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Structural and Spatial Considerations in the *N*,*N*′-Diacyl- and Bis(alkoxycarbonyl)bispidinone Series

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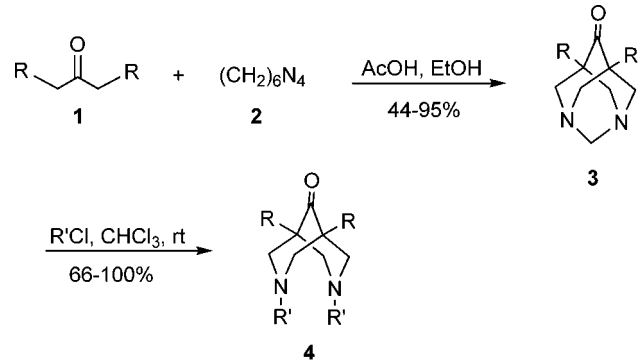
Diamidic and dicarbamic bispidinones show *trans*−*cis* isomerism, the relative population in solution of the *cis* form increasing with solvent polarity. The mutual proximity of the two amide functions in **4a** has no impact on the barrier to isomerization. The system represents a peculiar case of planar chirality posing a challenge to its specification.

Both 3,7-diazabicyclo[3.3.1]nonane (DABCN, bispidine) and 1,3-diazaadamantane based compounds exhibit interesting biological activity. Thus, bispidines possess attractive physiological properties as antitumor[1] and antiarrythmic[2−4] agents, as well as κ-opioid receptor ligands with analgesic activity.[5−7] The bispidine framework constitutes the central ring of a variety of lupin alkaloids, e.g., (−)-sparteine and (−)-angustifolline, which are effective muscarinic receptor binding agents.[8] Compounds having the rigid bidentate bispidine nucleus were employed as ligands for a number of coordinating metals[9−13] and were useful in enantioselective catalysis.[14−16] Physiologically active alkaloids with the 1,3-diazaadamantane structure are known,[17] and some synthetic derivatives are sodium channel blockers[18] and κ-opiate and σ-receptor ligands,[19] as well as oncolytics.[20] Consequently, substantial synthetic efforts have been directed toward both the bispidine and the 1,3-diazaadamantane scaffolds.

As a result of our interest in these compounds, we have come across a structural peculiarity of the bispidinone framework that, to the best of our knowledge, has eluded notice so far and of which we report here.

Several 6-oxo-1,3-diazaadamantanes **3** have been prepared by way of the quadruple Mannich cyclocondensation of the symmetrical ketones **1** with hexamethylenetetraamine (**2**).[21] Opening of the tricyclic cage of **3** was achieved by reaction with acyl chlorides or with chloroformate esters to yield the bispidinone derivatives 3,7-diacyl- or 3,7-bis(alkoxycarbonyl)-3,7-diazabicyclo[3.3.1]nonan-9-ones **4** (Scheme 1).[22,23]

SCHEME 1. Synthesis of 3,7-Diacyl- and 3,7-Bis(alkoxycarbonyl)-3,7-diazabicyclo[3.3.1]nonan-9-ones 4



3a: R = Bu **3b**: R = pentyl **3c**: R = Ph
3d: R = Bn **3e**: R = 4-CF_3-Bn **3f**: R = 3,5-$(CF_3)_2$-Bn
3g: R = 2-naphthalenylmethyl.

4a: R = Ph; R′ = Ac
4b: R = Ph; R′ = Bz
4c: R = Ph; R′ = 2-methylpropyl-OCO
4d: R = Ph; R′ = 2-propenyl-OCO
4e: R = Bu; R′ = 2-propenyl-OCO
4f: R = pentyl; R′ = 2-propenyl-OCO
4g: R = Bn; R′ = 2-propenyl-OCO
4h: R = 4-CF3-Bn; R′ = 2-propenyl-OCO
4i: R = 3,5-(CF3)2-Bn; R′ = 2-propenyl-OCO
4j: R = 2-naphthalenylmethyl; R′ = 2-propenyl-OCO.

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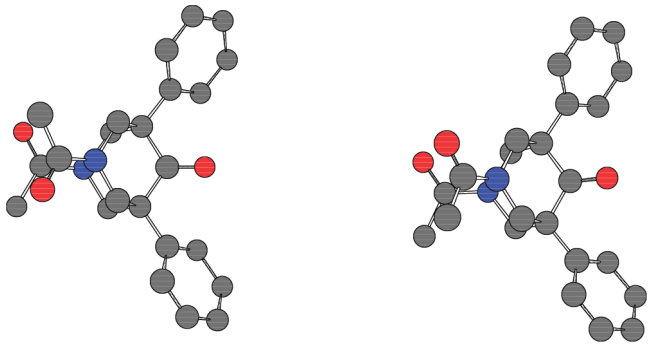

FIGURE 1. MM2 minimized 3D model of *trans*- (left) and *cis*-3,7-diacetyl-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one **4a**; gray = C, red = O, blue = N; hydrogen atoms are omitted for clarity.

These diamidic and dicarbamic bispidinones were obtained as crystalline materials in 66−100% overall yields. Their NMR spectra support a twin chair conformation of the bispidinone skeleton. As a typical case, the proton spectrum of bisacetamide **4a** displays a single set of phenyl group signals as well as one singlet for the two acetamide methyls in the higher field region (δ = 2.2 ppm). Two AB systems (δ = 5.71; 3.53 and 4.48; 3.97 ppm), each of four protons and with a ∼14 Hz geminal coupling constant and a ∼3 Hz long-range coupling constant, represent the four methylenes. The ^{13}C NMR spectrum features one set of signals for the phenyl groups, as well as one set for the acetamide function (methyl and carbonyl) and one signal for the quaternary carbon α to the ketone (δ = 52.5 ppm), while the four methylene carbons are represented by two signals (δ = 58.2; 52.1 ppm). These spectra are consistent with a double chair conformation of the bispidinone skeleton, holding the two acetamide functionalities in a *trans* mutual relationship (Figure 1).

Stereoelectronic factors have been invoked to explain the propensity of the 3,7-diazabicyclo[3.3.1]nonane system for the twin chair conformation in derivatives possessing trigonal nitrogens (amide, carbamate, and *N*-nitroso), as judged from X-ray crystallography.[24] The possibility of a rapid interconversion in solution between two degenerate boat-chair conformations seems unlikely in light of the overwhelming preference for the *trans* arrangement of the amide groups, as evidenced from the NMR spectra in less polar solvents: the mutual proximity of these groups in the double chair conformation is expected to yield a strong dipole−dipole repulsion in the case of a *cis* arrangement, whereas such an interaction would have been insignificant in the boat-chair conformation where the amide groups are widely separated from each other. Indeed, increasing the polarity of the solvent resulted in NMR spectra that show, in addition to the major set of signals of the *trans* diamide, a minor set of resonances belonging to the *cis* rotamer. As expected from its structure, this isomer features two sets of phenyl signals in its ^{1}H and ^{13}C spectra as well as two distinct signals in the ^{13}C spectrum for the quaternary bridgehead carbons of the bispidinone framework (δ = 52.2; 51.9 ppm in d_6-DMSO). Solvent−solute dipolar interactions are expected to stabilize the more polar *cis*-diamide in preference to the *trans* rotamer, thus increasing the *cis* to *trans* equilibrium constant (calculated from the relative peak areas in the ^{1}H spectra) as solvent polarity increases (Table 1 and Figure 2).

TABLE 1. Equilibrium Constant (*K*) and Free Energy ($\Delta G°$) of Bispidinone 4a at 301 K in Different Solvents

solvent	relative permittivity, ε_r[a]	K ([*cis*]/[*trans*])	$\Delta G°$, kcal mol^{-1}
d-chloroform	4.81[b]	0.026	2.19
d_6-acetone	20.7[c]	0.080	1.51
d_4-methanol	32.6[c]	0.13	1.23
d_3-acetonitrile	37.5[b]	0.15	1.12
d_6-DMSO	47[b]	0.20	0.95

[a] Reference 25; data correspond to the nondeuterated solvent. [b] At 293 K. [c] At 298 K.

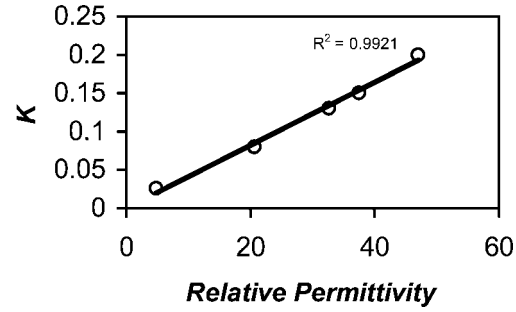

FIGURE 2. Equilibrium constant (K, [*cis*]/[*trans*]) of bispidinone **4a** at 301 K as a function of solvent permittivity.

Plotting the equilibrium constants versus other solvent polarity parameters (polarizability, dipole moment) resulted in excellent linear correlations, as well.

Dicarbamate **4c** exhibits a similar trend, although the respective values for the [*cis*]/[*trans*] equilibrium constants are higher (e.g., K = 0.22 in *d*-chloroform at 300 K), while the dependency of K on solvent polarity is less pronounced. Both facts are in accordance with the smaller dipole moment of the carbamate function relative to amides.

In view of the compactness of the 3,7-diazabicyclo[3.3.1]nonane double chair skeleton, it was interesting to check whether a possible mutual interaction between the proximal amide groups in the *N*,*N*′-disubstituted bispidinones **4** can be detected. Assuming that such an interaction would manifest itself in an abnormal barrier to internal rotation about the amide bonds, we followed the kinetics of this rotation in bispidinone **4a** by dynamic NMR spectroscopy. For simplicity reasons we examined the skeletal methylene and quaternary carbons' region in the ^{13}C NMR spectrum. Spectra were taken in d_6-DMSO, and upon raising the temperature, broadening of the methylene signals of the *trans* rotamer was observed until full coalescence occurred at 150 °C. This broadening was accompanied by disappearance of the minor resonances pertaining to the *cis* rotamer. Using the method of line shape analysis (LSA), the spectra taken at different temperatures were fitted to traces calculated from guessed rate constants. After a correction for the data at temperatures remote from coalescence has been made (applying the 2D procedure of exchange spectroscopy (EXSY)

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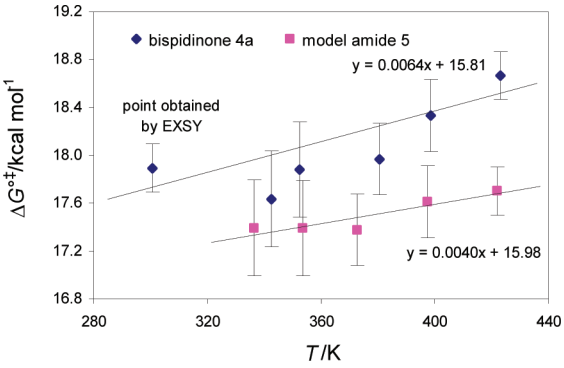
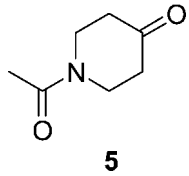


FIGURE 3. Temperature dependence of the barrier to rotation about the amide bonds in bispidinone **4a** compared to that in model amide **5**; data from dynamic NMR spectroscopy in d_6-DMSO solution.

at room temperature), a standard enthalpy of activation ($\Delta H^{\ddagger}$) of 16 kcal mol^{-1} and a standard activation entropy ($\Delta S^{\ddagger}$) of −6 eu were determined (Figure 3).

Both of these values are very similar to the corresponding activation parameters ($\Delta H^{\ddagger}$ = 16 kcal mol^{-1}; $\Delta S^{\ddagger}$ = −4 eu) obtained for the rotation barrier in a model amide, 1-acetyl-4-piperidone **5** (Figure 3), indicating that there is no interference of the amide groups in bispidinone **4a** with each other's rotation dynamics. A chair-to-boat inversion of one of the six membered rings, concomitant with nitrogen pyramidalization en route to the transition state for amide rotation, may provide an explanation, as such process would push the two amide groups away from mutual hindrance. The preference for a boat-chair conformation in bispidinones featuring pyramidal nitrogens has been observed[24] and the barrier to the chair-to-boat inversion in this system is expected to be considerably lower than that to amide rotation.[26]



5

It is noteworthy that 180° rotations about both of the amide (or carbamate) C−N bonds of the *trans* bispidinones **4** amounts to a transition between two enantiomers of the *trans* form, passing through an achiral *cis* intermediate. The stereochemical relationships in the diamide or dicarbamate **4** are best conceived as resulting from the presence of two *chiral planes* in the molecule, each identified with one of the amide (or carbamate) groupings. A mutual *trans* conformation of the two planar functions conveys identical sense to their chiralities, thus imparting chirality to the whole of the structure, which then possesses a C_2 symmetry axis, colinear with the ketone carbonyl bond. On the other hand, when the two amide (carbamate) functions are *cis* to each other, their planar chiralities are mutually opposing and the entire molecule is achiral as a result of a mirror plane lying in between the individual chiral planes and coplanar with the ketone carbonyl plane.

Molecular chirality caused by the presence of a stereogenic plane is typically encountered in the fields of cyclophanes and ansa compounds, annulenes, *trans*-cycloalkenes,[27] arenemetal,[28,29] and olefinmetal complexes,[30] and the specification of this kind of chirality has been dealt with already in the monumental paper by Cahn, Ingold, and Prelog.[31] However, the assignment in our case is not trivial, as the generic system in question is not considered explicitly by the original CIP rules[31] nor could we find any precedence in later literature. Thus, in accordance with the sequence rules (precedence of *Z* over *E*), we define as pilot atom, for each chiral (amide) plane in the *trans* form of Figure 1, that bridgehead skeletal carbon (C1 or C5) that is bonded to the methylene carbon collateral (*Z*) with the amide oxygen rather than with the amide methyl. Following then the *selection rule* for *planar chirality*[31] and the *general sequence rule*, both amide planes in the *trans* rotamer of Figure 1 become of p*R* configuration. Accordingly, the frontal amide plane in the *cis* rotamer of Figure 1 is of the p*S* configuration, while the rear one is p*R*.

In summary, the *trans* form in *N*,*N*′-diacyl- and di(alkoxycarbonyl)bispidinones **4** is more stable than its *cis* isomer due to dipole−dipole opposition, the difference in stability depending on solvent polarity. Despite the mutual proximity of the amide groups in **4a**, the barrier to rotation about the C(O)-N bonds is found to be essentially the same as in isolated amides. A chair-to-boat conversion upon rotation is postulated to account for this fact. Diamides and dicarbamates **4** represent a special case of planar chirality accompanied by a specification issue for which a solution is suggested.

Experimental Section

Preparation of 6-Oxo-1,3-diazaadamantanes (3). General Procedure.[21] A solution of hexamethylenetetraamine **2** (3.51 g, 25 mmol) in ethanol (10 mL) at 0 °C was neutralized by the slow addition of glacial acetic acid (∼3 mL), and then the ketone **1** (25 mmol) and additional ethanol (20 mL) were added. The resulting suspension was heated gently under reflux for a period of time varying according to the ketone employed (8 h to 5 d). The cooled reaction mixture was worked up by one of the following methods:

Method A. The product that crystallized out of the reaction mixture was collected and washed with ethanol.

Method B. The reaction mixture was diluted with ether (300 mL), the pH was adjusted to 3 with 70% aqueous perchloric acid, and the mixture was then stored overnight at −4 °C. The solid precipitate was removed by suction filtration and the fitrate was evaporated to yield the crude product.

5,7-Bis(phenylmethyl)-1,3-diazatricyclo[3.3.1.1^{3,7}]decan-6-one (3d). This compound was prepared from 1,5-diphenyl-3-pentanone (5.96 g, 25 mmol) following the general procedure above. The reaction mixture was refluxed overnight and then worked up according to method A to give 4.07 g (49%) of the clean product (**3d**). Mp: 199−200 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.19 (m, 6H, *m*,*p*-Ph), 7.17−7.10 (m, 4H, *o*-Ph), 3.88 (s, 2H, NCH_2N), 3.26 and 3.02 (AB q, J_{gem} = 12.6 Hz, 8H, CCH_2N), 2.82 (s, 4H, CH_2Ph);^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.6 (C, CO), 136.3 (C, *ipso*-Ph), 130.6 (CH, *o*-Ph), 128.4 (CH, *m*-Ph), 126.6

(25) (a) Relative permittivity (formerly called dielectric constant) is the ratio of the electric field strength in vacuum to that in a given medium.[32] (b) Values taken from *CRC Handbook of Chemistry and Physics*, 72nd ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, 1991−1992; pp 8-49; 9-27.

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(CH, *p*-Ph), 72.9 (CH_2, NCH_2N), 63.3 (CH_2, CCH_2N), 49.4 (C, CCH_2Ph), 37.4 (CH_2, CH_2Ph); HRMS (DCI^+ CH_4) *m/z* (%) 332.1889 (100) $[M]^+$ (calcd for $C_{22}H_{24}N_2O$ 332.1889).

Preparation of 3,7-Diacyl- and 3,7-Bis(alkoxycarbonyl)-3,7-diazabicyclo[3.3.1]nonan-9-ones (4). General Procedure.[22,23] To a 6-oxo-1,3-diazaadamantane **3** (1.0 mmol) in chloroform (10 mL) was added an acyl chloride or a chloroformate ester (2.0 mmol). The solution was stirred for 5 d at room temperature and then partitioned between water and chloroform. The combined organic phase was washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated to afford the product **4**.

1,5-Diphenyl-3,7-bis[(2-propenyloxy)carbonyl]-3,7-diazabicyclo[3.3.1]nonan-9-one (4d). This compound was prepared from **3c** (0.305 g, 1.0 mmol) and allyl chloroformate (0.241 g, 2.0 mmol), following the general procedure above, to furnish the clean product (**4d**) quantitatively. Mp: 123−124 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ [major (*trans*) rotamer] 7.41−7.24 (m, 10H, Ph), 5.97 (ddt, J = 17.0, 10.6, 5.9 Hz, 2H, internal vinylic), 5.33 (dq, J = 17.4, 1.5 Hz, 2H, terminal vinylic), 5.23 (dq, J = 10.4, 1.3 Hz, 2H, terminal vinylic), 5.10 (br d, J = 12.4 Hz, 2H, eq CCH_2N), 4.91 (br d, J = 12.6 Hz, 2H, eq CCH_2N), 4.78−4.62 (br m, 2H, allylic), 4.62−4.45 (br m, 2H, allylic), 3.84−3.64 (br m, 4H, ax CCH_2N); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ [major (*trans*) rotamer] 207.8 (C, CO), 155.0 (C, NCO_2), 135.9 (C, *ipso*-Ph), 132.8 (CH, vinylic), 128.4 (CH, Ph), 127.9 (CH, *p*-Ph), 127.5 (CH, Ph), 118.2 (CH_2, vinylic), 66.9 (CH_2, allylic), 55.8 (br CH_2, CH_2N), 55.3 (br CH_2, CH_2N), 53.1 (C, CPh); HRMS (DCI^+ CH_4) *m/z* (%) 460.2019 (18) $[M]^+$ (calcd for $C_{27}H_{28}N_2O_5$ 460.1998). Anal. Calcd for $C_{27}H_{28}N_2O_5$: C, 70.45; H, 6.08; N, 6.09. Found: C, 70.24; H, 6.39; N, 5.79.

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Supporting Information Available: Characterization data not included in the Experimental Section, copies of ^{1}H and ^{13}C NMR spectra of isolated products, and reproduction of the temperature dependence of the ^{13}C NMR spectrum of **4a** together with fitted, calculated spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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