Conformational Switching of 3,7-Diacyl-3,7-diazabicyclo[3.3.1]nonanes by Metal Binding and by Solvent Changes

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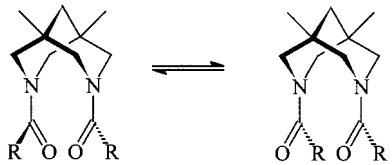
3,7-Diacyl-3,7-diazabicyclo[3.3.1]nonanes (3,7-diacylbispidines) can switch from antiparallel to parallel conformations upon addition of $LaCl_3$ thus serving as models for potential allosteric systems.

Molecular switches which are turned on or off by chemical signals can be allosteric systems, in which occupation of one binding site by an effector molecule induces conformational changes in a host compound. As a result of this a second binding site can be altered in the sense of positive or negative cooperativity,[1] and/or the allosteric host structure can assume conformational states with different physical properties. Such systems have, until now, mostly been based on photochemical initiators or responses.[2] We have recently described vicinal diamides which can bind effectors such as lanthanide ions to the carbonyl oxygen atoms only if the amide groups switch from the inherently more stable antiparallel (**ap**) to a parallel (**pa**) orientation, which must have a large dipole moment.[3] However, these conclusions were only indirect and the switching process was too fast even for measurement by NMR spectroscopy. In the present paper we report on a system where the barriers are so large that direct evaluation of ground state and of kinetic properties becomes possible. We also give experimental evidence for the change in dipole moments between the **ap** and **pa** states. Such changes might provide a basis for switching by external electric fields and thus open new ways for signal transmission and storage.[4]



Incorporation of the amide nitrogen atoms into the 3,7-positions of diazabicyclo[3.3.1]nonane skeletons leads to acyl groups with the possibility of alternative **ap** or **pa** orientations. The interconversion between these states is slow enough to determine their populations at room temperature by NMR spectroscopy, and the rates of interconversion by dynamic NMR spectroscopy. The structure of the isomers can be unambigously assigned by symmetry considerations (see below). Although the amide groups are not vicinal − unlike the earlier systems[3] − they are so close in the predominating chair-chair conformation of these bispidines[5] that added metal cations can make use of the bidentate binding to the carbonyl oxygen atoms, as expected, only in the less stable **pa** conformation.

In the present paper 3,7-diacetyl-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonane (**1**)[6] has been studied. The NMR spectra of the compound **1** (Figure 1) show two conformers; the spectra look similar with the exception of the methyl group signals at the 1,5-positions in the skeleton: for the **ap** conformer (C_2 symmetry) they appear as one singlet, while in the **pa** conformer (C_s symmetry) the methyl groups are not equivalent and give rise to two singlets. The integration of all non-overlapping signals shows that, in CD_3OD solution, the two conformers are present in a ratio of 86:14 (**ap/pa**). The equilibrium constants K are shifted substantially by changing the polarity of the solvent. The log$K$ values for the **ap/pa** ratio show a satisfactory linear correlation with the solvent polarity parameter[7] E_T (Figure 2), with the exception of DMSO: in this case specific solvation predominates over the generally observed stabilization of the **pa** conformer with the high dipole moment by the more polar medium.

Rotation of the acetyl groups around the N−Ac bonds for compound **1** was studied by ^{13}C NMR spectroscopy in terms of a nondegenerate, four-site exchange process according to Scheme 1: the equilibrium constant $K = k_1/k_2$ revealed no significant temperature dependence. It is equal to 0.138 for a [D_8]DMF solution of **1** in the temperature range under investigation (308−400 K). The most dramatic temperature effects occurred in the *N*-methylene range of the ^{13}C NMR spectrum. With rising temperature the exchange broadening effects (at 100.6 MHz for ^{13}C NMR[6]) were initially observed for the signals of $C_2(C_8)$ (δ = 51.38) and $C_4(C_6)$ (δ = 55.81) of the minor isomer **pa**. The broadening of the signals of the major isomer **ap** $C_2(C_6)$ (δ =

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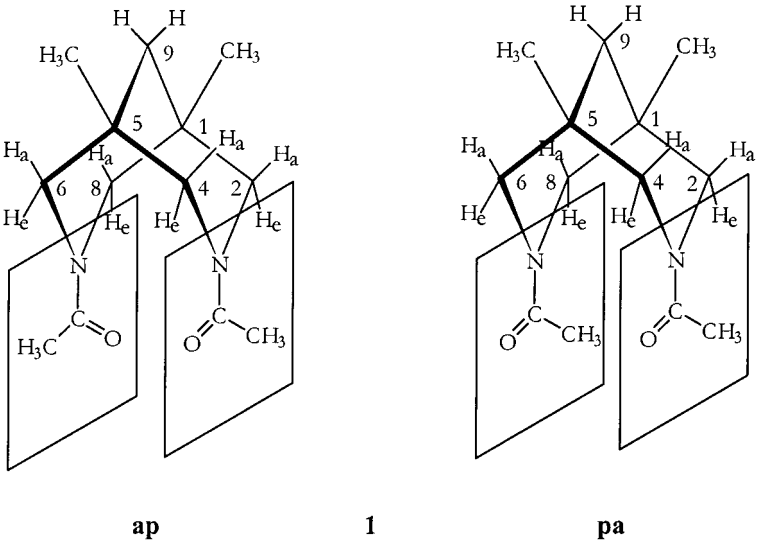


ap **1** **pa**

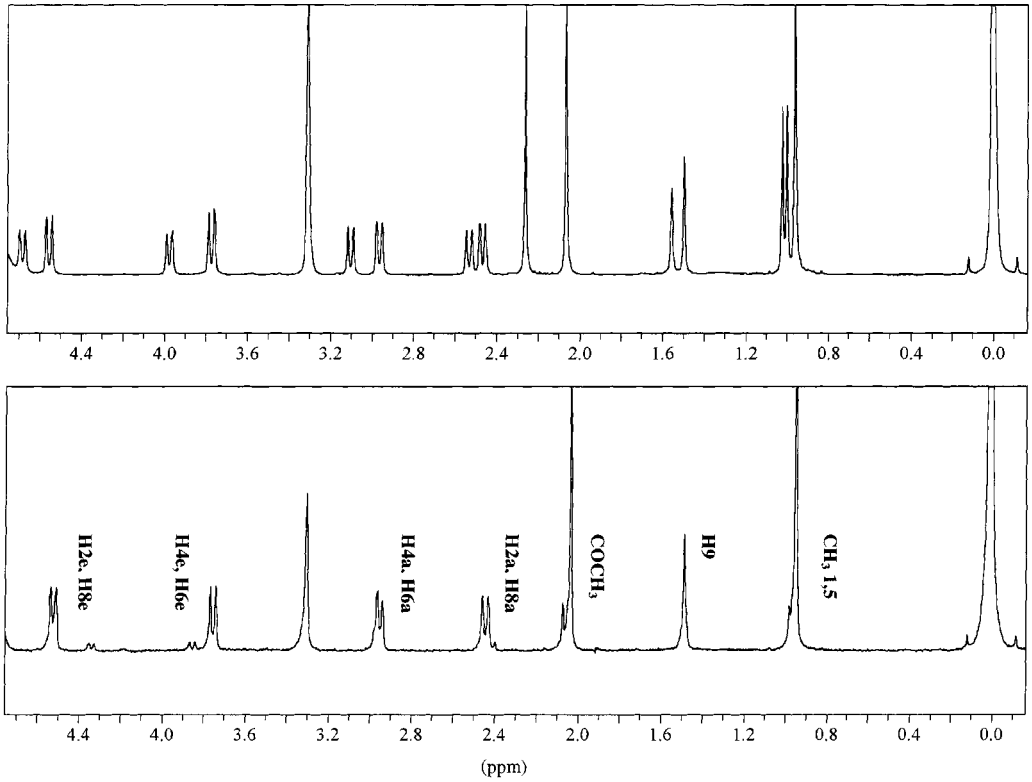
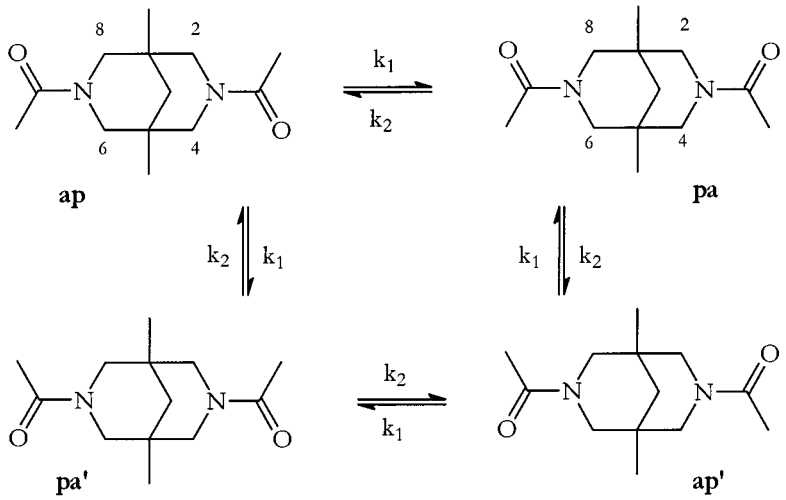


Figure 1. NMR spectra of **1** in CD_3OD, without (lower trace) and with (upper trace) added $LaCl_3$

56.11) and $C_4(C_8)$ (δ = 50.81) then takes place. The first step of coalescence was observed at a temperature of about 340 K, so that at higher temperatures only two signals are present in the spectrum which broaden further with increasing temperature. An analysis of the ^{13}C NMR lineshapes was performed with the DNMR5 program.[8] This gave the following activation parameters for the rotation of the acetyl groups in **1** (for the **ap** isomer): $\Delta H^{\neq}$ = 73.4(0.8) kJ/mol; $\Delta S^{\neq}$ = −9(4) J/mol K, which corresponds to $\Delta G^{\neq}_{298}$ = 76.1(0.9) kJ/mol. These values are close to the barriers observed with simple dialkylamides[9] (e.g. for *N*,*N*-dimethylacetamide $\Delta G^{\neq}_{298}$ varies in a range from 64.1 kJ/mol in the gaseous phase[9b,c] to 79.6 kJ/mol in aqueous solution[9c]) and indicate negligible interactions between the two acetamide functions in the rotational transition state.

Addition of metal cations such as $LaCl_3$ leads to a systematic concentration increase of the less stable **pa** conformer which provides two carbonyl sites for binding (see Figure 1). An NMR titration of a [D_4] methanol solution of **1** with $LaCl_3$, based on a nonlinear least-square fitting



Scheme 1

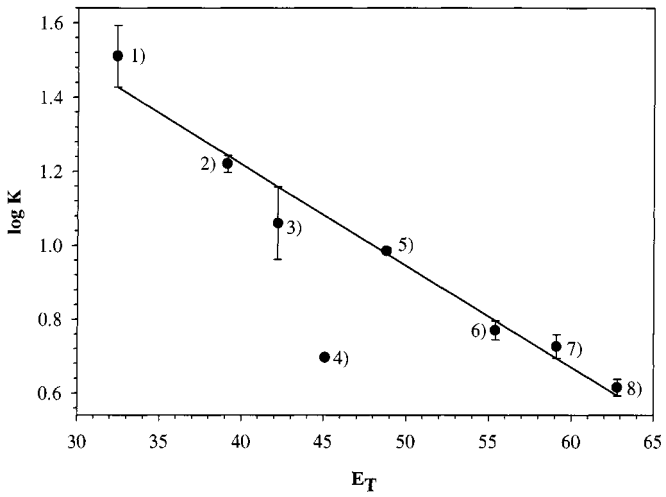


Figure 2. Correlation of logK values for the **ap/pa** equilibrium with the solvent polarity parameter[7] E_t; the points in the order from left to right refer to: CCl_4, $CDCl_3$, $(CD_3)_2CO$, $(CD_3)_2SO$, $(CD_3)_2CO/CD_3OD$ = 2:1 (vol); CD_3OD; CD_3OD/D_2O = 2:1 (vol); D_2O

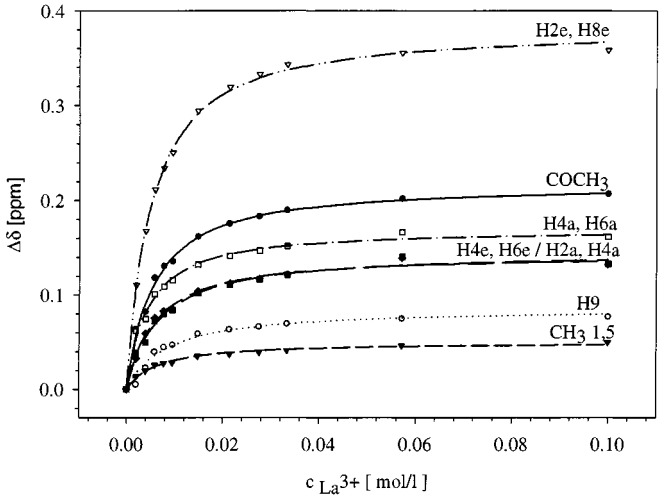


Figure 3. Example of an NMR titration with $LaCl_3$ with nonlinear least square fitting of the signal shift changes; the concentration of **1** changed during titration from 5×10^{-3} M to 2.5×10^{-3} M

of the signal chemical shift changes (see Table and Figure 3), following the usual protocols,[10] yields an association constant K_{Ln} = 200 l/mol, or ΔG = 13.1 kJ/mol at 298 K. These values are not far from those observed with vicinal diamides.[3]

Substituents other than methyl groups in the acyl function will allow us to introduce second binding sites for a variety of ligands, thus opening the access to new allosteric systems. Longer handles as substituents, such as oligopeptides or aryl- and alkyl chains may allow us to design new ligands which interfere in a switchable way with biopolymers.

Acknowledgments

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[6] Compound **1** (m.p. 194−195°C from dioxane) was prepared with 77% yield from 5,7-dimethyl-1,3-diazaadamantane[10] by its reaction with acetic anhydride without solvent. − $C_{13}H_{22}N_2O_2$ (238.33): calcd. C 65.54, H 9.24, N 11.76; found C 65.08, H 9.20, N 11.70. − ^{1}H NMR (400 MHz, [D_8]DMF, 308.6 K) **ap:** δ = 0.90 (s, 6 H, Me1,5), 1.42 (s, 2 H, H9), 1.94 {s, 6 H, Me(Ac)}, 2.34 (dd, *J* = 13.27 and 2.45 Hz, 2 H, H4a, H8a), 2.89 (dd, *J* = 13.14 and 2.45 Hz, 2 H, H2a, H6a), 3.72 (d, *J* = 13.14 Hz, 2 H, H2e, H6e), 4.53 (d, *J* = 13.27 Hz, 2 H, H4e, H8e); **pa:** δ = 0.90, 0.94 (2 × s, 2 × 3 H, Me1,5), 1.41 (s, 2 H, H9), 2.01 {s, 6 H, Me(Ac)}, 2.31 (d, *J* = 13.42 Hz, 2 H, H2a, H8a), 2.91 (d, *J* = 13.08 Hz, 2 H, H4a, H6a), 3.91 (d, *J* = 13.08 Hz, 2 H, H4e, H6e), 4.29 (d, *J* = 13.42 Hz, 2 H, H2e, H8e). − ^{13}C NMR (100.6 MHz, [D_8]DMF, 308.6 K) **ap:** δ = 21.72 Me(Ac), 24.44 Me(1,5), 30.83 (C1, C5), 47.02(C9), 50.81 (C4, C8), 56.11 (C2, C6), 168.05 (CO); **pa:** δ = 21.58 Me(Ac), 24.40, 25.10 Me(1,5), 30.27, 31.48 (C1, C5), 46.41(C9), 51.38 (C2, C8), 55.81 (C4, C6), 167.68 (CO).
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