions modelling biochemical systems where AG is surrounded by the environment of variable polarity.
2. Most of the absorption IR and Raman bands are assigned based on the comparative analysis of the deuterated AG, *N*-methylated GT and glutarimide, argon matrix isolation IR spectra and the theoretical ab initio RHF frequencies and intensities calculated within the harmonic oscillator approximation.

3. The IR spectra of AG solutions in CCl_4 and $CHCl_3$ of variable solute:solvent ratios reveal concentration-dependent peaks that originate from the formation of presumably hydrogen-bonded and centrosymmetric AG autoassociates.
4. In CH_3CN solutions the AG–CH_3CN associates are formed through hydrogen bonding.

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