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Stereochemistry of Seven-Membered Heterocycles: XLII.[1] A Theoretical Study of Stereochemistry of H Complexes Formed by Conformationally Nonuniform 2-R-1,3-Dioxacyclohept-5-enes with Some Proton Donors

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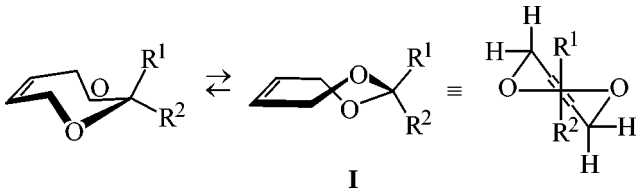
Abstract—According to semiempirical AM1 calculations, the stability of the *boat* and *twist* forms of 2-R-1,3-dioxacyclohept-5-enes depends on the size of substituents at the acetal carbon atom. The *twist* form gives diastereomeric H complexes with chloroform and methanol of the *cis* and *trans* structure, containing monocentered hydrogen bonds, whereas the *chair* conformation preferably forms complexes with a two-centered hydrogen bond. Based on theoretical data (ϑ_{OH}, ΔH, geometry of complexes), the specific features of H complexes of the conformers in electrophilic addition and cycloaddition were revealed. Considerable preferableness of the *exo* attack of the diastereotopic double bond in the H complex having the *chair* form is due to the steric accessibility of the *exo* side, whereas in the complexes of the twist form the facial selectivity is appreciably lower.

Studying the reactivity of equilibrium systems in cross reactions, which widely occur in the nature, is an urgent but extremely complicated problem. As shown by previous systematic studies in this field, seven-membered unsaturated acetals are extremely convenient model compounds for revealing a correlation between the steric structure of molecules and their chemical behavior [2–8].

According to results obtained by various physical methods, 1,3-dioxacyclohept-5-enes **I** having the planar carbocyclic fragment exist in solution in two conformations differing in the arrangement of the heterocyclic moiety: the *chair* and *twist* conformations.



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$R^1 = R^2 = H$ (**a**); $R^1 = H$, $R^2 = CH_3$ (**b**); $R^1 = H$, $R^2 = C_2H_5$ (**c**); $R^1 = H$, $R^2 = (CH_3)_2CH$ (**d**); $R^1 = H$, $R^2 = (CH_3)_3C$ (**e**); $R^1 = H$, $R^2 = Ph$ (**f**); $R^1 = R^2 = (CH_2)_5$ (**g**).

[1] For communication XLI, see [1].

An increase in the size of substituent at the acetal carbon atom leads to an increase in the repulsive 1,3-interactions in the flexible form and to relative stabilization of the *chair* structure with the equatorial position of the substituent in the series $C_6H_5 \approx H < CH_3 \approx C_2H_5 \approx (CH_3)_2CH \ll C(CH_3)_3$. At the same time, the position of the conformational equilibrium is virtually independent of the solvent [9–11].

Proceeding with studies of the chemical behavior of 2-R-1,3-dioxacyclohept-5-enes, we performed a theoretical study of the structure of H complexes of *chair* and *twist* conformations with chloroform and methanol, using different semiempirical methods (MNDO, AM1, PM3) from the MOPAC 6 program package [12–14]. Optimization was performed with the gradient norm of 0.01. In all the cases, we calculated the matrix of second derivatives and the bond vibration frequencies for the stable conformers. It was found that all the structures are characterized by local minima on the potential energy surface, with no imaginary frequencies.

At present, H complexes are widely studied by semiempirical as well as *ab initio* methods (see, e.g., [15, 16] and references therein). The H complexes of

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Calculated enthalpies of complex formation (ΔH^0, kJ mol^{-1}), interatomic distances O···H (*d*, Å), and wave numbers (ν, cm^{-1}) of vibrations of O–H bonds in the complexes of methanol with *chair* amd *twist* conformers of compounds **Ia**, **Ib**, **Ie**, and **If**

Comp. no	*Chair* conformer			*Twist* conformer			ν_{OD}^{a}
	$-\Delta H^{0\,b}$	*d*	ν^{c}	$-\Delta H^{0\,b}$	*d*	ν^{c}	
Ia	14.4	2.305	3464	15.3	2.198	3461	2598
Ib	16.2	2.258	3463	15.6	2.159	3458	2598
Ie	16.1	2.257	3438	15.1	2.209	3451	2586
If	16.4	2.232	3440	15.3	2.200	3461	2580
Ib[d]				14.3	2.183	3455	
Ie[d]				13.1	2.190	3457	

[a] Experimental wave numbers (ν_{OD}, cm^{-1}) in the complex of MeOD with compounds **I** were taken from [3]. [b] The enthalpy of complexation was calculated by the formula $\Delta H^0 = \Delta H_d + \Delta H_a - \Delta H_c$, where ΔH_d is the enthalpy of formation of the proton donor; ΔH_a, the enthalpy of formation of the proton acceptor; and ΔH_c, the enthalpy of formation of the complex. [c] The calculated frequency of the O–H stretching vibrations of the free methanol molecule (ν_{OH}) is 3504 cm^{-1}. [d] *cis* Complexes of the *twist* form (the methanol molecule is coordinated from the side of substituent at the acetal carbon atom).

four-coordinate phosphorus derivatives [17], hydrazones [18], and sulfenamide derivatives [19] were studied previously.

Comparison of the results obtained by MNDO, AM1, and PM3 calculations showed that the AM1 method provides the best description of acetals and their H complexes. The same conclusion was made from MNDO and AM1 calculations of the structure of acetals **I** in [20, 21].

The calculated enthalpies of formation ($-\Delta H^0$, kJ mol^{-1}) of **Ia**, **Ib**, **Ie**, and **If** are 322.8, 333.1, 383.1, and 178.7 (*chair* conformer), and 323.8, 336.5, 383.3, and 186.1 (*twist* conformers), respectively. Higher stability of the *twist* form of **Ia**, **Ib**, and **If** and relative stabilization of the *chair* form in going to acetal **Ie** is in qualitative agreement with the experimental data.

Steric structure of complexes. The enthalpies of formation (ΔH^0) of the H complexes of methanol with the *chair* and *twist* conformers of **Ia**–**Ie**, O···H interatomic distances *d*, and wave numbers of O–H stretching vibrations (ν) are listed in the table. The enthalpies of formation ($-\Delta H^0$, kJ mol^{-1}) of complexes of **Ia**, **Ib**, and **Ie** with chloroform are 14.4, 15.5, and 13.7 (*chair* conformation), and 9.8, 10.3, and 10.8 (*twist* conformation), respectively. The calculated heats of formation are close to the experimental data for the complexes of ethers with the corresponding donors of hydrogen bond [22].

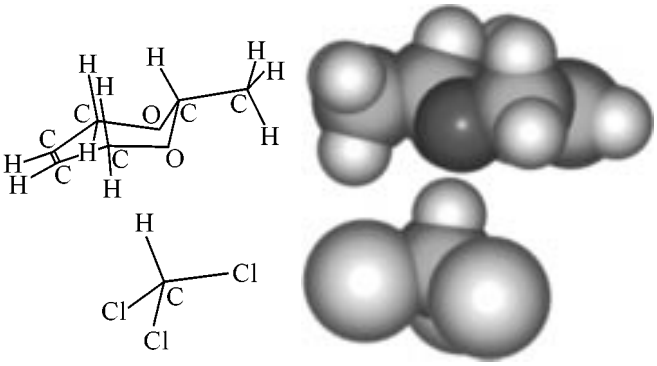
The complexes with methanol have the following structural features. For the *chair* conformation, there are two local minima related to the structures with different steric arrangements of the methanol molecule. The first structure is of the *trans* type. It is formed by interaction of the proton donor with one of the oxygen atoms of the seven-membered ring. The energy of formation of this complex is –13.1 kJ mol^{-1}, *d* 2.19 Å, ν 3468 cm^{-1}. Complex **IIb** of the *cis* structure is more stable. In this compound, a two-centered hydrogen bond involving both acetal oxygen atoms is formed. The energy gain in formation of the bifurcate complex is 3.1 kJ mol^{-1}, *d* 2.26 Å, ν 3463 cm^{-1}.

Studies of diastereomeric complexes of the *twist* form with methanol and chloroform showed that the energy of formation of the transoid H complex of **Ib** with methanol exceeds that of the *cis* complex by 1.3 kJ mol^{-1}, and for the *tert*-butyl derivatives the difference reaches 2 kJ mol^{-1}. Note that, in the case of complexes of the flexible form of acetal **Ib** with the methanol molecule, the latter acts not only as proton donor but also as proton acceptor, with the methanol oxygen atom being also involved in the bonding. This results in the presence of shortened contacts between the hydrogen atoms of methylene and acetal groups and the hydroxyl oxygen atom (*d* ~2.4 Å).

Comparative analysis of the experimental and calculated data. The wave numbers of O–D stretching vibrations in the complexes of a series of 2-R-1,3-dioxacyclohept-5-enes with methanol-d_1 were previously determined by IR spectroscopy using the Kagaya approach [3]. The relative basicity in this series is determined by the electronic and steric effects of substituents and by the steric structure of the heterocyclic moiety. For example, in the series H, Me, Et, *i*-Pr, the electron-donating powers of the compounds are the same within the experimental error. At the same time, in going to spiro- and then to *tert*-butyl- and phenyl-substituted compounds, the hydrogen bond becomes appreciably stronger, which follows from the considerable low-frequency shift of the O–D stretching band. Such a trend in the series of **Ia**–**Ig** was rationalized by us in terms of the dual character of alkyl substituents. The constant electron-donating power in the series H, Me, Et, *i*-Pr is due to superposition of two oppositely acting trends: an increase in

the energy of molecular orbitals in this series and an increase in the steric shielding of the reaction center. At the same time, in the case of the *tert*-butyl derivative, for which the steric hindrance is considerably more pronounced and the equilibrium is strongly shifted toward the *chair* conformation, the strengthening of the hydrogen bond in the structure with the C_s symmetry was attributed to involvement of both oxygen atoms of the proton acceptor. The same conclusion that the hydrogen bond is strengthened in going to compound **Id** in the dominating *chair* form also follows from the comparison of the calculated frequences of O–H stretching vibrations in the complexes with methanol (see table). As for the phenyl-substituted acetal, the calculated data disagree with the experiment. The calculations suggest that the introduction of the electron-accepting phenyl group does not alter the electron-donating properties of the *twist* conformation of the acetal, while the IR data for the same preferred conformation show a considerable low-frequency shift. Probably, the observed strengthening of the hydrogen bond (most likely due to involvement of the π-donor fragment of the proton acceptor) cannot be revealed by AM1 calculations. At the same time, the calculated energies of formation of the H complexes in this case agree with the experiment. Remember that the enthalpies of complex formation of the *twist* form with methanol in the series of 2-alkyl-substituted 1,3-dioxacyclohept-5-enes are close, whereas the *chair* form gives more stable complexes with hydrogen bond donors. Thus, it can be concluded that the relative stability of H complexes of the *chair* and *twist* forms of unsaturated seven-membered acetals with methanol and chloroform is determined, on the one hand, by the steric and electronic effects of substituents at the acetal carbon atom and, on the other hand, by the conformational features of the molecules.

Reactivity of H complexes. We have studied previously [7] the kinetics of the electrophilic addition of bromine across the multiple bond in the series of conformationally nonuniform 2-R-1,3-dioxacyclohept-5-enes **Ia**, **Ib**, **Ic**, **Ie**, and **If**. Using the previously developed approach [2] assuming that the electronic, steric, and conformational effects are additive, we obtained the partial rate constants of the reactions of the *chair* and *twist* forms and the parameters of sensitivity of the reaction to the electronic effects of substituents at C^2. We found that, in dioxane, both forms react at the same rate, while in proton-donating chloroform the rate constants for the *chair* and *twist* forms differ by a factor of 30. The specific features of the chemical behavior of the *chair* conformation in



Steric structure of the *cis* complex of acetal **Ib** (*chair* form) with chloroform.

chloroform were also demonstrated in the studies of the diastereoselectivity of Carboni–Lindsay cycloaddition of acetals **I** to 3,6-bis(methoxycarbonyl)-1,2,4,5-tetrazine [6]. A conclusion was made that the increased reactivity in combination with the considerable *exo* selectivity of the *chair* conformation is caused by stereochemical features of the H complexes.

The calculation results show that formation of H complexes is accompanied by insignificant changes in their electronic structure. For example, accumulation of the negative charge on the donor center (oxygen atoms) is only 0.02, and the HOMO (double bond orbital) energy changes by no more than 0.09 eV in going to the *tert*-butyl derivative. Hence, these factors are not the most important, and the difference in the reactivity of the compounds under consideration is due to steric hindrance produced by the coordinated proton-donor molecules. This conclusion primarily concerns the more stable complexes of proton donors with the *chair* conformer (as compared to the *twist* conformer) in which the chloroform molecule virtually completely shields the double bond from the *endo* side (see figure). Indeed, contrary to the substituents at C^2, remote from the reaction center, the CCl_3 fragment in the H complex is located near the double bond and must therefore exert a strong (exceeding the effect of the *tert*-butyl group) shielding effect on the reaction center in the electrophilic attack. In the *chair* form (C_s symmetry), the steric demands to the attack from the diastereotopic sides of the double bond are quite different. This attack is much easier from the side opposite to the location of coordinated chloroform molecule. At the same time, in the *twist* form (C_2 symmetry), the steric hindrance to attack of an electrophilic reagent is similar from both sides of the double bond. As a result, in bromination of a series of acetals **I** in chloroform, *chair* conformers react considerably faster than the *twist* conformers [7],

and the *exo* selectivity of cycloaddition in going to the *tert*-butyl derivative reaches 68% [6]. The observed effect resembles the well-khown directing effect of heteroatom, though it arises not from the secondary orbital interactions, but from the formation of complexes [23].

We believe that the stereochemistry of specific solvation of substrates (by formation of H complexes and donor–acceptor complexes) plays an important role not only in diastereoselective [24], but also in enantioselective synthesis [25].

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