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Investigation of Dynamic Equilibria Using NMR Spectroscopy II.[1] An Example of a Weak Intramolecular Interaction

Short Communication

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A weak intramolecular interaction between the 4,6-dioxo-1,3-dioxane and the phenyl residue in substituted spiro-cyclopropanes was found to determine the conformation of the molecules under investigation.

Untersuchung dynamischer Gleichgewichte mit Hilfe der Kernresonanzspektroskopie II.[1] *Ein Beispiel einer schwachen intramolekularen Wechselwirkung. (Kurze Mitteilung)*

Es wird gezeigt, daß eine schwache intramolekulare Wechselwirkung zwischen dem 4,6-Dioxo-1,3-dioxan- und dem Phenyl-Rest in den untersuchten substituierten Spiro-cyclopropanen für die Konformation in Lösung verantwortlich ist.

After a new class of spiro cyclopropanes has been synthesized[2], the nmr spectra of these compounds have been investigated extensively[3,4]. The nmr spectrum of the benzyl derivative (I) is shown in Fig. 1. The proton signals of the cyclopropane ring and both methylene protons have been analyzed and ascribed to an ABMNX spin system. The signals of the protons of the two methyl groups in the diketo dioxane ring have very different resonance frequencies which can be explained by a strongly hindered rotation of the aryl methylene group in these compounds. In the most predominant conformation the aromatic ring is bent over the diketo dioxane ring; the resulting anisotropy causes an upfield shift of the signals of the methyl group protons which are situated on the same side of the heterocyclic ring. The reason for the favoured position of the aryl ring is an attractive interaction of the π-

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Experiments were performed on solutions ($c \simeq 10^{-2} M$) in perfluorobutadiene with deuterated acetone as internal lock and tetramethylsilane as internal standard. Equipment used was a Varian XL-100 nmr spectrometer in FT mode, with a variable temperature probe and temperature controllers. The exact temperature has been measured before and after the experiment with a Fluke 2100 A digital thermometer with a copper-constantan thermocouple.

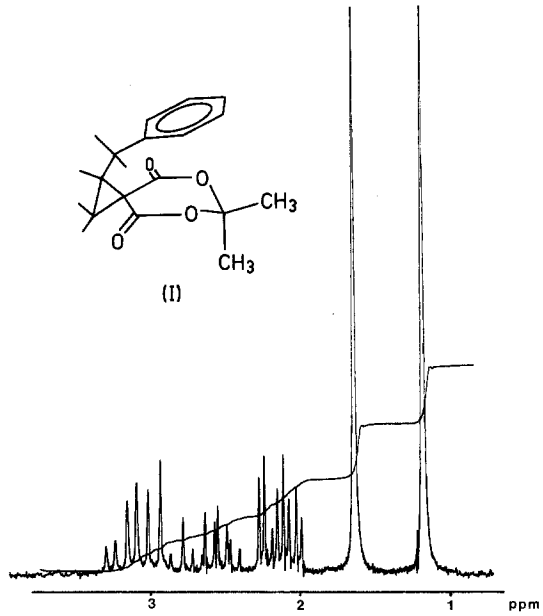

Fig. 1. NMR spectrum of I

The temperature dependence of the equilibrium constant of such a monomolecular reaction and the resulting change in the chemical shifts can be described quantitatively by a method similar to measurements used for solvent solute interactions[9] and neutralization reaction of some organic Lewis acids[10]. In this method the equilibrium constant of the intramolecular association process is calculated by the differences between the chemical shift of the protons of the methyl group at a certain temperature and the chemical shifts of the same methyl group at very high and very low temperatures. Fig. 2 shows the temperature dependence of the chemical shift with various ΔH values (plotted lines). For relatively small ΔH values, the direct estimation of δ_{diss} and δ_{ass}* is not possible, but if a sufficiently large range of the temperature

* δ_{diss} and δ_{ass} are the differences of the chemical shifts of the methyl groups in the case of a free rotating phenyl group (δ_{diss}) and in the case of a completely hindered rotation (δ_{ass}).

dependence curve is available, the three parameters δ_{diss}, δ_{ass} and ΔH can be fitted simultaneously with the help of a computer program. The dots (experimental points) correlate well with the line calculated by the method just described. The intramolecular association process in compounds of type I has been analyzed that way, the resulting values for ΔH are —8.0 kJ/mol (—1.9 kcal/mol) in the case of the benzyl

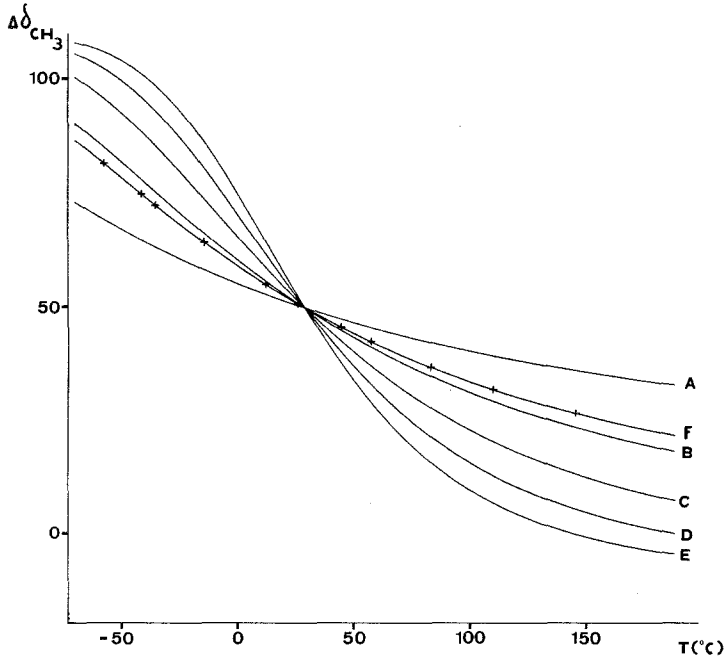

Fig. 2. Chemical shift difference of the two methylgroups versus temperature. A, B, C, D, E plotted from a theoretical calculation using —4.19 kJ (—1 kcal) respectively —8.37 kJ (—2 kcal), —12.6 kJ (—3 kcal), —16.75 kJ (—4 kcal), —20.93 kJ (—5 kcal). F experimental points (x) and theoretical plot for 4-nitroderivative of I

derivative, —7.5 kJ/mol (—1.8 kcal/mol) in the compound with a nitro group in the *para* position and at least —4.6 kJ/mol (—1.1 kcal/mol) in the *p*-methoxy derivative. The attractive force is somewhat smaller than the intramolecular association between the piperazinedione ring and the aromatic side chain in the mentioned cyclic dipeptides ($\Delta H \cong -5.0$ kcal/mol in D_2O, —2.5 kcal/mol in CD_3SOCD_3). Substitution at the aromatic ring also influences the intramolecular association. An electron donor seems to reduce the absolute value of the enthalpy and thus the attractive force. Electron acceptors show the same effect or an unsignificantly smaller one than the unsubstituted derivative.

system with the heterocycle or a part of it. Similar examples of such rotation hindrance due to attractive forces have been observed in diketopiperazines[5–8], in which the heterocyclic ring is found to exist in the boat form due to bonding interactions of the benzyl side chains. The temperature dependency of the nmr spectra can be used as a test for the interpretation of the nmr spectra and an attractive potential between aryl ring and diketodioxane ring in compounds of type I: The difference between the two signals of both methyl groups should decrease with increasing temperature. As expected, mainly the signal at lower field is affected, whereas the signal at higher magnetic field, which is attributed to the methyl group on the opposite side of the diketo dioxane ring, remains roughly constant, only influenced by changes in solvent interactions. Evidently, also the chemical shifts and coupling constants of the benzylic protons show a temperature dependency. To obtain more quantitative informations on the attractive interaction, we have measured the nmr spectra of compounds of type I over a relatively large temperature range. To avoid complications due to solvent anisotropies and solvent effects, we have chosen the difference between the two methyl group signals as a parameter for the calculation of the percentage of intramolecularly bonded molecules.

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