QUANTUM-CHEMICAL CALCULATION AS AN AID IN SYNTHESIS OF PROSTAGLANDINS. ATTEMPT OF PREDICTION OF RELATIVE STABILITY OF FOUR STEREOISOMERIC METHYL 7-HYDROXY-2-OXA-3-OXOBICYCLO[3.3.0]OCTANE-6-CARBOXYLATES

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Partial optimization of conformation structure of quantum-chemical models of the stereoisomeric lactones *I* to *IV* has been carried out by the CNDO/2 method. The calculated energy characteristic and electron distributions have been used for discussion of some factors affecting retention of 5,6-*trans*-6,7-*trans*-configuration in the key intermediate of prostaglandin syntheses (formula *I*) with regard to conditions of the preparative experiments.

In the Corey[1] general working scheme of prostaglandin synthesis a key role is played by the intermediate lactone type *I* having at its asymmetrical centres identical stereochemistry with that of the final products. In connection with a realization of one version of the Corey's procedure in our laboratories we were interested in the problem of application of the semi-empirical LCAO-MO calculation for evaluation of some conditions under which the necessary stereochemistry of the lactone-ester *I* (R = $= CO_2CH_3$) is maintained during the synthesis. For this purpose we chose the standard CNDO/2 method[2-5] involving explicitely all valence electrons and considering the electronic repulsion. The obtained results are presented in this communication.

CALCULATIONS

All the quantum-chemical calculations were carried out with the use of the standard CNDO/2 program on a ICL 4—72 computer with usual parametrization. The energy contribution of the electron-electron repulsion was expressed by the simple approximation of point charges[5]. As pre-geometry of the studied compound type is not known, a partial assessment was carried out starting from evaluation of the Dreiding models and available knowledge[6-8] about structurally similar compounds, the individual atomic centres of the bicyclic system being placed as far as possible from each other. Having fixed the shapes of the both five-membered rings in this way, we carried out simultaneous variation of the torsion angles about C—OH and C—CO_2CH_3 bonds within 0° to 360°, and for each conformation we calculated the approximate SCF energy E_{CNDO} by interruption of the iteration procedure after the 5th step. This way was chosen for

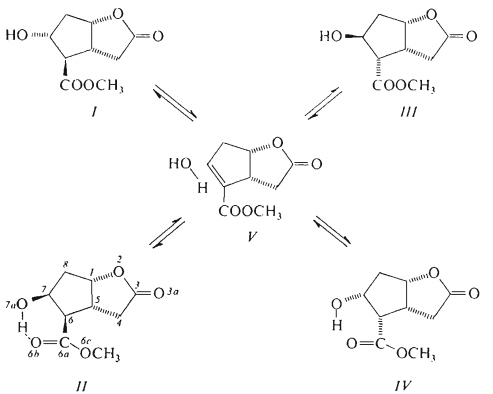
economical reasons after it was found by orientation calculations that order of the SCF energies is not changed by further iterations. The obtained E_{CNDO} energies were minimized with respect to the both mentioned torsion angles, and the thus obtained partially energy-optimized conformations of the molecules (in x, y, z coordinate system) are given in Figs 1 and 2. For these conformat ons precise values of the electron energy E_{CNDO} were calculated up to complete self-consistency (15 to 30 iterations). The obtained electron energies E_{CNDO} of the lactones *I* to *IV* are given in Table I along with the theoretical dipole moments calculated[5] on the basis of the CNDO/2 electron distribution. Further calculated characteristics of the studied stereoisomers *I* to *IV* are given in Table IV and in Fig. 3. The CNDO models of the compounds *I*—*IV* are described by 68 MO's φ_1 to φ_{68} occupied by total 78 valence electrons, so that φ_{39} and φ_{40} can be considered HOMO and LUMO, respectively.

EXPERIMENTAL

The dipole moment of the stereosiomer *I* prepared in our laboratories according to ref.[9] was measured by the Halverstadt–Kumler method[10] in which the atomic polarization was approximated by 5% of the electronic polarization. The value obtained in benzene solution at 25°C was $1{\cdot}55 \cdot 10^{-29}$ Cm (4·64 D). The discussed NMR characteristics of the compound *I* were taken from ref.[6].

RESULTS AND DISCUSSION

General aspects. The laboratory operations carried out in the presence of reagents or side products catalyzing dehydratation of β-hydroxy esters allow the system to tend to equilibrium to be established among the four stereoisomeric ester-lactones *I* to *IV* (Scheme 1). If, for simplicity, complete establishment of the thermodynamic



SCHEME 1

equilibrium is presumed, then the intermediate *V* can be excluded from our considerations, and the free energy changes ΔG of the elementary equilibrium steps $I \rightleftharpoons II$, $I \rightleftharpoons III$, $I \rightleftharpoons IV$, $II \rightleftharpoons III$, $II \rightleftharpoons IV$, $III \rightleftharpoons IV$ can be taken as a measure of probability of occurrence of the individual stereoisomeric forms. According to the relation $\Delta G = \Delta H - T\Delta S = -RT\ln K$, for a given temperature *T*, it follows that the more negative is the ΔG value the more the equilibrium is shifted in favour of the stereoisomer at the left-hand side of the elementary step (*i.e.* the isomerization velocity "to the right" will be higher than that "to the left"). Hence it is likely that under the conditions of preparative experiments (not always allowing the equilibrium to be completely established) the isomerization of a stereoisomer A to a stereoisomer B, *i.e.* $A \rightarrow B$, will be, at least in the initial phase, the more probable the more negative is ΔG of the corresponding equilibrium $A \rightleftharpoons B$. This simplification allows, for the present, to exclude the unknown structures of the transition states from the theoretical treatment, *i.e.* it allows not to specify mechanisms of the individual isomerizations. This reasoning led us to try to use the simple differences of the CNDO/2 electronic energies $\Delta E_{CNDO} = E_{CNDO}(B) - E_{CNDO}(A)$ calculated for the

TABLE I

Calculated Energy Characteristics and Electric Dipole Moments of the Ester-Lactones *I*—*IV*

Isomer	E_{CNDO}, eV	E_{rel}, eV	E_{HOMO}, eV	E_{LUMO}, eV	$\mu_{CNDO} \cdot 10^{-29}$, mC
I	—4 504·4434	0·4454	—13·2370	3·8800	1·403
II	—4 504·5607	0·3281	—12·9956	3·7083	1·076
III	—4 504·8888	0·0000	—12·9852	3·9499	1·167
IV	—4 502·6355	2·2533	—12·0388	3·3961	1·356

TABLE II

CNDO/2 Prediction of Facility Order of Isomerizations among the Ester-Lactones *I*—*IV*

Order[a]	A→B	$-\Delta E_{CNDO}$ kJ mol^{-1}	Order[a]	A→B	$-\Delta E_{CNDO}$ kJ mol^{-1}
1	*IV*→*III*	51·9	4	*I*→*III*	10·3
2	*IV*→*I*	44·4	5	*II*→*III*	7·6
3	*IV*→*II*	41·7	6	*I*→*II*	2·7

[a] The probability decreases from No 1 to No 6.

ester-lactones *I*–*IV* as microscopic analogs of the mentioned free energies ΔG, at least, their ΔH components. The E_{CNDO} values used in this way can present a satisfactory picture of relative stability of the compounds either in gas phase or in solutions of non-polar solvents. For solutions in polar aprotic solvents it is necessary to take into account another additional factor *viz.* the predominating dipole–dipole interactions between the solvent and solute (*i.e.* *I*–*IV*) molecules: the greater is the electrical dipole moment of solute the higher stabilization of its configuration by aprotic polar solvents can be anticipated. Therefore, we calculated the so far unknown dipole moments of the ester-lactones *I*–*IV* with the use of the CNDO/2 electron distribution which for such purposes is usually successful[5,11].

Energy characteristics. From Table I it can be seen that the value E_{CNDO} of the isomer *IV* is 2 eV higher than those of the remaining isomers *I*–*III* whose mutual differences are, on the contrary, less than 0·5 eV. Hence it can be concluded that the

TABLE III

The Most Important Terms with Higher Absolute Values of the Expansion Coefficients AOs in the LCAO Expansion for the Molecular Orbital[a] φ_{40} (LUMO)

Ester group	Lactone grouping	The rest of the molecule
	Isomer *I*	
−0·23p(6a) + 0·18p(6b)	−0·18p(4) − 0·65p(3) +0·17p(2) + 0·52p(3a)	+0·25s(H-4) − 0·26s(H-4)
	Isomer *II*	
+0·67p(6a) − 0·51p(6b) −0·16p(6c) + 0·14s(H-6)	+0·25p(3) − 0·21p(3b)	−0·12s(H-4) + 0·14s(H-4) −0·11s(5) + 0·16p(5)
	Isomer *III*	
−0·37p(6a) + 0·30p(6b)	+0·16p(2) − 0·59p(3) +0·48p(3a)	+0·16s(H-4) − 0·24s(H-4) −0·18p(4)
	Isomer *IV*	
+0·27s(H-6) − 0·11p(6) −0·66p(6a) + 0·53p(6b) +0·16p(6c)	−0·21p(3) + 0·18p(3a)	+0·12s(H-4) + 0·13s(H-5) −0·11s(5)

[a] For numbers of the atomic centres see Scheme 1.

all-*cis*-configuration of the ester-lactone *IV* will be extremely unfavourable energetically and will tend to be converted (in the equilibrium reactions) into one of the remaining configurations *I*–*III*. The data of Table II, furthermore, provide information about relative velocities of the mutual isomerizations of the compounds *I*–*IV* under the presumption of energetically close transition states. It is obvious that in all cases the isomerization of the all-*cis*-isomer *IV* to any of the remaining isomers should proceed much more easily than the isomerizations among the remaining group *I*–*III*. In non-polar medium, however, a certain danger can be expected of transformation of the *cis-trans-trans* isomer *I* with the required "prostaglandin" stereochemistry into the isomer *III* due to inversion of configuration at the carbon centres in both 7 and 6 positions. However, due to possible hydrophobic interactions the *cis-trans-cis* isomer *II* also can be stabilized, since it shows (on the basis of optimization of the E_{CNDO} values) an intramolecular H-bond (Fig. 1) in contrast o the compounds *I* and *III*.*

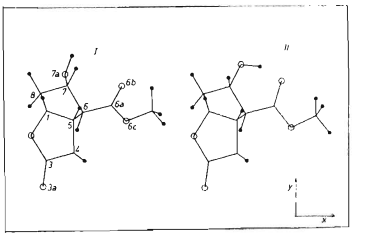


FIG. 1

The Conformations of Ester-Lactones *I* and *II* Partially Optimized with the Use of E_{CNDO} Values (see Calculations) and their Location in Coordinate System

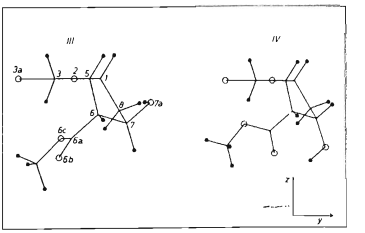


FIG. 2

Conformations of Ester-Lactones *III* and *IV* after Partial Optimization with the Use of E_{CNDO} Values (see Calculations) and their Location in Coordinate System

* In accordance therewith IR spectrum of the compound *I* dissolved in chloroform does not show any characteristics of an intramolecular H-bond in the region of stretching vibrations of OH and C=O bonds. The same applies to the proton chemical shift of OH in NMR spectrum.

From the viewpoint of the perturbation theory the calculated HOMO and LUMO energies are also noteworthy. From Table I it follows that the E_{HOMO} values and E_{LUMO} show the order $IV > III > II > I$ and $III > I > II > IV$, respectively. Again, the all-*cis* isomer *IV* appears unambiguously the most reactive and, hence, the least stable from the viewpoint of the donor-acceptor properties. On the contrary, the "prostaglandin" isomer *I* should be relatively the most stable towards electron--acceptors (oxidants, acids) and, along with the *III* isomer, also towards electron--donors (reducing agents and bases). Generally, the energy data show that the intramolecular H-bond, in spite of being an important factor for the energetically favourable shapes of the molecules *II* and *IV* (see Figs 1 and 2), is not sufficient to make *II* and *III* more advantageous than *I* and *II* from the energetical stability viewpoint.

With respect to preparative importance of reduction[7] of the ester-lactone *I* it was useful to examine more closely the LUMO character in the studied models *I*–*IV*.

TABLE IV

Connection of the Calculated CNDO/2 Electron Charges $Q \cdot 10^2$ with Formation of Intramolecular H-Bonds

Isomer	H—(O)	O—(H)	O=(C)	(O)=C	(CH_3)—O
I	+14·59	—26·39	—30·60	+37·06	—23·72
II[a]	+20·30	—32·29	—30·82	+38·32	—23·57
III	+13·90	—26·81	—31·42	+38·16	—24·46
IV[a]	+15·93	—27·43	—28·78	+37·84	—24·46

[a] The compounds with intramolecular H-bond.

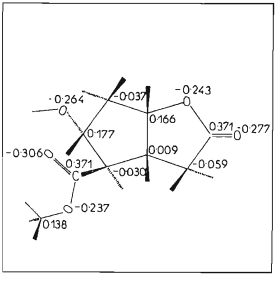


FIG. 3

Electron Charges at Heavy Atomic Centres Calculated by CNDO/2 Method for the Ester-Lactone *I* with "Prostaglandin" Configuration of the Molecule

With respect to the presumption that the electrons of reducing agent will be transferred into the substrate molecules most likely in the surroundings of the atomic centres with the highest absolute values of coefficients of AOs in the corresponding LCAO expansion for LUMO, the calculated values of these coefficients can enable prediction of relative reducibility of the lactone and the ester functions in the investigated compounds. From Table III it can be seen that the LUMO of all the compounds *I*–*IV* is localized predominantly in the region of the π-electron system of the —C(6)—CO_2CH_3 and —C(1)—OCO—C(5)-groups, which agrees with the general experience of organic chemists that out of the given possibilities these functions are the most reducible.

According to the highest absolute values of the expansion coefficients of *p*-AOs −0·65 and 0·52 it can be concluded that the "prostaglandin" isomer *I* will be reduced most easily at the carbonyl group of its lactone ring, which agrees with experimental findings[7]. Analogous behaviour can be expected with the isomer *III* (the values −0·59 and 0·48), too. On the contrary, in the case of the isomers *II* and *IV* with intramolecular H-bonds the analogous values of the expansion coefficients indicate rather an enhanced reactivity of the carbonyl group in their ester functions.

Electron distribution. The calculated electronic charges of the compounds *I*–*IV* are usually little influenced by configuration of the individual isomers, and their typical values are given in Fig. 3 for the most important isomer *I*. A certain exception represent those atomic centres which are immediately involved in potential formation of intramolecular H-bonds. Existence of these bonds can be formally represented by the fragment C—O···H···O=C—OCH_3, and, hence, it should make itself felt by increased values of the charge *Q* at the hydrogen centre of the bond and by decreased *Q* value at the oxygen atom 7a of the compounds *II* and *IV* as compared with the pair *I*, *III*. Table IV shows that this is really the case, the effect being more marked with the isomer *II* than *IV*. Therefrom it can again be concluded that the intramolecular H-bond in the latter case contributes less to stabilization of the configuration *IV*, which agrees with the theoretical conclusions based on energy data. Table IV also shows that the electronic charges *Q* at the carbon and oxygen centres of the 6a and 6c positions are not markedly influenced by formation of the mentioned H-bonds.

The electric dipole moments of the compounds *I*–*IV* represent another investigated characteristics of the overall electron distribution in *I* to *IV*. From Table I it is seen that their theoretical values decrease in the order *I* > *IV* > *III* > *II*; in roughly the same sequence we can expect also relative stabilization of the corresponding configurations by dipole–dipole interactions with molecules of aprotic polar solvents. If the unambiguously energetically discriminated all-*cis* isomer *IV* is excluded, then it can be expected that in polar solutions (in which preparative experiments are frequently carried out) it is just the isomer with the "prostaglandin" configuration *I*

which can be markedly stabilized relative to the practically undesirable isomers *II–IV*.

CONCLUSIONS

Within the probable equilibrium isomerizations of the ester-lactones *I–IV* the configurations *III* and *I* can be considered the most stable in gaseous or non-polar media and in strongly polar aprotic media, respectively. Intramolecular H-bonds are not decisive factors affecting relative energetic stability, but they control the shape of the molecules of the considered configurations *I–IV* in the case of the compounds *II* and *IV*. In the practically most significant stereoisomer *I* the lactone fragment of the molecule can be considered more easily reducible and more sensitive to nucleophilic attack than the ester group at the position 6.

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