Вісник ХДУ, № 434 БІОФІЗИЧНИЙ ВІСНИК, вип. 3 1999

УДК: 577.3 : 577.33 : 615.281

МОЛЕКУЛЯРНА БІОФІЗИКА

QUANTUM CHEMICAL STUDY OF DECAMETHOXINUM AND RELATED DICATIONS

M.V. Kosevich, V.A. Pashinskaya, S.G. Stepanian, V.S. Shelkovsky, V.V. Orlov, Yu. P. Blagoy

B.Verkin Institute for Low Temperature Physics and Engineering of the National Academy of Sciences of Ukraine, Kharkov, 310164, Lenin Avenue 47; e-mail: mvkosevich@ilt.kharkov.ua

Поступила в редакцию 25 января 1999 г.

The structural and electronic parameters of the dication of antimicrobial drug decamethoxinum and a set of model ammonium dications with various size of alkyl substituents at quaternary nitrogens were determined by means of AM1 quantum mechanical calculations. It is shown that the most favourable conformation of the decamethoxinum dication in the absence of water solvent is an extended one with side substituents in the *trans*-position with respect to the central chain and intramolecular solvation of ammonium groups by carboxyl oxygens. The positions of two centers of charge distribution in the decamethoxinum dication are close to the location of quaternary nitrogens while the analysis of the set of model dications revealed a strong dependence of the positions of such centers on type and size of the alkyl substituents. Possible correlations of the molecular parameters and the biological activity of ammonium salts are discussed.

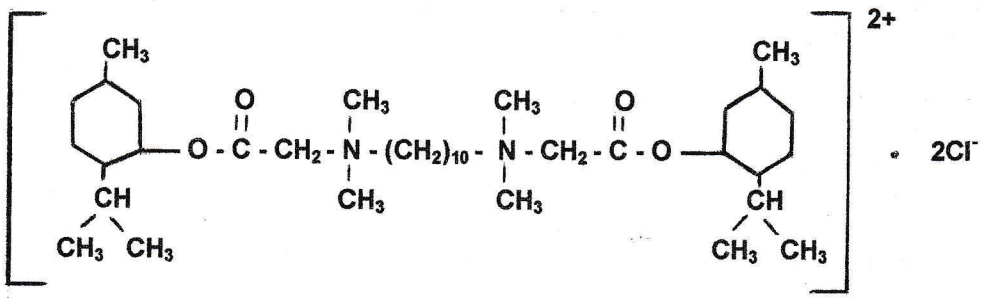
KEY WORDS: diquaternary ammonium antimicrobial agents, decamethoxinum, quantum chemical calculations

A class of salts of diquaternary ammonium compounds embraces the substances the distinctive feature of which is the presence of two quaternary nitrogens in the structure of their dications. At the same time the possibility of practically unlimited variation and combination of types of the substituents at quaternary nitrogens offers a variety of compounds with a wide spectrum of chemical properties and biological action, including poisons and antidotes, chemotherapeutic antimicrobial and anticancer agents, miorelaxants, herbicides, dyes, and many others. In this connection investigation of the relations between the structure of substituents at quaternary nitrogens and the physico-chemical properties of bisquaternary compounds is of great interest for elucidation of possible mechanisms of their biological action.

The cationic surface active compounds based on quaternary and bisquaternary salts possess antimicrobial properties and some of them, such as decamethoxinum developed in Ukraine, are used as medicines [1-3]. In this type of compounds the substituents provide surface active properties and facilitate the adjustment of the drug to its molecular receptors in the bacterial cell [3]. The nature of these receptors, however, is not yet entirely known. The obvious interaction of surfactants with cell membranes does not explain all the effects of bisquaternary agents, and more complicated mechanisms of intrusion of the drugs in the cell metabolism and biopolymers functioning may be involved [3]. In this connection a knowledge of structure, conformational mobility, charge distribution in the dications of the drugs is necessary for evaluation of the possibility of their interactions with biologically important molecules.

Such data are also vital for interpretation of the results of experimental, in particular, spectroscopic, studies of these compounds. Recently in the frames of mass spectrometric technique an approach was developed, which allows to estimate experimentally the energy of coulomb repulsion in multiply charged molecules [4, 5]. Awareness of actual charge distribution over the atoms of ionic species is required in these experiments.

The aim of the present work was to perform quantum chemical calculations of structural and electronic parameters of a number of diquaternary compounds which vary in type and length of substituents at quaternary nitrogens, and to estimate intramolecular repulsion energy in the dications. The objects of the study were a dication of decamethoxinum, an antimicrobial drug widely applied in composition of relevant medicines the formula of which is as follows



and a set of model dications with variable length of central inter-nitrogen and side alkyl substituents.

THEORETICAL METHODS

Calculations of structural and electronic parameters of the above listed quaternary ammonium dications were performed in the frames of semiempirical AM1 procedure using the MOPAC 6 program package [6]. A good agreement between the dipole moment values determined using charges on atoms, obtained by the AM1 technique and measured experimentally for a large row of organic compounds proved the validity of application of the present method for evaluation of charge distributions [6].

Intramolecular coulombic repulsion energy **U** between two charged parts of the dications was calculated using formula (1)

$$U = \sum_i \sum_j U_{i,j} = \sum_i \sum_j c \frac{q_i \cdot q_j}{r_{i,j}} \quad , \qquad (1)$$

which accounts the interactions between each pair of charges q_i and q_j located on atoms i and j, taken from two symmetrical halves of the dication, and the interatomic distances r_{ij} between the corresponding pairs of atoms (c is a constant being 1.439 nm/eV in CI units [5]). Knowledge of the total coulomb energy allowed to estimate the distance $r_{w1\text{-}w2}$ between two geometrical centers of weight (w1, w2) of the charge distribution in the ion:

$$r_{w1\text{-}w2} = \frac{c\, q_1\, q_2}{U} \qquad (2)$$

RESULTS AND DISCUSSION

The geometry fully optimized in the AM1 calculations geometry and the charges on atoms of the dication of decamethoxinum are presented in Fig. 1 a, b. The optimal conformation of the central polymethylene chain $-(CH_2)_{10}-$ (with no influence of a solvent) of the dication is completely extended. The length of the organic dication in this extended conformation is 2.75 nm, the distance between two quaternary nitrogens $r_{N\text{-}N}$ is 1.39 nm.

The methyl substituents at quaternary nitrogens (N31, N44, here and further the atom labeling is as in Fig. 1) occur in opposite directions in relation to the chain axis and the menthyl rings in decamethoxinum are in *trans*-position in relation to the chain as well. It should be mentioned that, along with the structure featured in Fig. 1, there is a number of close energy minima for the positions of menthyl rings and their own conformers. Heat of formation of such conformers differs from that of the most favourable structure (71.96 kcal/mole) by 1-3 kcal/mole. The ionization potential of doubly charged species is comparatively high and comprises 14.09 eV.

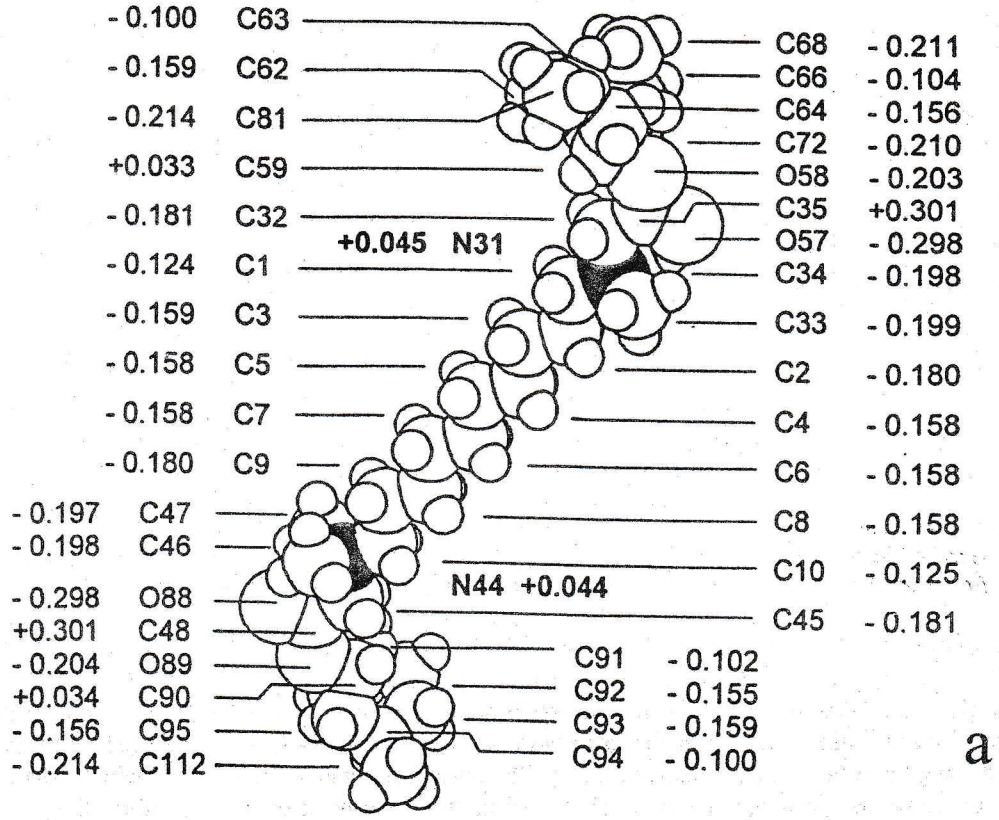
Another interesting feature of the structure of the dication of decamethoxinum is that the positively charged quaternary groups are «solvated» by carboxyl oxygens. For example, the distance between O57 and C33 or C34 of the methyl groups at N31 is 0.27 nm, the value of which is comparable with the average length of hydrogen bonds. The analogous effect was reported in the literature, for example, for a cyclic antibiotic gramicidin S, in which structure neutral [7] or charged due to protonation [8] amino groups on the ends of side chains of two ornitine residues were solvated by carboxyl oxygens of the polypeptide backbone. An intramolecular solvation may contribute to the stabilization of decamethoxinum dication.

Analysis of the atomic charge distribution shows that a partial charge on quaternary nitrogens themselves is rather small, being 0.044 of electron unit. The positive charge of the dications is distributed over the hydrogens, mainly those at four carbons adjacent to a quaternary nitrogen and some hydrogens in the central polymethylene chain (Fig. 1).

An assessment of the distributions of the positive charge over four radicals connected with a quaternary nitrogen in one of the two symmetrical halves of the decamethoxinum dication is presented in Fig. 2. One can see that about 83% of one-electron charge is concentrated on a fragment which could be conventionally called as the first coordination sphere of a quaternary nitrogen. This involves the nearest-to-nitrogen two methyl and two methylene groups, including C1, C32 and C33, C34 for N31 or C10, C45 and C46, C47 for N44, and hydrogens connected with them. The rest of the charge is shifted to the other atoms of the central and terminal radicals.

Thus, in the decamethoxinum dication (as in some other calculated bisquaternary ammonium structures [9]) the «excess» charge has no point localization but is smeared over the ion. Since four substituents at each quaternary nitrogen differ significantly in their structure and size, the charge distribution is not symmetrical, which is to say that it is not valid to assume *a priori* that the geometrical center of charge distribution (w1 or w2) coincides with the position of a quaternary nitrogen.

As it was mentioned in the Introduction, theoretical determination of charge distribution and geometrical positions of w1, w2 is of interest not only for evaluation of biological properties of the dications, but for interpretation of some experimental results on their molecular parameters. In particular, one of the mass spectrometric



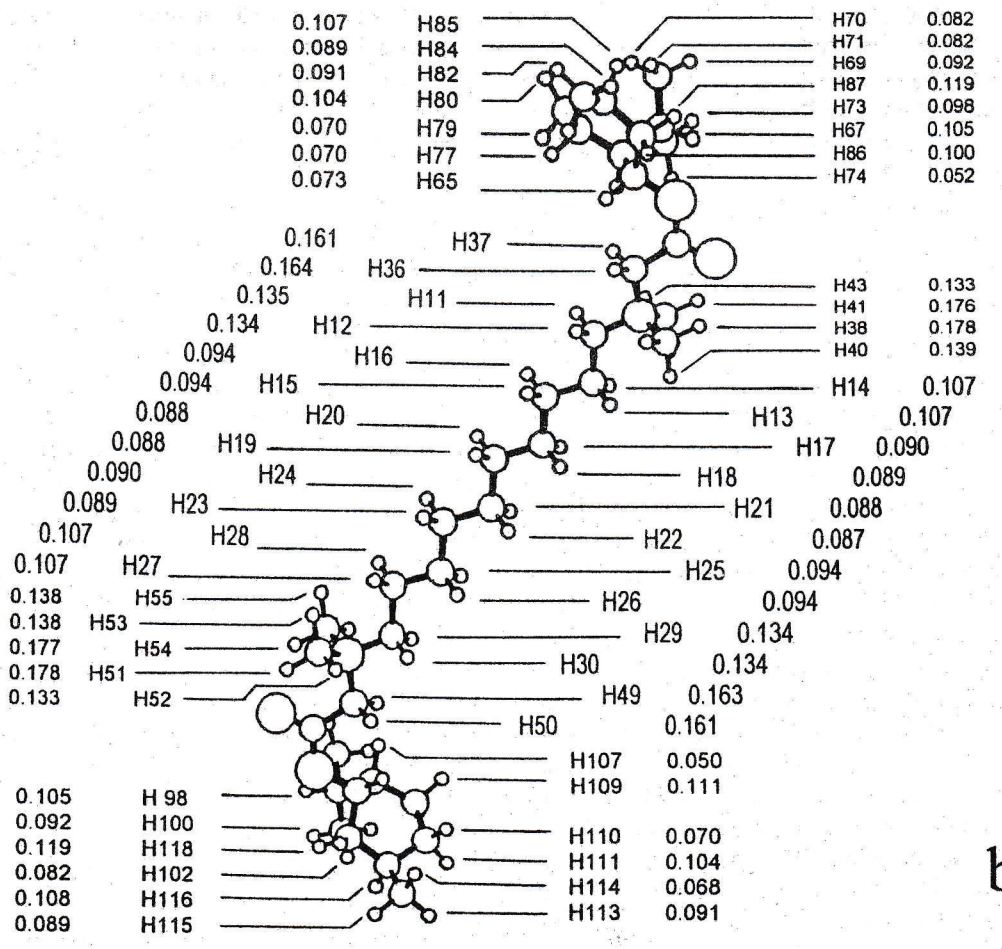


Fig. 1. Optimized in AM1 calculations geometry of the dication of decamethoxinum with indication of charges on atoms of C, O, N (a) and H (b). (Radii of spheres in (a) are conventional and do not correspond to van-der-Waals radii).

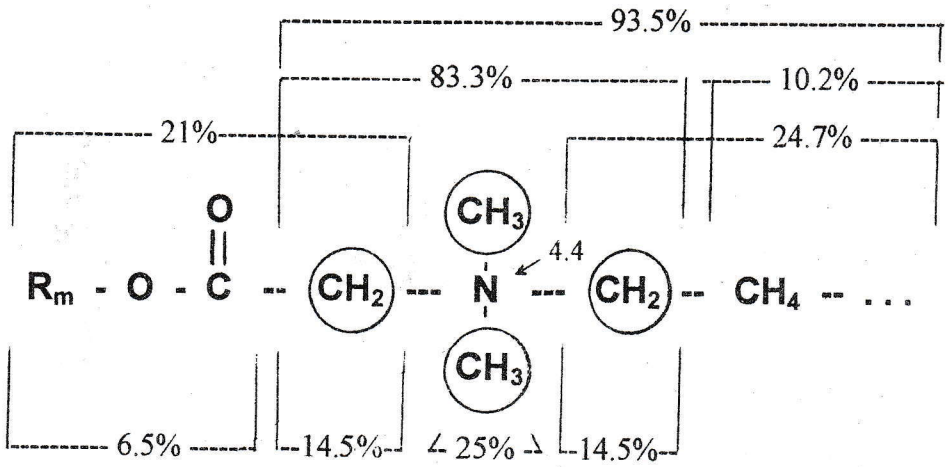
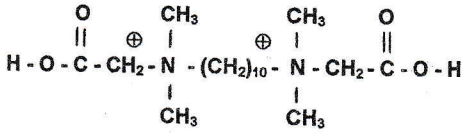


Fig. 2. The scheme of distribution of positive, one electron in absolute value, charge over functional groups of one-half of the decamethoxinum dications. «Excess» charge on each hydrocarbon group was calculated as a difference between the absolute values of a sum of charges on the hydrogens minus the charge on the carbon.

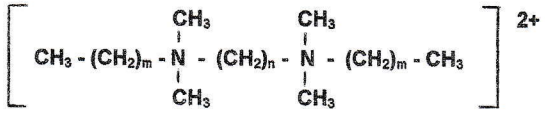
techniques, described in details elsewhere [4, 5] allows direct experimental determination of coulomb repulsion energy U on the basis of measurement of the kinetic energy released during fragmentation of a doubly charged ion to two singly charged fragments. This technique was designed to provide a tool for determination of the conformation of ionized chain molecules in the gas phase, as the distance between the charged sites can be easily calculated using the experimental U value in Eq. 2. Obviously, the coincidence of the experimentally determined $r_{w1\text{-}w2}$ value with a maximum possible value for a given molecule means its extended conformation, while smaller $r_{w1\text{-}w2}$ values evidence the bend structure. It is also obvious, that in the case of complicated molecules the measured r value corresponds to the distance between the centers of charge distribution w1, w2, which, in general, can be shifted from the positions of heteroatoms (such as a quaternary nitrogen) due to the mentioned above asymmetry of the charge distribution. The necessity of accounting of such a shift has not been paid proper attention up to now. Its effect, however, can be noticeable. For example, an interesting fact was encountered in our recent mass spectrometric measurements by the above technique [10] of coulomb repulsion it two species - decamethoxinum itself and its doubly charged fragment



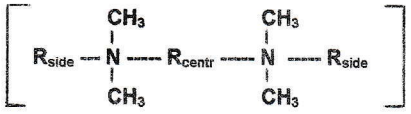
which differs from the intact dication by the lack of two side menthyl rings (⊕ symbol denotes delocalization of a unit charge). In the assumption that the overwhelming part of the charge is concentrated in the first coordination sphere and geometrically centered on quaternary nitrogens, no difference in U values for the two similar structures must be observed. In practice, however, the measured coulomb energy for the above fragment appeared to by in about 0.2 eV larger than that for the whole decamethoxinum dication.

Calculations of U value by using in Eq. 1 the actual charge values and the intercharge distances determined in the present AM1 studies for the most extended conformation of the both dications, all atoms of the molecules being taken into account, showed that U = 1.07 eV for decamethoxinum is indeed smaller than U = 1.12 eV for the fragment, and there is a good qualitative agreement between the experimentally and theoretically determined values. Thus, while the distance between the quaternary nitrogens in the two dications is the same ($r_{N\text{-}N}$ =1.39nm), the calculated distances between the centers of charge distributions differ, being 1.34 nm and 1.28 nm in decamethoxinum and its fragment, respectively. This means that the smaller intercharge distance in the fragment is due to different charge distribution, but not due to its presumable bent conformation. The value of coulomb energy in decamethoxinum is lower as compared to that in its smaller fragment because about 6% of each «excess» charge is shifted to more distant from the center menthyl radicals.

The above described effect points to the necessity of accounting the influence of type and size of substituents at quaternary nitrogens on position of the center of charge distribution in the bisquaternary ions. To establish some general rules of such an influence, the of charge distribution and coulomb energy were calculated for a number of model dications of the following type



In the above structures the dependence of charge distribution on n and m values, that is the size of the central R_{centr} and side R_{side} radicals, marked in the next scheme, was analysed:



The main results are as follows. Firstly, the variations in n and m values show, that roughly 25±5% of a unit charge is distributed over each of the four substituents (see Fig. 2 as example), that is the deviation from one fourth share per radical varies within no more than ±5% in the dependence of the size of the radicals.

Secondly, the dependence of charge distribution in the central substituent R_{centr} on its length, that is the number of methylene groups n in the polymethylene chain $(CH_2)_n$, was analyzed for a set of dications $[(CH_3)_3 - N - (CH_2)_n - N - (CH_3)_3]^{2+}$ with R_{side} = const = CH_3 . In Fig. 3 schematic representation of charge distribution on carbons and hydrogens in a set of central chains with even n values is shown (the structures with odd n values gave qualitatively similar results). For comparison the data for a neutral extended polymethylene chain are presented in the same plots. Calculations for hydrocarbons $(CH_3)_3 - (CH_2)_n - (CH_3)_3$ with n up to 12 show that a $-(CH_2)_n-$ chain has equal charges on all carbons (-0.158) and hydrogens (0.079x2H), which compensate each other. It can be seen that in the case of dications the highest charges are located on the hydrogens of the first three methylene groups next to nitrogen (Fig. 3b). The shorter the chain, the relatively higher charges are on the hydrogens. The tendency for a decrease of the partial charge per hydrogen from a terminus to the center of the chain is nonlinear. For longer chains the charges on the hydrogens of the central links decrease noticeably, but they do not reach the value characteristic of pure polymethylene even for a chain as long as of 16 groups. In contrast to hydrogens, the charges on carbons (Fig. 3 a), showing peculiarities for the atoms in α and β positions in relation to nitrogen, reach neat hydrocarbon values for chains with n > 4

Thirdly, several sets of dications $[CH_3 - (CH_2)_m - N(CH_3)_2 - R_{centr} - (CH_3)_2 N - (CH_2)_m - CH_3]^{2+}$ with constant length of the central chain and varying length of the side radicals (m = 0, 1, 2, 3) were considered. Again, the hydrogens of the closest to nitrogen methylene groups have the largest charge. In contrast to the central chain, the positive charges on CH_2 groups in the side chain decrease down to the values characteristic of pure hydrocarbons at m = 8.

From the above data it follows that the influence of the excess charge, that is the deviations from the charge distribution characteristic of a similar neutral polymethylene chain, extends for a distance as large as 0.5-0.6 nm (which corresponds to 2-3 methylene groups) from the position of quaternary nitrogen in the directions both of the central and side substituents.

One more interesting peculiarity was observed: a variation in the length of the side radicals does not affect the distribution of charges in the inter-nitrogen central chain, which remains the same as in Fig. 3 for corresponding n. Two methyl groups and nitrogen lose only several percent of charge with increase of the length of the fourth alkyl radical. The most substantial loss in favour of other links of the R_{side} radical bares hydrogens of the methylene group next to nitrogen in the fourth side radical. The shift of some share of the charge along the side chain away from nitrogen decreases the total charge in the first coordination sphere of the nitrogen, which must reduce the coulomb repulsion energy and enhance the stability of the dication.

In Fig. 4 comparison of the coulomb repulsion energy and the intercharge distances calculated in two different assumptions for a set of dications with R_{side} = const and R_{centr} variable is presented. In the first case an approximation, traditionally believed to be sufficient, was applied: two unit charges were considered to be centered on the sites of two quaternary nitrogens. In the second case the distribution of charges on all atoms of the molecule was accounted in Eq. 1 and the intercharge distances were calculated using Eq. 2. Noticeable deviations of two sets of data which change their sign in the dependence on n was observed. In comparison with the simplified point-charge model, the account of real charge distribution shows that the dications with smaller central chains appear to be more stable due to the shift of the center of charge distribution to the side radicals, while in the dications with larger R_{centr} the center of distribution is shifted to the inter-nitrogen substituent, which cause some destabilization. The «switching» point where the center of charge distribution coincides with the position of nitrogen, was observed at n = 6. As to quantitative values, the most significant difference by about 0.85 eV between the U values calculated in the two assumptions was revealed for n = 2 (Fig. 5). The same data demonstrated that an error in estimation of intercharge distances due to the use of too rough approximations may reach 10-15%.

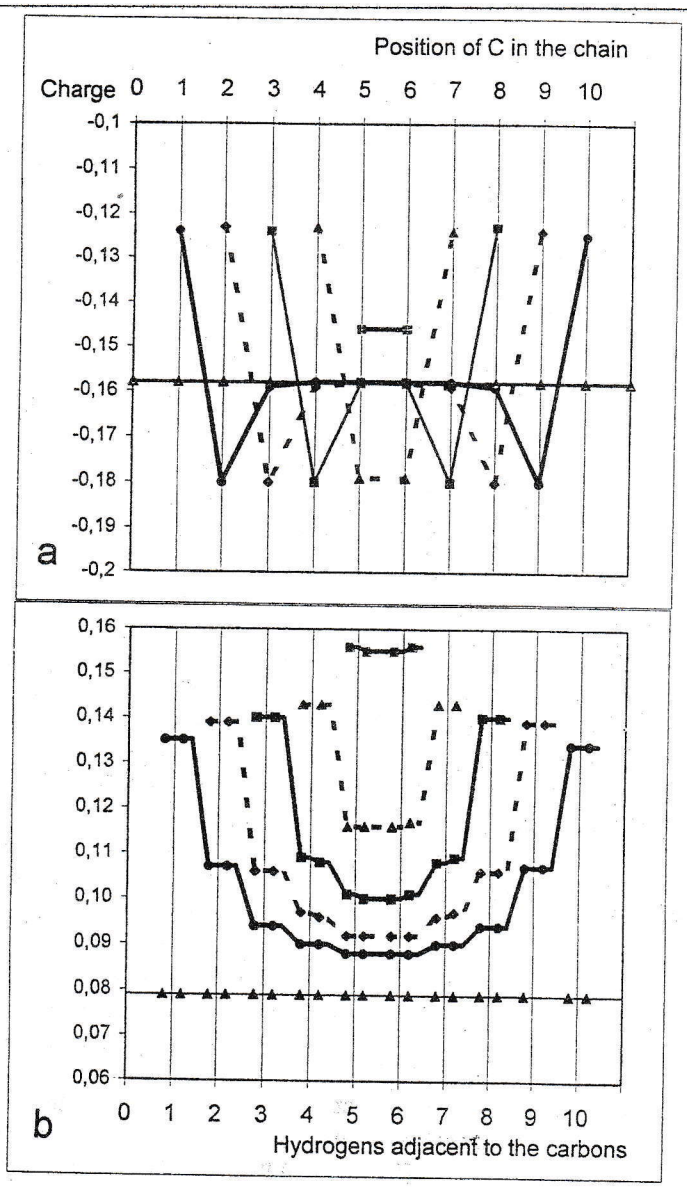


Fig. 3. Schematic representation of the distributions of the charges on atoms of carbon (a) and hydrogen (b) in the dependence of the number of atoms n in the central polymethylene chain - $(CH_2)_n$- of dications $[(CH_3)_3 - N - (CH_2)_n - N - (CH_3)_3]^{2+}$ (n = 2, 4, 6, 8, 10, 12). Straight base lines represent the equal charges on C and H atoms in the «infinite» linear polymethylene chain.

Although the alkyl part of the side chain of decamethoxinum is presented not by a linear chain, but by a cyclic menthyl ring, the effect of this type of substituent is similar to that of the chain of the same number of carbons. As it was shown above, the side menthyl radicals which «pump» some share of charge from the first coordination sphere increase the stability of the decamethoxinum dication by ~5% as compared with its analog with only one CH_2 group in the side radicals.

It should be marked that some of the above model dications are miorelaxants, that is they have the mechanism of action different from that of decamethoxinum. In contrast to these compounds a chain of heteroatoms COO is included to the side chains of decamethoxinum and related drugs, such as ethonium. This atomic group, obviously, has its effects on intermolecular interactions and methabolism of the antimicrobial drugs.

The previous discussion concerned the charge distribution in the most extended conformation of the dications, which appeared to be the most favourable in the gas phase. To analyse possible reasons of this favourability, several conformers of decamethoxinum were calculated using fixing of at least one «kink» in the polymethylene chain. The change of conformation did not affect the general pattern of charge distribution determined above for the linear dication, except of some changes in charges on hydrogens at the carbons directly participating in the «kink». The coulomb energy calculated for the structure with one kink in the middle of the central chain appeared to be 1.18 eV, which is grater as compared to the extended conformation due to shortening of distances between all charged atoms. The distance $r_{w1\text{-}w2}$ = 1.22 nm calculated with account of all atoms was close to $r_{N\text{-}N}$ = 1.24 nm for this conformation.

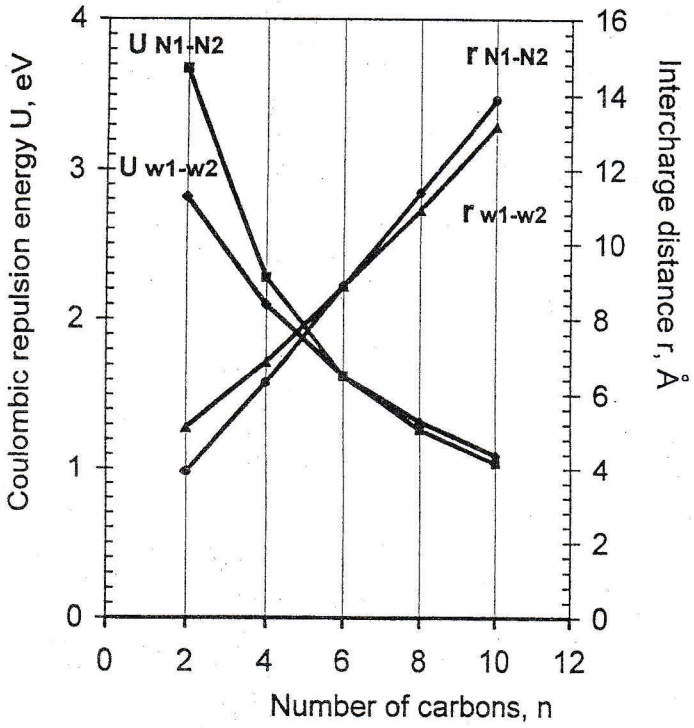


Fig. 4. The coulomb energy and the intercharge distances for a set of dications in the extended conformation with R_{side} = const = CH_3 and the number of -(CH_2)- groups in R_{centr} varied from 2 to 10, calculated in two assumptions: 1) point unit charges are centered on quaternary nitrogens (r_{N1-N2} , U_{N1-N2}); 2) charge distribution over all atoms of the dication is accounted (r_{w1-w2} , U_{w1-w2}).

From the above at least three reasons for stabilization of extended conformation of the central polymethylene chain of decamethoxinum follow. Firstly, any bend of the chain provokes repulsion between partially positive hydrogens; secondly, kinks distort the symmetry of charge distribution in the chain (that is deviations from the symmetrical plots in Fig. 2); thirdly, the coulomb repulsion increases upon shortening of the distance between the centers of charge distribution. It should be noted that all the considerations presented are valid for the isolated molecules (ions) in the gas phase, and the interactions with the solvent may have relevant effects on this type of amphyfilic compounds. However, some biologically important processes such as interaction of the surfactants with cell membranes, proceed in a deficit of water molecules, in which case the data on molecular parameters in the absence of the polar solvent may be appropriate.

It has been earlier determined that the spectrum of antimicrobail action of bisquaternary cationic surfactants depends on size of side substituents R_{side} and inter-nitrogen distance r_{N-N} which is connected with the size and conformational mobility of R_{centr} [11, 12]. The data reported here show that the differences in charge distribution and charge density over the dication may be responsible for the binding of a particular drug to a specific receptor. It is established that two unit charges have no point localization but are smeared over the organic ion. The first coordination sphere of each quaternary nitrogen has a mean radius of 0.214 nm, and only 83% of a unit charge is distributed over its surface. This may suggest that not a point negative charge, but an extended zone of negative electrostatic potential is necessary for a more firm coordination of the quaternary group with the surface of its virtual receptor; spatial distribution of charge and a particular the value of charge density may provide specific recognition of a definite receptor [13]. The energy of interaction of the species with delocalized charges with other molecules must be smaller in comparison with the ions with localized «point» charges as well. Delocalization of charge increases the area of the positively charged surface of the dication, in particular, on account of the hydrocarbon substituents, which decreases their lipofility as compared with the pure hydrocarbon species of the same size.

CONCLUSIONS

The structural and electronic parameters of the dication of antimicrobial drug decamethoxinum were determined by the AM1 quantum chemical method. It was shown that the most favourable conformation of the decamethoxinum dication in the isolated state is extended (which was confirmed by mass spectrometric data [10]). Two positive charges of the ion are distributed over the hydrogens of alkyl substituents at quaternary nitrogens, which reduces the intramolecular coulombic repulsion in comparison with the virtual point-charge species and

thus stabilize the dication. The positions of two centers of charge distribution in the dication, however, are close to the location of quaternary nitrogens (r_{w1-w2} = 1.34 nm *vs* r_{N-N} = 1.39 nm); the calculated intramolecular coulomb repulsion energy comprises 1.07 eV. Solvation of quaternary groups by carboxyl oxygens stabilize the structure as well.

Theoretical calculations for a set of model dications with varied size of inter-nitrogen and side substituents allowed some general conclusions to be made concerning structural and electronic parameters of bisquaternary compounds:

- in quaternary ammonium ions the charge has no point localization but is distributed over the substituent radicals at quaternary nitrogens;
- the influence of the «excess» charge extends for a distance as long as 0.5-0.6 nm from the position of a quaternary nitrogen;
- in the case where four radicals are of different length and structure, roughly one fourth (±5%) of the one electron charge occurs at each radical, but the geometrical center of weight of the charge distribution does not obligatory coincide with the position of quaternary nitrogen and can be shifted to one of the substituents;
- larger side radicals «pump» the charge from the nearest to nitrogen CH_2 group and thus reduce the coulomb repulsion in the bisquaternary ions due to the decrease of charge in the first coordination sphere; the presence of heteroatoms (groups) in the side chain could influence this effect;
- the distribution of charges in the central inter-nitrogen chain, on the contrary, seems to be insensitive to the changes in other radicals and remains the same at a given $-(CH_2)_n-$ length.

Information on the structure and charge distribution in the decamethoxinum dication can be used in further evaluation of its interactions with its virtual molecular receptors in a microbial cell.

REFERENCES

1. Машковский М.Д. Лекарственные средства. М. Медицина. 1978. Ч. II. С. 311.
2. Волянский Ю.Л. Противомикробная активность новых азот- и фосфорсодержащих органических соединений, фенолов и ферроценов: Автореф. дисс. ... д-ра мед. наук. - Москва, 1981.
3. Виевский А.Н. Механизмы биологического влияния катионных поверхностно-активных веществ. Москва. Б.И. 1990. 249 с.
4. Cooks R.G., Beynon J.H.,Caprioli R.M., Lester R.G. Metastable Ions. Elsevier. Amsterdam, 1973.
5. Szilagyi Z., Vekey K. // Eur. Mass Spectrom. 1995. V.1. P.507-518.
6. Dewar M.J.S., Zoebisch E.G.,Healy E.F., Stewart J.J.P. // J.Amer.Chem.Soc. 1985. V. 107. P.3902-3909.
7. Hull S.E., Karlsson R., Main P., Woolfson M.M. Dodson E.J. // Nature. 1978. V.275. P.206-207.
8. Gross D.S., Williams E.R. // J Am. Chem. Soc. 1995. V.117. P.883-890
9. Szilagyi Z., Drahos L.,Vekey K. // J. Mass Spectrom. 1997. V.32. P.689-696.
10. Pashinskaya V.A., Kosevich M.V., Shelkovsky V.S., Czira G., Szilagyu Z., Vekey K. Abstr. of the 15th Inform. Meeting on Mass Spectrom., 4-6 May 1998, Budapest, Hungary, P. 86.
11. Денисенко В.П., Рудь В.П. В сб.: Физиологическая роль поверхностно-активных веществ. Черновцы. 1975. С. 40-41.
12. Гудзь О.В., Овчинников В.Г., Писько Г.Т., Смирнова Н.А., Тарасенко В.С. // Микробиол. журн. 1987. 49. С. 82-85.
13. Zakrzewska K., Lavery R., Pullman B. // Nucl. Acid Res. 1983. V.11. P. 8825-8839.

КВАНТОВОХІМІЧНЕ ДОСЛІДЖЕННЯ ДІКАТІОНУ ДЕКАМЕТОКСИНУ ТА ПОДІБНИХ ДІКАТІОНІВ

М.В.Косевич, В.А.Пашинська, С.Г.Степанян, В.С.Шелковський, В.В.Орлов, Ю.П.Благой

Физико-технічний інститут низьких температур ім. Б.І.Вєркіна НАН України, Харків, 310164, пр. Леніна, 47, e-mail: mvkosevich@ilt.kharkov.ua

Структурні та електронні параметри дікатіону протимікробного препарату декаметоксину та ряду модельних амонієвих дікатіонів з різним розміром алкільних радікалів при четвертинному азоті були встановлені за допомогою квантово-хімічного методу AM1. Показано, що найбільш вигідна конформація дікатіону декаметоксину у відсутності розчинника-води є витягнутою, а заступники розташовані у транс-положенні відносно центрального ланцюга, та має місце сольватація амонієвих груп карбоксильними киснями. Положення двух центрів розподілу заряда у декаметоксині близькі до центрів четвертинних азотів, у той час як аналіз серії модельних дікатіонів дозволив виявити сильну залежність позицій таких центрів від типу та розміру алкільних заступників. Обговорюються можливі кореляції молекулярних параметрів та біологічної активності амонієвих солей.

КЛЮЧОВІ СЛОВА: бісчетвертинні амонієві сполуки, протимікробні агенти, декаметоксин, квантово-хімічні розрахунки