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QUANTUM-CHEMICAL INVESTIGATION OF SOME FEATURES OF THE INTERCONVERSIONS OF THE GOSSYPOL MOLECULE

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The electron conformations and tautomeric transformations of the gossypol molecule have been investigated by the MO LCAO method in the AM1 approximation. On the basis of an analysis of the electronic structures of 24 model molecules, each forming, as it were, a component part of gossypol, the role of dynamic intramolecular processes in its tautomeric interconversions has been elucidated. The exceptional role of intramolecular hydrogen bonds in the formation of the electron patterns in different structural forms has been shown. The correlation of the dependence of the chemical shifts of the ^{13}C nuclei on the electron density distribution in the structural forms of gossypol has been studied.

In recent years, the mathematical methods of quantum chemistry have been widely used for the study of the dynamics of the structural transformations of molecular systems [1]. In particular, thanks to the presence of an aldehyde group in its structure, the aldehydonaphthol gossypol (GP), consisting of two identical naphthyl fragments united by an ordinary bond, exists in solution in various structural forms — aldehyde, lactol, or quinoid, depending on the nature of the solvent [2, 3]. The range of physiological action of gossypol is unusually broad, but hitherto no investigation whatever has been made of its electronic structure, the mechanism of its physiological action has not been studied, and features of its reactivity have not been discussed. In order to investigate these problems we have used not only spectral but also quantum-chemical methods.

The predominance of a definite structural form of GP in solution depends on a number of factors, and our aim was to reveal an energetically favorable form of the molecule taken individually in the free state when there is no influence of a medium. One of the possible variants of the evaluation is a quantum-chemical calculation of the energetically stable form of GP. We used the semiempirical MO LCAO method in the AM1 approximation, which has well recommended itself in the solution of the most diverse problems [4].

The optimum structures of the nuclear skeletons of gossypol and its structural forms corresponding to the minimum total energy were calculated by the Fletcher–Powell–Davidon method of a direct search for an extremum [5]. The accuracy of the calculated geometry of the molecule was evaluated in a comparison of the calculated and experimental results (electron-diffraction method). As a test we took the naphthalene molecule — a compound related to the molecular skeleton of gossypol.

It must be mentioned that of the three most widely used methods — MNDO, PM3, and AM1 — the last gives results closest to those of the electron-diffraction method. According to the results of analysis, the AM1 results and those of an electron-diffraction experiment agree within the limits of experimental error. On the other hand, because of the different phase states, the gossypol geometry obtained by the AM1 method differs considerably from the results of an x-ray structural investigation for the solid-phase state [6], regardless of the nature of the solvent used for growing the crystal.

Relative Energies of the Gossypol Tautomers

According to calculation, on the complete optimization of the geometric parameters all three of the above-mentioned structural forms of GP are energetically stable. The difference between the lowest-energy lactol form (the heat of formation

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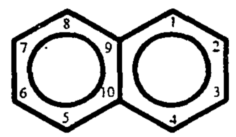
TABLE 1. Bond Lengths of the Naphthalene Molecule Found by Electron-Diffraction [7] and Quantum-Chemical (MNDO, AM1, PM3) Methods (Å)

	l(1–2)	l(2–3)	l(4–10)	l(9–10)
MNDO	1.382	1.429	1.439	1.435
AM1	1.373	1.416	1.422	1.418
PM3	1.369	1.415	1.421	1.410
ED	1.371(4)	1.412(14)	1.422(4)	1.420(7)



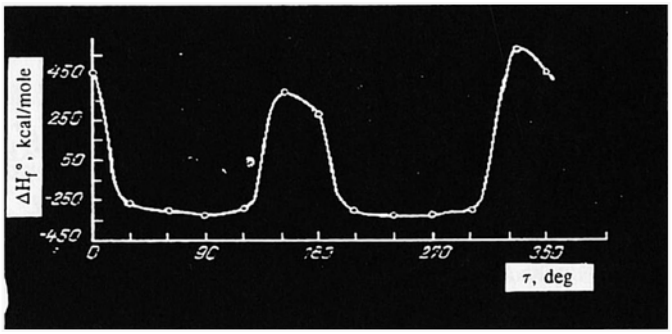


Fig. 1. Diagram of the potential curve of the dependence of the dihedral angle of the bridge bond on the heat of formation of the gossypol molecule in the aldehydic structural form.

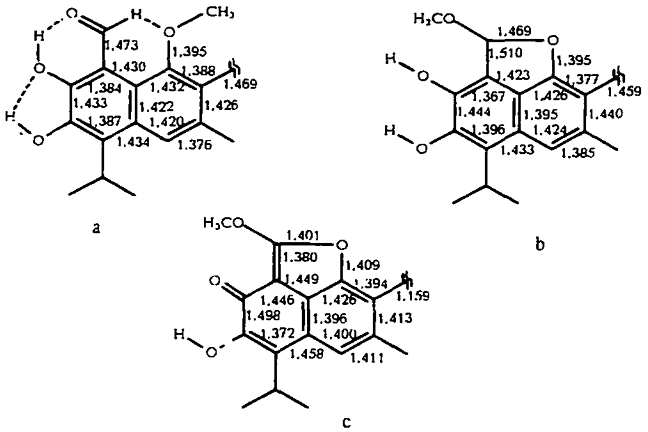


Fig. 2. Bond lengths of the skeletons of the tautomeric forms of gossypol in the gaseous state, Å.

of which is −246.205 kcal/mole) and the other forms is not significant. For example, the lactol form is preferable to the aldehyde form (−244.807 cal/mole) by −1.398 kcal/mole. The dilactol and monolactol-monoaldehyde (−246.077 kcal/mole forms are almost equiprobable, with a small advantage of the first (by 0.128 kcal/mole). The substantial difference of the components in the native mixture observed from experiment is therefore obviously due to the influence of the solvent.

In actual fact, it has been shown in [8] that in DMSO solution gossypol exists predominantly in the lactol form, and in acids, alkalis, and inert solvents it is in the aldehyde form. At the same time, the ratio of the aldehyde and lactol tautomers depends greatly in the degree of dilution of a solution of gossypol in DMSO with CCl_4. A dependence of the ratio of the components on the nature of the solvent has also been shown in [9-11]. Consequently, the realization of a particular form of gossypol depends on the reactivities of its active functional groups.

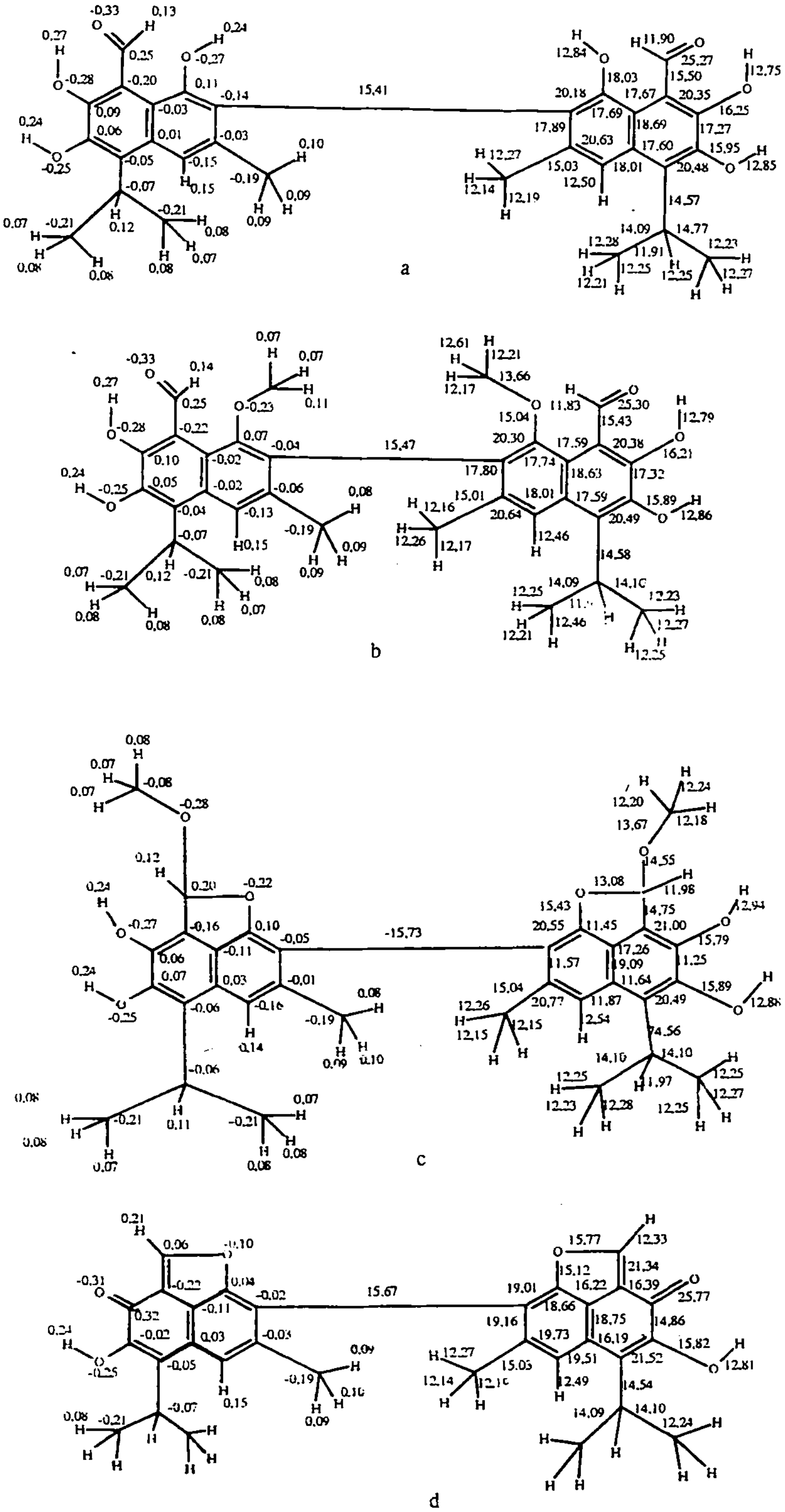


Fig. 3. Distribution of charges on the atoms (in the left-hand part of the molecule, in electron units, *e*), and bond energies (in the right-hand part of the molecule, eV) of the structural forms of gossypol: *a, b*) aldehyde form; *c*) lactol form; *d*) quinoid form [sic; but *b* and *c* relate to gossypol dimethyl ether — Translator].

Calculations of the Geometric Structures of the Gossypol Tautomers

The mobility of the two halves of the molecule around the central ordinary bond creates definite prerequisites for regulating the directions of the side chains. In view of this, it appeared of interest to determine the limit of permissible rotation in terms of the dihedral angle between the naphthyl fragments, since voluminous substituents of the aldehyde and isopropyl types create definite limitations to free rotation.

The diagram of Fig. 1 shows the potential curve of the dependence of the dihedral angle between the planes of the naphthyl nuclei on the heat of formation ($\Delta H_f°$) of the gossypol molecule in the aldehydic structural form calculated by scanning the torsional angle of the bridge bond within the framework of the AM1 method. As can be seen, global minima indicating the most stable states of the molecule correspond to a mutually perpendicular orientation of the two halves of the molecule.

Deviations of up to 30-40° do not greatly raise the heat of formation, but a further increase or decrease in the angle leads to a sharp rise in $\Delta H_f°$. It must be mentioned that the passage from one local minimum to another is restricted by high potential barriers. The difference in the heights of the barriers is due to the mutual influence of the voluminous methyl groups, which are closest to one another. A high barrier corresponds to the case when the methyl groups are closest to one another, and a low barrier to a remote position.

A comparative analysis of the bond lengths of the structural forms of gossypol is given in Fig. 2. According to AM1, the quinoid form possesses an aromatic nature to only a small degree: the bond lengths correspond to the values expected for a ketonic structure. For example, the C_6-C_7 bond is longer by 0.054 Å than in the lactol form, by 0.082 Å than in naphthalene, and by 0.107 Å than in benzene. On the whole, in the quinoid form, as compared with the lactol form, the ordinary bonds are shortened and the double bonds are lengthened.

Evaluation of the Reactivities of the Gossypol Tautomers

Thanks to its unique set of functional groups, the gossypol molecule possesses unusual properties. Thus, active groups in the form of hydrophobic and hydrophilic substituents exist separately on different sides of a naphthyl fragment. The strong inductive effect ($-I$) of the aldehyde and hydroxy groups, which is capable of repelling electron density from the aromatic ring, coincides in direction with the inductive effects ($+I$) of the alkyl substituents, which still further intensify the shift of the π-electrons in the direction of the aldehyde group

As can be seen from Fig. 3, the decrease in charge is particularly pronounced in the *ortho* and *para* positions to the aldehyde group, which, to all appearances, is due to the superposition of similarly directed electronic effects of the aldehyde and the other groups (0.06 *e* on C_6 and 0.01 *e* on C_{10}).

According to the distribution of electron density over the atoms, the highest concentrations of negative and positive charges are found on the aldehyde and hydroxy groups, while the alkyl substituents are impoverished with them. Thus, the actual skeleton of the naphthyl fragment is, at it were, polarized into two parts along a line passing through the bridge bond linking the two planar naphthyl fragments.

The strongest nucleophilic center is located on the oxygen atom of the carbonyl group (−0.33 *e*). Then come the atoms of the hydroxy groups:* $O(C_2)$ (−0.28 *e*), $O(C_{10})$ (−0.27 *e*), $O(C_3)$ (−0.25 *e*), and so on. Among the atoms of the naphthyl fragment the most nucleophilic is C_1 (−0.22 *e* for the aldehyde and quinoid forms, and −0.16 *e* for the lactol form). Electrophilic points are present on the hydrogen atoms of the OH groups. The $H(C_2)$ atom possesses the highest activity (0.27 *e*). Then follow the carbon atom of the carbonyl group (0.25 *e*), and the hydroxy group hydrogens $H(C_3)$ and $H(C_{10})$, each 0.24 *e*.

It must be mentioned that in a solvent with proton-accepting groups the $H(C_2)$ proton will probably participate in intermolecular hydrogen bonds with a further increase in the role of electrophilic addition and/or substitution reactions at the carbonyl carbon, since with respect to the distribution of charges over the atoms the highest affinity for electrophilic reagents on the $H(C_2)$ atom passes to $C(C_1)$.

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*From this point the numbering of the atoms is sometimes incomprehensible — in particular, no longer corresponding to the generally accepted scheme shown in Table 1 — Translator.

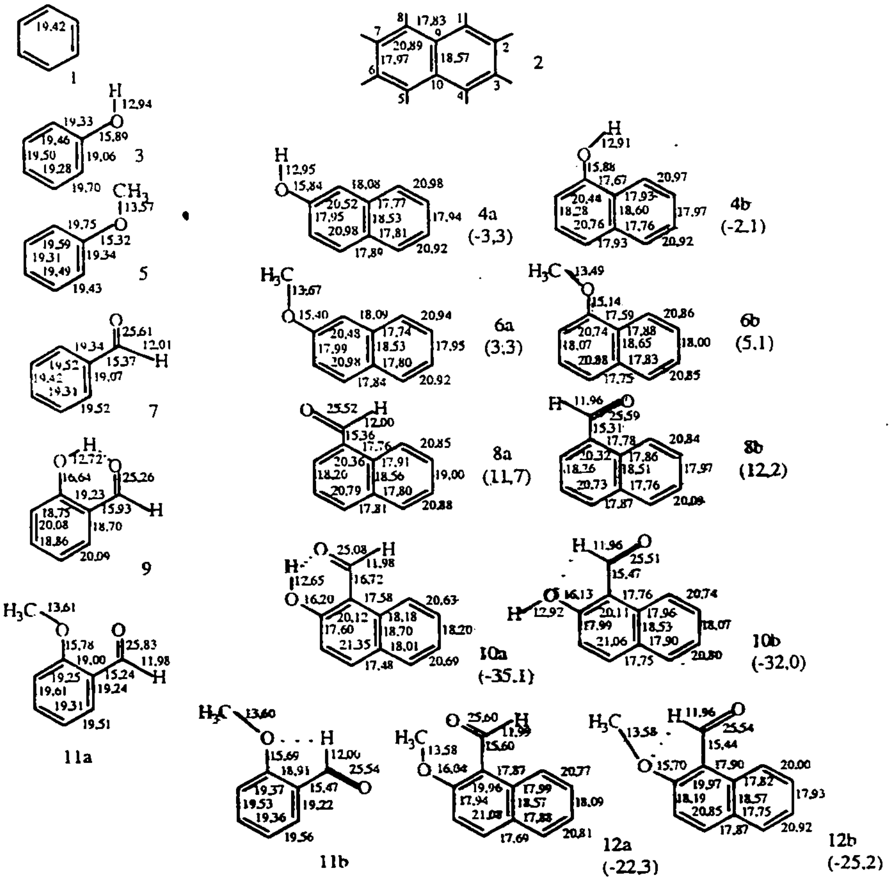


Fig. 4. Bond energies (eV) and heats of formation (kcal/mole) of aromatic molecules according to the AM1 method.

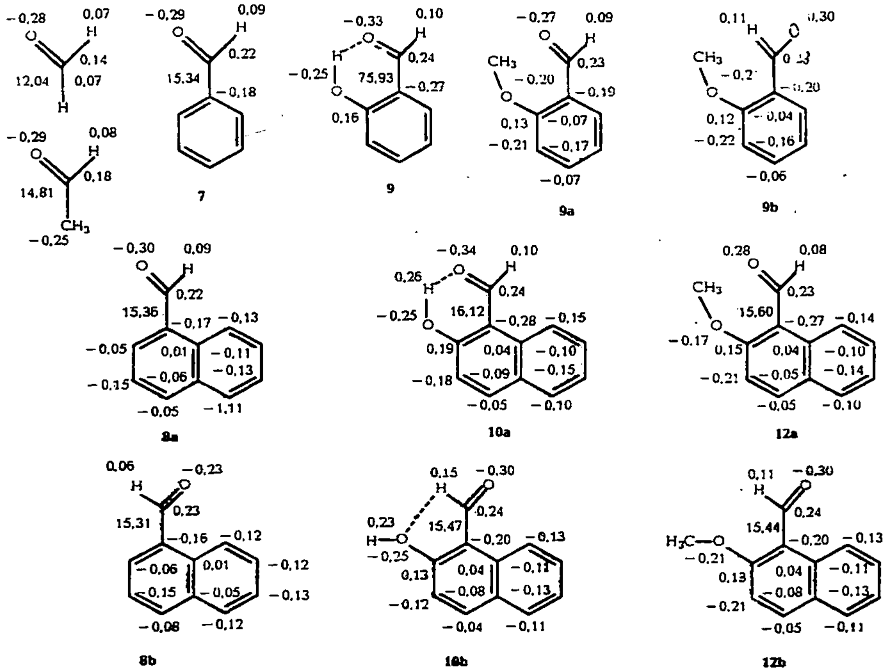


Fig. 5. Charge distribution on the atoms ($-e$ units) and energies of the carbonyl C–C bond (eV units).

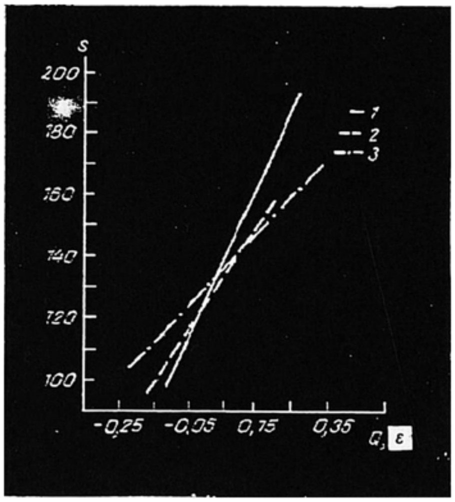


Fig. 6. Dependence of the NMR chemical shifts of the ^{13}C atoms of structural forms of gossypol on the atomic charges: *1*) aldehyde form; *2*) lactol form; *3*) quinoid form.

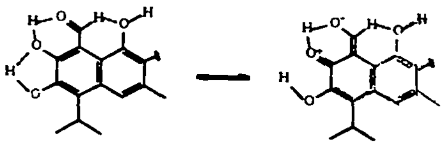
However, according to experimental observations, the carbonyl carbon atom does not participate in chemical reactions with reagents — the lowered sensitivity of the carbon atom of the aldehyde group is connected with an overlapping of the π-orbitals of the carbonyl group and of the aromatic ring. The process of electrophilic addition is thermodynamically less favorable in view of the high loss of resonance energy in the process of converting a trigonal carbon atom into a tetrahedral center. And, which is the main point, the access of this center for reagents is sterically hindered by the voluminous neighbors.

Running ahead, we may note that the difficulty of nucleophilic addition to the carbonyl group has been confirmed by the results of a calculation of frontier molecular orbitals (MOs) within the framework of the AM1 method. Thus, the contribution of the atomic orbitals of the carbon atom of the aldehyde group to the lowest unoccupied MO, which determines the reactivity of gossypol in relation to nucleophilic reagents such as OH^-, is insignificant at only 2.4%. These results therefore additionally confirm the passiveness of the $C(C_1)$ atom.

According to the distribution of electron density over the atoms, the hydroxy groups of a naphthyl fragment are reactive centers. The most sharply defined H-bond at the C_2 atom acts as a strong electron-accepting group of an acid reagent, since the bond is highly polarized (the charges on the oxygen and hydrogen atoms are -0.28 *e* and 0.27 *e*, respectively). The loss of a proton would lead to a delocalization of the electrons, in which the negative charge would not be localized on the oxygen but be redistributed over the whole unsaturated conjugated system synchronously with the cleavage of the O−H bond, leading to the appearance of the quinoid form.

Influence of the Peripheral Intramolecular Hydrogen Bonds on the Structure and Energy Characteristics of the Skeleton of the Gossypol Molecule

The formation of intramolecular hydrogen bonds (intraHBs) has a substantial influence on the energy characteristics of the molecules as a whole. Thus, a hydroxy group in the *ortho* position to an aldehyde group favors the appearance of a strong intraHB with the formation of a six-membered chelate ring. The molecule then exists predominantly in the structural form with two intraHBs illustrated below.



As it appears to us, for a clear idea of the dynamics of the intramolecular processes connected with the tautomeric interconversions it is desirable to analyze the change in the electronic structure of the system by passing successively from the simplest model without intraHBs through the addition of individual fragments (functional groups) to form complex models with intraHBs resembling gossypol (Fig. 4).

If we compare the energies of the C=O and C−C bonds of the aldehyde groups of the intraHB-free model molecules of benzaldehyde (7) (25.61 and 15.37 eV, respectively) and α-naphthaldehyde (25.52 and 15.36 eV for (**8a**) and 25.59 and 11.98 eV for (**8b**)) and of the intraHB-containing *o*-hydroxybenzaldehyde (**9**) (25.26 and 15.93 eV) and 2-hydroxy-1-naphthaldehyde (**10a**) (25.08 and 16.12 eV), it can be seen that on passing from (**9**) to (**10a**) (see Fig. 4) the nature of these bonds is greatly changed. For (**9**) the double bond of the carbonyl group is weakened by 0.35 eV while, conversely, the C−C bridge bond is strengthened by 0.56 eV. For 2-hydroxy-1-naphthaldehyde the changes are more pronounced — the formation of a chelate ring weakens the carbonyl group by 0.44 eV while, conversely, the C−C bond is strengthened by 0.76 eV. It is obvious that the formation of an intraHB between the oxygen atom of the carbonyl group and the hydrogen atom of the hydroxy group substantially delocalizes the electron density of the molecule, as far as the rearrangement of the skeleton of the molecule itself into a mesomeric structure, which is reflected in the values of its bond lengths. Here, as in the aldehyde group, the formation of an intraHB leads to a strengthening of the hydroxylic C−O bond (by 0.75 eV for (**9**) and by 1.04 eV for (**10a**)) as compared with its initial values in (**3**), (**4a**), and (**4b**), while for the O−H bond, conversely, it leads to a weakening (by 0.22 eV in the case of (**9**) and by 0.30 eV in (**10a**)). At the same time the benzene and naphthalene nuclei lose some aromaticity (as can be seen in Fig. 4, with the passage to *o*-hydroxybenzaldehyde and 2-hydroxy-1-naphthaldehyde an alternation of strong and weak bonds appears).

If we compare the bond energies of the model molecules with gossypol and its structural forms (see Fig. 3), it can be seen that the strength of the intraHB in the chelate ring of gossypol is lower. The energies of the carbonyl and hydroxy bonds of gossypol are raised (by 0.04 and 0.22 eV relative to the model compounds (**9**) and (**10a**) for the C=O bond and by 0.07 and 0.14 eV relative to (**9**) and (**10a**) for the O−H bond), while in the linking units, conversely, the bond energies are lowered: for C−C by 0.50 and 0.69 eV, respectively, and for C−O by 0.43 and 0.69 eV.

Consequently, in the aldehydic tautomeric form of gossypol the presence around the chelate ring of neighboring OH groups bound by intramolecular hydrogen bonds with the chelate-forming rings deactivates the originally strong hydrogen bonds, making possible the formation of weak and neutral H-bonds, which, in their turn, because of their passive behavior, facilitate structural rearrangements into other tautomeric forms. Moreover, the substantial fall in aromaticity in gossypol as compared with the initial compounds and, namely, with benzaldehyde (7), α-naphthaldehyde (**8**), *o*-hydroxybenzaldehyde (**9**) and 2-hydroxy-1-naphthaldehyde (**10**) confirms the idea of the appearance of chelate-forming rings with all possible intraHBs.

Analysis of the Electron Conformations and Structures of Molecules Analogous to Gossypol

In the investigation of gossypol it is of interest to calculate the energies of the bonds of the aromatic nucleus and of the side groups using the scheme proposed by Zhixing [12]. Since he gives no experimental results whatever, for comparison we calculated in parallel molecules forming component parts of gossypol and in sum making up the desired molecule: benzene (**1**), naphthalene (**2**), phenol (**3**), α-naphthol (**4a**), β-naphthol (**4b**), methoxybenzene (**5**), 1-methoxynaphthalene (**6a**), 2-methoxynaphthalene (**6b**), benzaldehyde (7), *trans*-α-naphthaldehyde (**8a**; the oxygen atom of the carbonyl group is in the *trans*- orientation to the seventh position of naphthalene, see Fig. 1), *cis*-α-naphthaldehyde (**8b**), *o*-hydroxybenzaldehyde (**9**), *trans*-2-hydroxy-1-naphthaldehyde (**10a**), *cis*-2-hydroxy-1-naphthaldehyde (**10b**), *o*-methoxybenzaldehyde (with the *cis*-orientation (**11a**); *trans*- (**11b**)), and 2-methoxy-1-naphthaldehyde (*cis*- (**12a**); *trans*- (**12b**)) (Fig. 4).

In its turn, the investigation of the electron conformations of the molecules concerned impelled us to undertake additional analyses unconnected with gossypol but supplementing the general idea of the properties of the parental compounds and gossypol. A comparison of the results for *o*-hydroxybenzaldehyde (**9**) with those for the *o*-methoxybenzaldehyde (**11**) molecules, on the one hand, and the results for 2-hydroxy-1-naphthaldehyde (**10**) with those for 2-methoxy-1-naphthaldehyde (**12**), on the other, shows (see Fig. 4) that the carbonyl groups in the methoxy derivatives are stronger (by 0.22 and 0.52 eV, respectively), while, conversely, the C−C bridge bond of the aldehyde group is weaker (by 0.13 and 0.52 eV, respectively).

Consequently, the energy supplements of the bonds of the aldehyde group observed in *o*-hydroxybenzaldehyde (**9**) and 2-hydroxy-1-naphthaldehyde (**10**) and characteristic for the formation of a chelate ring are absent in the case of the *o*-methoxy derivatives.

The bond of the carbonyl group in (**11a**) was shortened in comparison with "pure" benzaldehyde (by 0.003 Å) and, as a consequence of this, its bond energy increased. Analogous changes are characteristic for naphthaldehyde. The C–O and O–C ether bonds of the methoxy group in (**11a**) were shortened in comparison with the original molecule (**5**) (by 0.008 and 0.001 Å, respectively). The energy of the C–O bond had increased by 0.46 eV, and that of O–C by 0.04 eV, Moreover, the plane of the aldehyde group had turned by 42° relative to benzene and the whole group was inclined, as if repelled from the methoxy group, through a valence angle of 2.3° and through a C–C–H angle of 4.7-5° (while in isomer (**11b**) these angles were 0.9 and 4.7°, respectively), which obviously shows repulsion of the electron-donating carbonyl group from the methoxy group. And this, in its turn leads to a slight deformation of one conjugated π-system, with a disturbance of the form of the overlapping orbitals. In all probability this circumstance is also responsible for a fall in the energy of the bridge C–C bond of the aldehyde group in (**11a**).

It must be mentioned that in the isomer (**11b**) the valence angle of the hydrogen atom of the aldehyde group is 4.7° less than the standard value (120°), and the distance from the oxygen atom of the methoxy group to the hydrogen (**11b**) of the aldehyde group is 2.346 Å, so that in this isomer there is an intraHB forming a five-membered chelate ring. The same circumstances, connected with the presence of an intraHB in a five-membered ring, are repeated in a number of naphthaldehydes. The possibility of the formation of an intraHB in a conformer of the methoxy derivatives (**12b**) is clearly traced in a comparison of geometric parameters. Thus, characteristic features for the five-membered ring in (**12b**) are, in the first place, a shortening of the bond between the oxygen and the oxygen-carbon atoms (the atoms from the methoxy and aldehyde groups) in comparison with (**12a**) (by 0.200 and 0.142 Å, respectively) and, in the second place the plane of the aldehyde group is turned relative to the plane of the naphthalene fragment by 22° in (**12b**) and by 4° in (**12a**). It is known that the formation of even a weak side-chain intraHB in such rigid aromatic rings requires at least a partial overlapping of some orbital or other of the unshared electron pairs of the oxygen atom with the *s*-orbital of the hydrogen. It is obvious that the rotation of the plane of the aldehyde group and the shortness of the distance between the heteroatoms in (**12b**) are due to just this factor. Moreover, a comparison of the heats of formation of the two conformers shows that the presence of the intraHB in (**12b**) stabilizes the system by 2.9 kcal/mole as compared with (**12a**).

Attention must be directed to some internal valence angles of the five-membered chelate ring, since their magnitudes may to some degree affect the strength of the intraHB. Thus, in the 2-hydroxy derivatives of naphthaldehydes the internal angles of the chelate ring at the naphthalene skeleton exceed 120°; for example, the C–C–C angle at the aldehyde group is 121.0°, and the C–C–O angle at the hydroxy group in the *ortho* position is 126.3°. At the same time, in the 2-methoxy derivatives, conversely, these values are less than 120.0°. In (**12a**), the C–C–C valence angle at the aldehyde group is 119.7° and the C–C–O angle at the methoxy group is 116.3°.

The structure of the ring in (**12b**) appears similar. And in conformers (**12a**) and (**12b**) with an intraHB between the oxygen atom of the methoxy group and the hydrogen of the aldehyde group the C–C–O angle is 0.3° less than in the absence of an H-bond. Consequently, the magnitude of the valence angle does not depend significantly on the presence of an intraHB in the ring: the criterion is, rather, the nature of the substituent of the oxygen atom in the second position.

In contrast to *o*-hydroxybenzaldehyde, where an alternation of strong and weak bonds with an amplitude of 1 eV is observed within the benzene ring, in *o*-methoxybenzaldehyde there is almost no alternation of energies (see Fig. 4). In the case of naphthaldehyde derivatives, if as the basis of the criterion of aromaticity we take the situation for naphthalene, the presence of an intraHB with a chelate ring fairly substantially changes the aromaticity of the condensed rings (but more feebly than in *o*-hydroxybenzaldehyde). Passage to *o*-methoxy-1-naphthaldehyde restores the initial pattern of aromaticity. Consequently, a chelate ring with an intraHB of the O–H···H type in *o*-hydroxybenzaldehyde and in *o*-hydroxynaphthaldehyde exerts a substantial influence on the degree of aromaticity of the benzene and naphthalene fragments.

In a number of compounds (**9**, **11a**, **11b**) the weakest link of the benzene ring is the bond between *ortho*-oriented voluminous substituents, and this bond is weakened to a greater extent the less the functional groups are in contact with one another. Thus, in (**9**) the bond energy is 19.23 eV, and in (**11a**) and (**11b**) 19.00 and 18.91 eV, respectively. It can be seen that the formation of the chelate ring in (**9**) leads to an increase in the strength of the conjugated $\pi-n$-system. In (**11a**) the $\pi-n$-conjugation is retained, but, because of the mutual repulsion of the oxygen atoms the energy of the C_1-C_6 bond in (**11a**) has fallen. In (**11b**) this bond is weakened still further since the five-membered ring is more strained and the energy of the H-bond formed is too small.

Calculations of the Bond Energies of the Gossypol Tautomers and their Analogs

The energies of the bonds within a naphthalene fragment of the aldehyde form of GP are far lower than those of the analogous bonds in naphthalene. With characteristics closer to the naphthalene values, the bonds between unsubstituted or angular carbon atoms are retained as strong, and the analogous strong bonds are also retained in the case of the lactol and the quinoid forms. To all appearances, as was stated above, on passing from naphthalene to gossypol forms the aromaticity of the molecules is partially lost, with an overall fall in bond energy. In the quinoid form the aromaticity of the skeleton has fallen still further.

The absence of an aldehyde function in the lactol form is expressed by a strengthening of the C_1-C_2 bond. It is obvious that in the rearrangement of the aldehyde form into the lactol form the electron density from the hydroxy and aldehyde groups is delocalized onto the neighboring C_1-C_2 bond, with a further displacement of it to the carbonyl group on subsequent conversion into the quinoid form. The formation of an anhydride bond had a substantial influence on the overall electron-density distribution of the molecular skeleton. The C_8-C_9 and C_1-C_9 bonds, condensing the naphthalene and heterocyclic rings, are lengthened in comparison with the aldehyde form, which leads to a lowering of the bond energy. At the same time the bonds of the nucleus adjacent to a heterocycle — C_6-C_7, C_9-C_{10}, and C_1-C_2 — are strengthened, showing the retention of their bond lengths.

In the case of the quinoid form, because of the substantial loss of aromaticity of the molecule, the double and single natures of the bonds appear more strongly. For example, the nodal bonds C_1-C_9 (16.22 eV) and C_8-C_9 (18.66 eV) are closer in energy to the analogous bonds of the saturated systems. In addition, the appearance of additional double bonds at the sides of the molecules of the quinoid form leads to a expansion of the scale of conjugation, including the anhydride part of the molecule. This circumstance leads to an increase in the energy of the ether bonds of the $O-C_{11}$ type.

Role of the Aldehyde Group in the Formation of Reactive Centers

Let us consider the influence of the electron cloud of the skeleton of the molecule and of substituents of different kinds on the reactivity of the aldehyde function. As can be seen from Fig. 5, which shows the charges on the atoms and the energies of the C–C bonds (in the first molecule, of the C–H bond), the affinity for nucleophilic substances rises from left to right as the π-electronic system grows on passing from the simplest cases to gossypol. At the same time, as can be seen, the polarity of the carbonyl double bond rises. While in the first and second molecules the displacement of the π-electrons of the substituents liquidates to a slight extent the deficit of electrons on the carbon atom of the carbonyl group, in the aromatic systems, conversely, the carbon becomes more electrophilic and the repulsion of electrons in the direction of the oxygen atom increases, thereby creating a basis for the formation of an intraHB. At the same time, in *o*-hydroxybenzaldehyde and 2-hydroxy-1-naphthaldehyde and in the aldehyde form of gossypol, because of the displacement of the π-electron cloud of the aromatic nucleus the energy of the C_1-C_7 bond is raised, acquiring an intermediate nature, halfway between single and double.

While in the lactol form, regardless of the formation of an anhydride bond, the overall distribution of the charges on the atoms is identical with that of the aldehyde form, in the quinoid form the pattern has changed substantially through the presence of the carbonyl function conjugated with the π-unsaturated double bond. The most characteristic changes are those on the C_7 carbon of the carbonyl group of the naphthyl fragment (by 0.26 *e*), and then on the C_8 and C_6 atoms (by 0.06 and 0.09 *e*, respectively). The charge on the C_{11} atom due to delocalization of electron density from the naphthyl nucleus is 0.06 *e*.

Analysis of the Link of the Chemical Shifts of the ^{13}C Nuclei with the Electron Densities of the Carbon Atoms

Aromatic compounds are widely used as models in determining the relationship between the chemical shifts of ^{13}C nuclei and charge densities [13]. In view of this, it appears of interest to consider the relationship of the chemical shifts of the ^{13}C carbon atoms in the NMR spectra to the electron densities of the atoms of gossypol and its structural forms, as aromatic systems with unusual properties. The chemical shifts of the ^{13}C nuclei of gossypol and its structural forms and derivatives have been determined previously [11]. On the other hand, the study of such a correlation would enable us to approach the nature of the structure–properties relationship in a series of physiologically active gossypol molecules.

As follows from Fig. 6, in the majority of cases the chemical shifts of the carbons of gossypol and its structural forms are determined by the density of the electron cloud of the nucleus under observation. The deviations from a linear relationship are possibly connected with the influence of the magnetic anisotropy of the neighboring groups and bonds. In addition, this dependence of chemical shift on charge corresponds to a general law of the downfield shift of the signals with an increase in the charge on the atoms. Within each group of points relating to a given structural form, a definite linearity of the correlation appears.

EXPERIMENTAL

The quantum-chemical investigations of the molecules of gossypol and its analogs were performed by the MO LCAO semiempirical method in the MNDO, PM3, and AM1 approximations. The AM1 method was used as the most suitable for heteroaromatic systems.

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