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Effect of the Medium on the Equilibrium between Stereoisomeric Six- and Seven-Membered Cyclic *chair*-Like Acetals. Role of Nonspecific and Specific Interactions

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Abstract—Principles for establishing the nature of solvation effects in stereoisomeric equilibria have been formulated. Using ^{1}H NMR spectroscopy, the equilibrium constants have been determined in 12 solvents for the *endo* and *exo* isomers of 1,9,10,11,12,12-hexachloro-4,6-dioxatricyclo[7.2.1.0^{2,8}]dodec-10-ene which is characterized by a high barrier to stereoisomeric transformations. The results of correlation analysis have shown that solvation of the conformers with dissimilar orientations of the hexachloronorbornene fragment with respect to the *chair*-like acetal moiety is determined by the polarity and proton-acceptor properties of the medium. Comparison with the data on solvent effect on the equilibrium between 2-isopropyl-5-methoxy-1,3-dioxane epimers suggests that the formation of H-complexes is controlled by electronic and conformational factors.

A fundamental problem in the chemistry of solutions is establishing relations between solvation and steric structure of the solute. Most data in that respect were obtained by studying thermodynamic parameters of conformational equilibria. Taking into account that more polar solvents always stabilize conformers with a greater dipole moment, a conclusion was drawn [1–4] that electrostatic interactions are determining here. On the other hand, there is no doubt that such interpretation is not quite rigorous, for the term *solvent polarity* implies not only nonspecific but also specific interactions (formation of donor–acceptor and H-complexes) between the solvent and dissolved substance [5, 6]. Identification and differentiation of these kinds of interactions constitute a nontrivial problem whose solution requires studying of appropriate substrates in a wide series of solvents with essentially different properties. The latter aspect is important, for most of the examined conformational equilibria are characterized by relatively low activation barriers and in most cases reliable data on the populations of different conformers were obtained by low-temperature NMR spectroscopy.

Obviously, such representative but high-melting solvents as DMSO, DMF, HMPA, benzene, dioxane, etc., cannot be used for the above purposes. This strongly reduces the amount and quality of obtainable information. We believe that the following two methods for obtaining data on stereochemical aspects of solvation are free from the above limitations. The first of these is based on determination of equilibrium constants through epimerization of a pair of diastereoisomers. This method is widely used for estimation of conformational energies of substituents in six-membered cyclic acetals (dithioacetals) [7, 8]. In such a way, Eliel and co-workers [9] studied the effect of the medium on the axial–equatorial equilibrium of 2-isopropyl-5-methoxy-1,3-dioxane (**I**). Here, the alkyl substituent on C^2 plays the role of an anchor group, and it is generally believed that equilibrium between epimers simulates conformational equilibrium [7, 8].

The second method takes advantage of conformationally heterogeneous compounds with a sufficiently high activation barrier to conformational transitions (higher than 17 kcal/mol). In this case, the state of equilibrium in a variety of aprotic, proton-acceptor, and proton-donor solvents, including high-melting ones, can be determined with a high accuracy from the intensities of NMR signals belonging to different forms [10]. The procedure was tested using a model conformationally heterogeneous compound with soft

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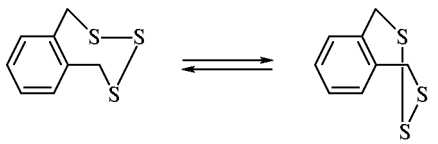
(according to Pearson) sulfur atoms, 1,2,3-trithia-5,6-benzocycloheptene, which exists in solution as *chair* and *boat* conformers having similar dipole moments:

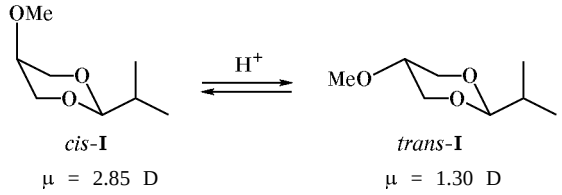


chair *boat*

Even at room temperature, this system is characterized by a slow exchange on the NMR time scale, and the ^{1}H NMR spectral pattern is a superposition of the spectra of two stereoisomers. The corresponding thermodynamic parameters, ΔH and ΔS, were determined in nine solvents and in a solution of lithium perchlorate in acetone. Correlations were found between components of the Gibbs energy of conformational equilibrium (compensation effect), as well as between the enthalpies of the *chair–boat* equilibrium and Meier's solvent acceptor numbers. On the basis of the obtained data it was concluded that donor–acceptor interactions predominate in the solvation of conformers [10].

We thought it reasonable to analyze solvation effects in equilibria of conformationally heterogeneous compounds which are also characterized by high activation barriers but have different dipole moments. As model compound, we selected *endo*-adduct **II** of hexachlorocyclopentadiene and 1,3-dioxa-5-cycloheptene, which is formed in high yield by the Diels–Alder reaction at 80°C under a pressure of about 5000 atm. [11].

According to the results of our previous X-ray diffraction and IR spectroscopic studies, the molecule of acetal **II** in crystal is characterized by *chair* conformation of the heterocyclic moiety and *exo* orientation of the hexachloronorbornene fragment. The IR and ^{1}H NMR data showed that acetal **II** in solution gives rise to a two-component equilibrium involving the *endo* and *exo* structures (Fig. 1) [11, 12]. The NMR signals were assigned on the basis of the X-ray diffraction data for diastereoisomeric 1,9,10,11,12,12-hexachloro-5-methyl-4,6-dioxatricyclo[7.2.1.0^{2,8}]dodec-10-enes with *endo*- and *exo*-oriented carbocyclic moieties and equatorial orientation of the substituent. The NMR spectra of the diastereoisomers and conformers of **II** were almost identical (except for the 5-H signals).



cis-**I** *trans*-**I**

μ = 2.85 D μ = 1.30 D

Table contains the Gibbs energies (ΔG^0) for equilibria of stereoisomeric acetals **I** and **II** in a wide series of aprotic, proton-donor, and proton-acceptor solvents. The error in determination of the equilibrium constants did not exceed 3%. It should be specially

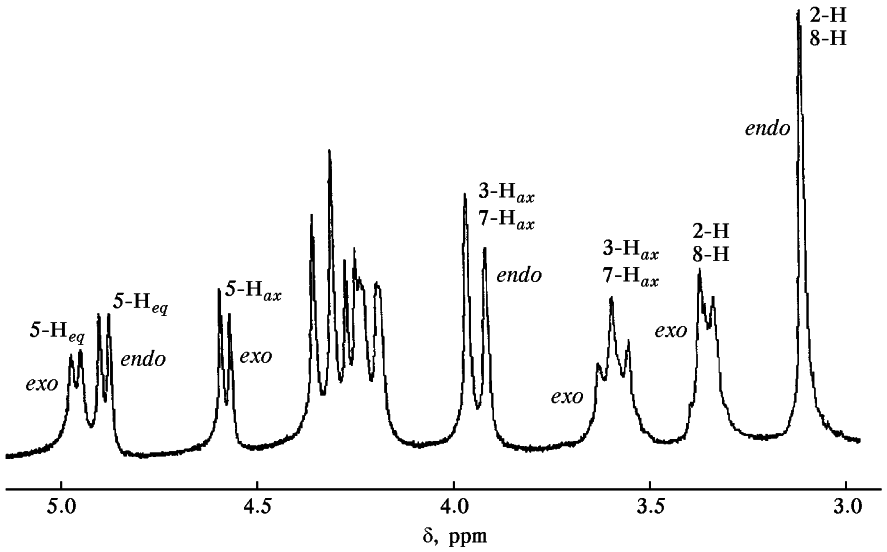
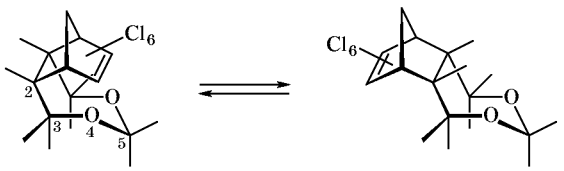


Fig. 1. ^{1}H NMR spectra of the *endo* and *exo* isomers of 1,9,10,11,12,12-hexachloro-5-methyl-4,6-dioxatricyclo[7.2.1.0^{2,8}]dodec-10-ene (**II**) in acetone-d_6 at 298 K.



endo-**II** μ = 3.04 D

exo-**II** μ = 2.37 D

emphasized that compounds **I** and **II** belong to a class of acetals which exhibit fairly similar conformational properties. Classical equilibrium between the 1,3-dioxane stereoisomers with equatorial and axial substituent on C^5 corresponds to equilibrium of structures **II** with *exo* and *endo* arrangement of the hexachlorocyclopentene fragment fused through the C^1-C^2 and C^8-C^9 bonds with the *chair*-like seven-membered ring. Furthermore, the available X-ray diffraction data for six- and seven-membered *chair*-like acetals show that the geometric parameters of the acetal fragments are similar [13–17]. Therefore, comparison of the solvent effects on thermodynamic parameters of the equilibria involving acetals **I** and **II** can be regarded as quite reasonable.

Standard Gibbs energies (ΔG^0, kJ/mol) for the *cis–trans*-isomerization of compound **I** and conformational equilibrium between the *endo* and *exo* isomers of compound **II** in various solvents and solvent parameters according to Kamlet and Taft [18]

Solvent	$-\Delta G^0$		π^*	β	α
	I[a]	**II**[b]			
Hexane	4.44	–	–0.08	0	0
Cyclohexane	4.31	–	0	0	0
Carbon tetrachloride	3.77	4.07	0.28	0	0
Carbon disulfide	–	4.03	–	–	–
Mesitylene	3.64	–	–	–	–
tert-Butylbenzene	3.47	–	–	–	–
Toluene	2.97	2.12	0.54	0.11	0
Benzene	2.47	1.54	0.59	0.10	0
Diethyl ether	3.47	–	0.27	0.47	0
1,1,1-Trichloroethane	2.43	–	–	–	–
Tetrahydrofuran	2.72	0.82	0.58	0.55	0
Chloroform	0.67	3.16	0.58	0	0.44
Methylene chloride	0.42	2.08	0.82	0	0.30
Nitrobenzene	0.84	–	1.01	0.39	0
Acetone	1.42	0.06	0.71	0.48	0.08
Acetonitrile	–0.04	0.13	0.75	0.31	0.19
DMF	–	–0.51	0.88	0.69	0
DMSO	–	–0.97	1.00	0.76	0
Methanol	0.13	0.48	0.60	0.62	0.93

[a] Data of [9].
[b] In deuterated solvents.

The data given in table were processed in terms of the Onsager, Dimroth–Reichardt (E_T^{30}), Gutman–Meyer (*AN*, *DN*), Krygowski–Fawcett (E_T^{30}, *DN*), Kamlet–Taft (π^*, α, β), and Koppel'–Palm (*Y*, *P*, *E*, *B*) one-, two-, three-, and four-parameter equations. A satisfactory description of the data for acetal **II** was obtained only with the use of the Kamlet–Taft two-parameter model including the polarity–polarizability (π^*) and proton-acceptor parameters (β). The pair correlation coefficients *r* for ΔG^0 with π^* and β were 0.80 and 0.89, respectively. Here, the contribution of the proton-donor parameter α was statistically insignificant.

$$\Delta G^0_{\mathbf{II}} = (3.44 \pm 1.07)\pi^* + (3.33 \pm 0.70)\beta - (4.57 \pm 0.63); \quad R = 0.95,\ S = 0.91,\ N = 11. \qquad (1)$$

The *exo* isomer predominates in nonpolar media. Increase in the solvent polarity and proton-acceptor power favors stabilization of the *endo* structure which is characterized by a greater dipole moment. The contributions of specific and nonspecific solvation are comparable. Figure 2 shows the dependence of ΔG^0 on the mole fraction of the proton-acceptor component in the binary mixture carbon tetrachloride–acetone. The dependence is nonlinear, which provides an additional support to the existence of specific interactions in the examined solvent series.

While studying influence of the medium on the acid-catalyzed *cis–trans* isomerization of 2-isopropyl-5-methoxy-1,3-dioxane (**I**), Eliel and Hofer [9] found that the application of the Onsager model and its versions gives no positive results. The best description of the experimental data was obtained with the use of the Dimroth–Reichardt empirical solvent parameter E_T (r = 0.94). Inclusion of the data for proton-donor methanol strongly impaired the correlation (r = 0.87).

Taking into account structural similarity of acetals **I** and **II**, it seemed reasonable to analyze the data obtained in [9] using the same scheme as that applied to seven-membered acetal **II**. We found that the Kamlet–Taft model also provides a satisfactory description of the solvent effect. However, apart from the solvent polarity, the main contribution was that of proton-donor rather than proton-acceptor power of solvents:

$$\Delta G^0_{\mathbf{I}} = (3.76 \pm 0.48)\pi^* + (2.74 \pm 0.56)\alpha - (4.46 \pm 0.28); \quad (2)$$
$$R = 0.96,\ S = 0.92,\ N = 13.$$

Here, the pair correlation coefficients r with the parameters π^* and α were 0.85 and 0.65, respectively.

Thus the above correlations suggest considerable contributions of both polar and proton-acceptor properties to the equilibrium between epimers, and of polar and proton-donor properties, to conformational equilibrium. These conclusions seem to be valid. First, as with model *exo*- and *endo*-1,9,10,11,-12,12-hexachloro-4,6-dioxatricyclo[7.2.1.$0^{2,8}$]dodec-10-enes, rise in the solvent polarity leads to displacement of the equilibrium toward isomer with a greater dipole moment. Second, qualitative change of the terms responsible for formation of H-complexes occurs in parallel with the change of electronic effect on the acidity of C–H bonds in the acetal ring, i.e., in going from methoxy group at the six-membered ring to more electron-acceptor hexachloronorbornene fragment. In the latter case, we actually deal with differences in selective solvation of stereoisomers via formation of hydrogen bonds between lone electron pairs of heteroatoms in solvent molecules and methine or methylene protons of the acetal ring in the conformers. As applied to dioxanes **I**, the selectivity of solvation is controlled by the different donor abilities of the isomeric heterocycles.

Thus, comparison of the data on solvation of acetal **II** with those on the solvent effect on the *cis–trans* equilibrium of 2-isopropyl-5-methoxy-1,3-dioxane leads us to conclude that complex formation between the acetals and proton donors or acceptors is governed by the inductive effects of substituents and their spatial arrangement. Presumably, the revealed specific "biphilicity" of the acetal ring should be taken into account while analyzing kinetic and thermodynamic parameters of reactions involving H-complexes of heterocyclic structures [19]. Moreover, the information obtained with the the use of simple models may be important for discussion of stereochemical problems intrinsic to more complex systems, where steric interactions (including those with participation of C–H bonds [20–23]) play a significant role.

EXPERIMENTAL

Compound **II** was synthesized by the procedure reported in [11], mp 104–105°C. The ^{1}H NMR spectra were recorded on Varian Unity-300 and Bruker WM-250 spectrometers (pulse duration 1 μs, delay 15 s, scan number 64). The ratio of the conformers was determined from the intensities of signals belonging to the CH and CH_2 protons of the heterocyclic fragment. In all cases, the concentration of samples was 5×10^{-2} M, and tetramethylsilane was used as internal reference. Variation of the concentration of acetal **II** in toluene from 1×10^{-3} to 1×10^{-1} M did not change the conformational equilibrium constant.

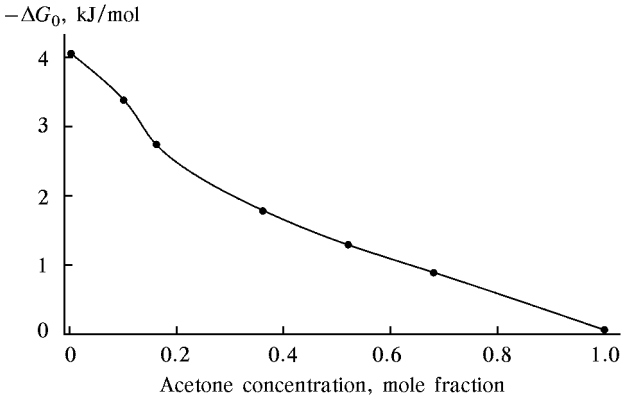


Fig. 2. Plot of the Gibbs energy ΔG^0 of the conformational equilibrium between the *endo* and *exo* isomers of acetal **II** versus mole fraction of acetone in a binary mixture with carbon tetrachloride.

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