^{127}I NQR Spectra of Iodobenzoic Acid and Iodophenol Derivatives. H-Bonds and C-I Characteristic Bonds of These Substances*

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This is a review of investigations on iodo-benzoic acid, iodohippuric acid, and iodophenol derivatives by NQR, NMR, and emission Mossbauer spectroscopy. The influence of intermolecular, intramolecular, and bifurcated O–H· · ·I and O–H· · ·O bonds on the properties of iodine-carbon bonds is demonstrated. Ionized and non-ionized forms of tyrosine differ by the probability of H-bond formation. The simultaneous use of ^{127}I NQR and emission Mössbauer ^{125}I spectroscopy open the possibility to determine the types of tellurium-organic substances formed in the process of K-decay of ^{125}I.

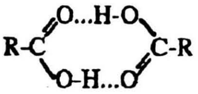
Key words: NQR, NMR, iodobenzoic acid, iodohippuric acid, iodophenol.

Iodoorganic substances are used in the diagnostic medicine as X-ray contrast compounds and as radiopharmaceuticals (RPC) labeled by radioactive iodine isotopes. The radiochemical stability of the preparations in aqueous solutions depends on the strength of the radioactive label and, therefore, on the properties of the iodine-carbon bonds.

Since fifteen years we are using ^{127}I NQR for control of the identity and purity of these RPCs. More than 30 RPC and parent compounds were studied (see [1 - 3] and Table 1).

Admixtures giving rise to inhomogeneous widening of NQR lines result in a decrease of the line amplitude. Therefore the amplitude and width of NQR signals from different samples of the same substance can be used as criterion of purity. This effect is shown in Fig. 1 for 5 NQR lines from 5 lots of (ortho-iodobenzoyl-)tyrosyl. The first through third lot contains 0.6% admixtures, the fourth about 1% admixtures, the fifth 0.4% admixtures. Therefore fourth lot can not be used.

The NQR frequencies depend on the nature and the mutual orientation of the substituents. For example, the ^{127}I NQR spectrum of triiodotrast (the substance is in use as X-ray contrast compound) consists of five signals, one of them having double intensity (Table 1) [2]. If it results from the superposition of two independent lines, the spectrum is composed of six lines. This indicates the existence of two independent molecules in the unit cell. There are a few possible configurations of the triiodotrast molecule (Fig. 2) owing to rotations about the axes C_{arom}–C_{exo}, C_{arom}–N, N–C. It is necessary to take into account the formation of the H-dimer



There is a small energy difference of the two dimer tautomers in the solid state [4]. Due to energetic degeneracy of the dimer tautomers the difference of influence of the C=O or the C–O group upon the NQR frequencies of I-2 and I-6 atoms will be small. Crystal lattice effects and the presence of two ortho-substituents can result in a change (decrease or increase) in the energy difference.

Libration around the N–C axis (configurations 1 and 2 or 3 and 4) are least hindered as to molecular over-crowding. Transfer from configurations 1-2 to 3-4 is more difficult because of the large volume of the methyl group (free rotation is improbable).

In the configuration 2(4) the carbonyl oxygen is outside the aromatic position and the common

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Table 1. The quadrupole coupling constants (*eQq*) and asymmetry parameters of the electric field gradient (η) of ^{127}I for some iodine - containing compounds.

Nr.	Substance	*eQq*	η, %	
1.	1-I-2-NH_2-5-COOEt-Ph*	1794.8	0.0	
		1841.9	5.5	
2.	1,3-I_2-2-NH_2-5-COOEt-Ph	1840.1	7.0	
		1873.2	6.0	
3.	1-I-2-NHX**-5-COOEt-Ph	1917.0	4.5	
		1923.0	4.0	
4.	1-I-2-COOH-5-NO_2-Ph	2046.9	16.0	
5.	1-I-2-COOEt-5-NO_2-Ph	1999.7	5.0	
6.	1-I-3-CH_2Br-Ph	1842.76	8.0	
	1-I-3-CH_2-^{79}Br-Ph	$\nu = 263.22$		
7.	1-I-3-CH_2NH_2 -Ph	1728.40	25.5	
8.	1-I-3-CH_2NH_2-Ph·HCl	1840.26	6.0	
9.	(1-I-3-CH_2NHC-	1778.74	6.3	(1)***
	(NH)(NH_2)-Ph)$_2H_2SO_4$	1849.1	6.0	(5)
10.	1-I-4-$CH_2CH(NH_2)CH_3$-Ph	$\nu_1 = 283.36$		
		$\nu_2 = 284.50$		
11.	I-$CH_2SO_3Na \cdot H_2O$	2000.00	0	
12.	C_6F_5I	2186.15	8.1	
13.	5-I-uracyl	2037.50	6.1	
14.	1-^{79}Br-2,4,6-$(CH_3)_3$-3-NH- $COCH_2N(CH_2COOH)_2$Ph	$\nu = 225.09$		
15.	Triiodotrast	1914.37	5.0	(1)***
		1980.32	9.3	(2)
		1988.14	8.6	(1)
		1996.51	8.6	(1)
		2071.66	7.0	(1)

* Ph - phenyl, ** X = COCH(NHCOPh)CH_2PhOCOPh, *** relative intensities of lines.

conjugation system is disturbed. On the other hand in the configuration 1(3) there is the possibility of the arrangement of the carboxyl oxygen in the aromatic position in the vicinity of the I-2 (I-4) atom and the formation of intramolecular N–H· · ·I-4 (I-2) .Hence the configurations 1 and 3 have more energetic advantages than configurations 2 and 4.

In both model configurations (1 and 3) the atom I-6 has the same surrounding and can have the same NQR frequency (line with double intensity in the spectrum *eqQ* = 1980.3 MHz). The highest frequency (*eqQ* = 2071.7 MHz) can have the I-2 in configuration 1 because of the vicinity of two oxygen atoms, while the frequency of the I-4 in that configuration is the lowest (*eqQ* = 1914.4 MHz). The other frequencies can belong to iodine atoms in the configuration 3 (I-4: *eqQ* = 1988.1 MHz, I-2: *eqQ* = 1955.5 MHz).

In the same manner the NQR frequencies in the spectra of triombrine and its sodium salt [1] can be attributed.

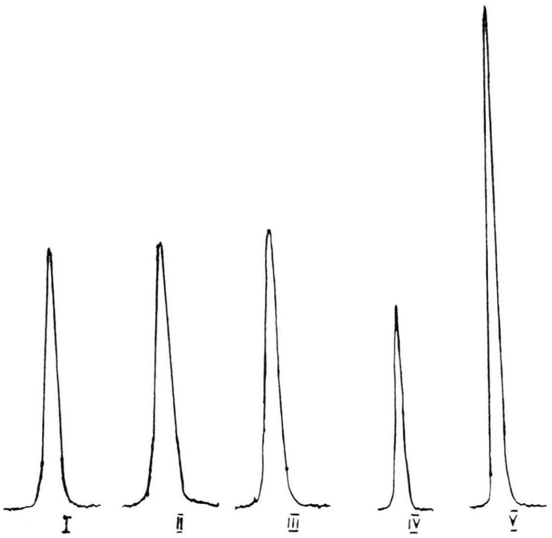


Fig. 1. ^{127}I NQR signals of (ortho-iodobenzoil)-tyrosyl.

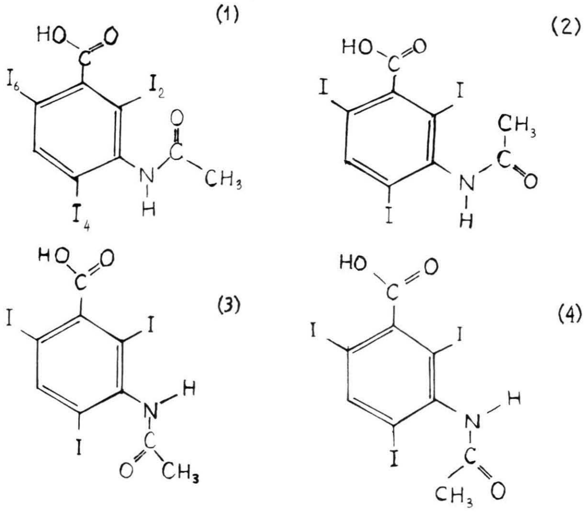


Fig. 2. Possible configurations of the triiodotrast molecule (rotation of $COCH_3$ group around the N–C bond and rotation of the $NHCOCH_3$ group around the C_{arom}–N bond).

These examples show that the intramolecular H-bond with one or more iodine atoms plays an important role in the stabilization of either configuration. The same is true for the two conformers of ortho-iodohippuric acid (two NQR frequencies) and for its sodium salt [1].

According to X-ray analysis [5, 6] and our earlier work [2] the intramolecular or bifurcated O–H· · ·I bond is absent in ortho-halogen-benzoic acids. Therefore we are used proton magnetic resonance (PMR) in

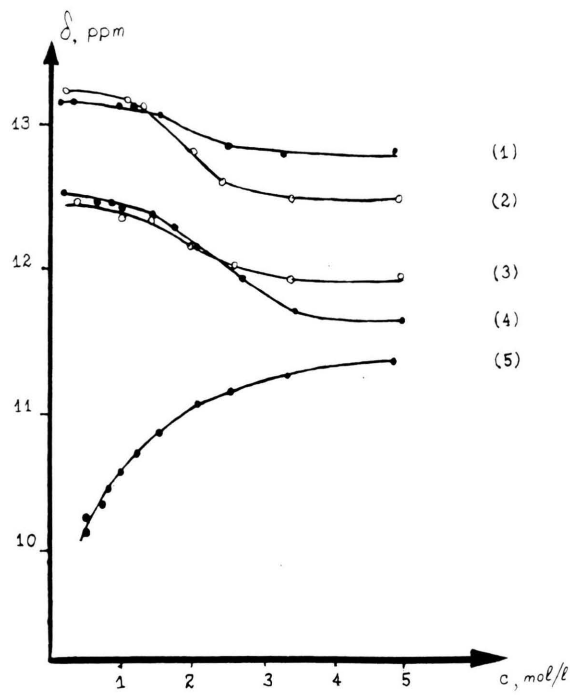
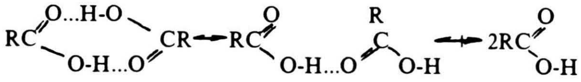


Fig. 3. The concentration dependences of the OH proton chemical shift of ortho-halogen-benzoic (1, 2, 5) and ortho-halogenhippuric (3, 4) acid in DMSO (1-4) and TGF (5) solutions; Hal = Br (2, 3), I (1, 4, 5).

different solutions to study the rate and activation energy of proton transfer in O–H· · ·O bonding dimers of ortho-I(Br)-benzoic and ortho-I(Br)-hyppuric acids.

In [7, 8] the dissociation of aliphatic carboxylic acid dimers was studied. Simultaneous breaking of two H-bonds or breaking of one H-bond is possible:



In both cases the effective dissociation energy is close to the sum of the two bonds energy, but in the second case the limiting stage comprises internal rotation around the H-bond. The slowing down of this motion is possible by H-bond formation with solute molecules.

We studied the competitive interactions in the formation of H-bond dimers or complexes with H-bond-acceptors for ortho-I(Br)-benzoic and hippuric acids in different solvents. The chemical shifts of O-H proton signals depend on the concentration and the solvent, as shown in Figure 3. A decrease of substance concentration in DMSO solution results in a OH-signal shift to the weak field (see Fig. 3), while in TGF or CD_2Cl_2 it results in a OH-signal shift to the high field (see Figs. 3 and 4).

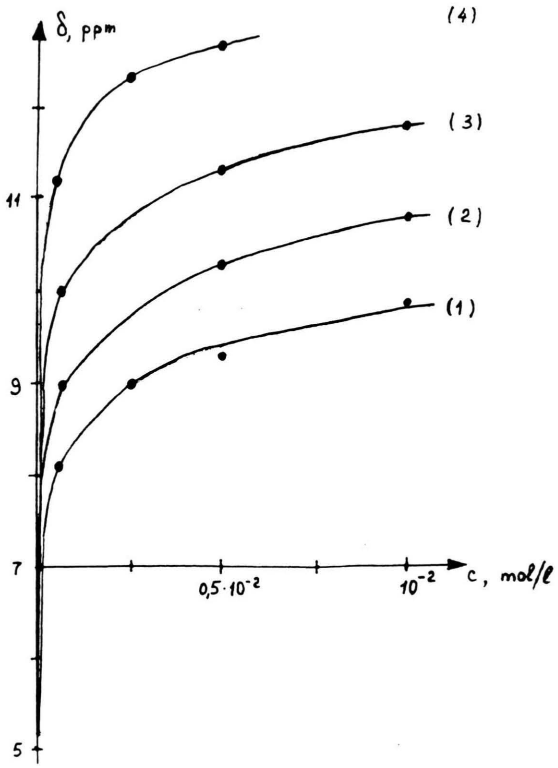
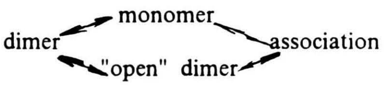


Fig. 4. The concentration dependences of the OH proton chemical shift of ortho-Br-benzoic acid in CD_2Cl_2 solution at 293 K (1), 273 K (2), 253 K (3), 233 K (4); $\delta_d(OH)$ = 13.48 ppm (178 K), $\delta_m(OH) = 5.3$ ppm.

At the high concentration in DMSO solution the OH signal is narrow and its shift is in accordance with the dimer shift with correction for the small content of associates with solute molecules is done.

The different direction of the shift with the dilutiuon in DMSO and TGF (CD_2Cl_2) solutions points to a stronger H-bond of substances with DMSO than with TGF.

A decrease of substances in DMSO solution results in a shift of the exchange process



towards association, but in TGF solution from dimer to association and monomer. The association of a substance with TGF through H-bond is less strong than in

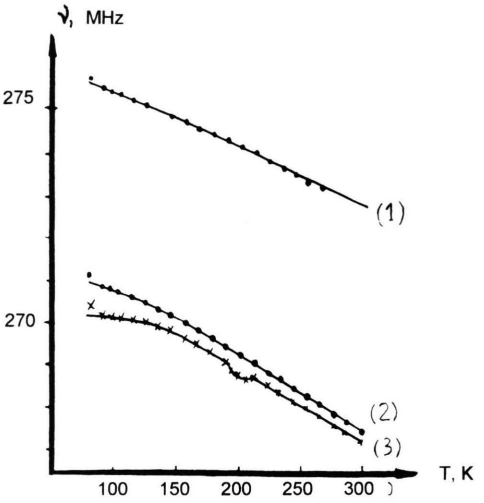


Fig. 5. The temperature dependence of ^{127}I NQR in para-iodobenzoic acid (1) (Δm = 1/2 - 3/2), para-bromobenzoic acid (2), and para-bromohippuric acid (3).

dimer, but the association of a substance with DMSO through H-bond is the same as in dimer.

The temperature and concentration studies of the O–H proton chemical shift of ortho-Br-benzoic acid were made in CD_2Cl_2 solution at 178 - 308 K and in the concentration range 6.10^{-4} - 10^{-2} M (see Figure 4). The curve shapes of $\delta(OH) = f(c,T)$ and the temperature coefficient $\Delta_{dimer}/T = -0.001$ ppm/T permit to conclude that the dimerization process for halogen-benzoic acids at low temperature is analogous that in aliphatic carboxylic acids. However the equilibrium constant $k_d = (1.5 - 5) \cdot 10^2$ l/mol is smaller than for aliphatic carboxylic acid $k_d \sim 10^7$ l/mol [7]. Enthalpy value $\Delta H_d = -7 \pm 2$ kG/mol points out also that H-bonds in halogen-aromatic acids are weaker. Our value is comparable to $\Delta H_d = -12 \pm 2$ kG/mol of the dimerization process of thiocarboxylic acid [9, 10].

To study the influence of dimerization on the C–I bonds in the para-halogen-benzoic and hippuric acids we have used the NQR method the more since the NQR ^{127}I frequencies in para I-isomers of acids and corresponding salts are different [2]. But no peculiarities of the NQR temperature curves up to 300 K were observed (Figure 5). Evidently the temperature was too low to feel the influence of the H-bond weakening on the NQR frequencies.

In the ortho-iodo-phenol derivatives (mono-I-tyrosine, triiodo-thyronine T3, thyroxine T4, and bilitrast) the existence of intramolecular or bifurcated O···H···I bonds is possible. The NQR frequencies of these compounds are in Table 2.

Table 2. Parameters of ^{127}I NQR spectra of iodo-tyrosine derivatives at 77 K.

Substance Δm =	ν MHz 1/2-3/2	ν MHz 3/2-5/2	eQq MHz	η %	Relative intensity
Mono-5-iodotyrosin L-α-NH_2-β(5-I-4-hydroxy-phenyl)-propionic acid	287.48	571.3	1906.2	7.0	
Di-iodotyrosin L-α-NH_2-β(3,5-I_2 4-hydroxy-phenyl)-propionic acid	281.45 292.00 (non-ionized form)				
Di-iodotyrosin L-α-NH_2-β(3,5-I_2 4-hydroxy-phenyl)-propionic acid	289.94 297.11 (ionized form)	577.48 551.1	1926.0 1971.6	5.0 7.0	1 1
Tri-iodothyronin L-α-NH_2-β[3,5-I_2-4-(3'-I-4'-oxyphenoxy)-phenyl]-propionic acid	282.45 292.10 303.75	564.64 580.30 601.10	1882.0 1936.5 2007.2	3.0 7.0 9.0	1 1 2
Thyroxin [1] L-α-NH_2-β[3,5-I_2-4-(3',5'-I_2-4'-oxy-phenoxy)-phenyl]-propionic acid	283.10 284.65 293.60 295.20 297.85				1 1 2 3 1
Bilitrast [1] L-α-NH_2-β(3,5-I_2 4-hydroxy-phenyl)-propionic acid	281.45 292.00				1 1

The thyroid hormons T3 and T4 play a great role in the control of metabolic activity including the consumption of oxygen by tissues and synthesis and metabolism of proteins. The molecular conformation of T3 and T4 is very important in the process of T3 and T4 bonding with receptors and proteins. Aromatic rings of these molecules are perpendicular to one another. In active T3 the iodine atom I-3' is in distal position relative to the OH group (4'). The non-ionized phenol OH group reacts with receptors as a proton donor and exerts electronic and space influence on the ortho-substituent. Ionized OH is bonded to transport protein [11].

A great number of ortho-halogen phenol derivatives 2,6-Hal_2-4-XC_6H_2OH has been studied by NQR. Most of these substances have two (or four) NQR signals with much different frequencies. Probably these splittings in NQR spectra are caused by intramolecular or bifurcated H-bond. This effect can

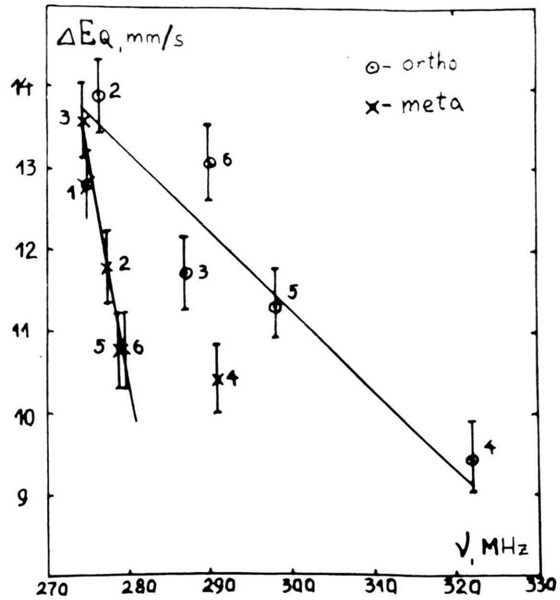


Fig. 6. Comparison of the ^{127}I NQR frequencies (Δm = 1/2 - 3/2) with the quadrupole splitting (ΔE_Q), ^{125}Te in di-substitued iodobenzene and in substances forming after K-decay of ^{125}I of its radiactive analogs; X = H(1), CH_3(2), OCH_3 (3), NO_2 (4), COOH(5), $CONHCH_2$ COOH(6).

be evaluated by the additive scheme [12]

$$n = n_0 + \sum_i a_i,$$

where n_0 is the frequency of the mono-halogenbenzene and a_i a substituent increment.

There are two increments for the ortho- OH substituent [13]. If one supposes that H-bond in tyrosine derivatives are analogous to 2,6-I_2-4-NO_2-C_6H_2OH, one can evaluate the NQR frequencies of our substances. For that we must subtract the metha-NO_2-increment (15,9 MHz) from NQR frequencies of 2,6-diiodo-4-NO_2-phenol (297.7 and 308.76 MHz) [13]. The obtained frequencies 281.8 and 293.8 MHz are close to the average ones of T4, bilitrast, and I form of diiodo-tyrosine. This means that in these substances one of the ortho-iodine atoms forms an intramolecular (or bifurcated) H-bond with the proton of the OH group.

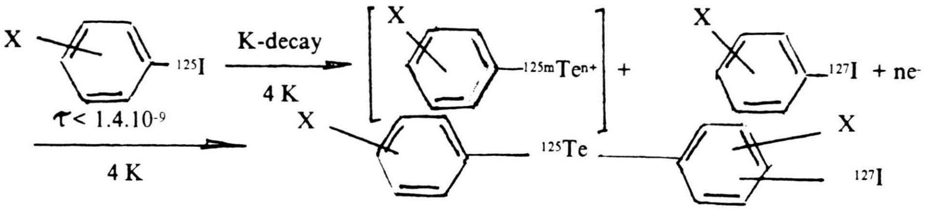
The frequencies of the II form of diiodo-tyrosine are higher than those evaluated with the additive scheme. Therefore we suppose that II is an ionized form. The multiplicity of the T3 NQR spectrum accords with two independent molecules in the unit cell. One of the molecules is non-ionized (282.45 (1I) and 292.10 (2I) MHz), the other is ionized (292.1 (1I) and 303.75 (2I) MHz). The same can be said about the forms and NQR frequencies of T4.

The last part of our work relates to the problem of structure determination of tellurium organic substances formed in the process of K-decay of ^{125}I in iodo-derivatives of benzoic and hippuric acids.

The emission gamma-resonance (EGR) spectra of ^{125}I at 4.2 K were studied. The quadrupole splitting (ΔE_Q) in EGR spectra and ^{127}I NQR frequencies are compared in Figure 6. In ortho- and meta-derivatives of iodobenzene the ΔE_Q values change in the direction opposite to that of change in NQR frequencies [14].

Considering all available data one can conclude that only one chemical state of ^{125}Te was stabilized after K-decay of ^{125}I in IC_6H_4X for less than $1.4 \cdot 10^{-9}$ s at $T > 4$ K. The organic compounds of divalent tellurium RTeR' are isoelectronic with the corresponding iodo-derivatives. In these tellurium-organic compounds the Z axis of EFG is perpendicular to both C–Te bonds making an angle close to 100°. The substituents in the benzene ring change the populatiioons of the $5p_x$ and $5p_y$ orbitals of Te atoms and the population of the $5p_z$ orbital of the I atom.

This can explain the difference in the behaviour of the ^{127}I NQR frequencies and ΔE_Q. From this follows that there is no break of the C–Te bond during ^{125}I K-decay in the matrix of iodo-aromatic compounds at 4 K. The cation ArTe^{n+} reacts probably with the medium forming intermediate, see below. One must take into account the orientation effect of the substituents in the benzene ring since ArTe^{n+} is electrophilic. Therefore for every X one can suppose the structure of the tellurium-organic substance.



Thus the complex using of ^{127}I NQR, ^{1}H NMR and ^{125}I EGR spectroscopy makes it possible to identify, to determine of the purity and to study the properties of iodo-organic compounds which are the base for radiopharmaceuticals.

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