Conformational and configurational behaviour of κ-agonistic 3,7-diazabicyclo[3.3.1]nonan-9-ones—synthesis, nuclear magnetic resonance studies and semiempirical PM3 calculations

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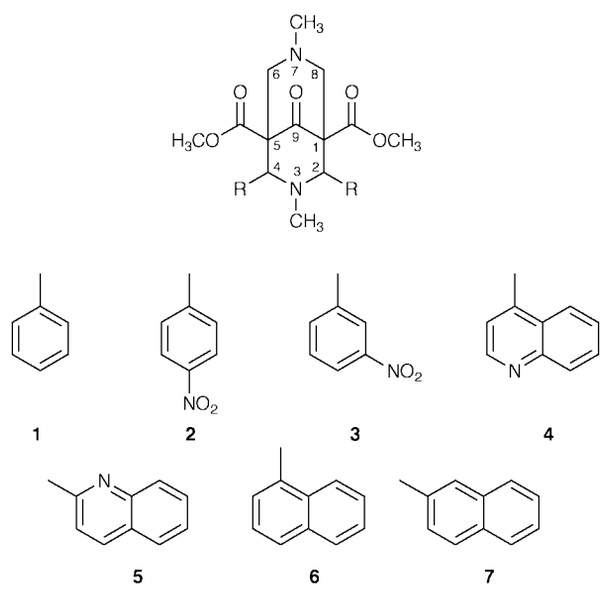
2,4-Diaryl substituted 3,7-diazabicyclo[3.3.1]nonan-9-one 1,5-diesters were found to have a high affinity for κ-opioid receptors. To develop highly potent analgesics, the purpose of this study was the synthesis and the structural characterisation of the novel 2,4-bis(4-nitrophenyl), 2,4-bis(3-nitrophenyl), 2,4-bis(4-quinolyl), 2,4-bis(2-quinolyl), 2,4-bis(1-naphthyl) and 2,4-bis(2-naphthyl) substituted 3,7-diazabicyclo[3.3.1]nonan-9-one 1,5-diesters by means of NMR spectroscopy and molecular modelling. It could be proved that several derivatives undergo *trans–cis*-isomerisation of the aromatic rings linked to the rigid skeleton whereas others show rotational isomerisation. Semiempirical quantum-chemical PM3 calculations were performed to analyse the thermodynamic stability of the isomers as well as the mechanism of the *trans–cis*- or *cis–trans*-conversion.

Introduction

2,4-Diaryl substituted 3,7-diazabicyclo[3.3.1]nonan-9-one 1,5-diesters were found to have a high affinity for κ-opioid receptors with agonistic properties and, thus, are attracting interest as highly potent analgesic drugs.[1] Even though the bicyclononanones are almost rigid features, several conformational and configurational isomers can be found, concerning the conformation of the bicyclic system as well as the substituents on the skeleton: theoretically, the bicyclic system is able to adopt a chair-chair (cc), a chair-boat (cb), a boat-chair (bc) and a boat-boat (bb) conformation.[2,3] In the case of the aforementioned highly substituted 3,7-diazabicycles and 3-oxa-7-azabicycles, a bb conformation was found to be energetically unfavourable.[4,5] Thus, this conformation was not taken into account. A cb conformation (c in the higher substituted piperidone) can be observed either in molecules with bulky substituents at N7[4,6] or in double protonated diazabicycles.[5] In this series of compounds, a bc conformation (b in the higher substituted piperidone) is impossible unless an epimerisation of the aryl substituents has taken place in an initial c conformation.[7] In addition to the various ring conformations, restricted rotations of the aryl substituents at C2 and C4 were observed. Especially in the case of *N*3-methylation, the rotational barrier was high enough to prevent the rings from rotating.[8] In very few cases, instead of the symmetrical *cis*-configuration of the aryl substituents, a *trans*-configuration was observed.[9]

Since the diazabicyclononanones should specifically bind to a receptor protein, the spatial arrangement of the molecule is pivotal for a high biological effect. As part of a larger project dealing with the development of highly potent analgesics,[1] the purpose of this study was to elucidate the structure of isomers isolated, the reaction pathway of the isomerism, and to find out whether the diazabicycles are able to isomerise under physiological conditions.

As probes, 2,4-bis(4-nitrophenyl), 2,4-bis(3-nitrophenyl), 2,4-bis(4-quinolyl), 2,4-bis(2-quinolyl), 2,4-bis(1-naphthyl) and 2,4-bis(2-naphthyl) substituted dimethyl 3,7-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylates **2**–**7** (Scheme 1) were synthesized and their stereochemistry elucidated by means of NMR spectroscopy in solution. For the sake of comparison, the 2,4-diphenyl substituted compound[9] **1** was taken into account. In order to explain the experimental findings and to clarify whether thermodynamic stability differences or kinetic processes govern the stereochemistry, force field calculations as well as semiempirical quantum-chemical PM3 calculations were performed. Moreover, the mechanism of *cis–trans*-isomerisation was theoretically studied.



Scheme 1 2,4-Diaryl substituted dimethyl 3,7-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylates.

Results

NMR investigations

All compounds could be achieved by a double Mannich reaction (*cf.* ref. 9). In the first step, 1 mole of dimethyl 3-oxo-

Table 1 ^{1}H NMR data for the compounds **2**–**7**

Compound	H2/4	H6/8	-N^{4}CH$_3$	-N^{7}CH$_3$	-OCH$_3$
2 (*trans*)	4.92/5.03	2.71–2.75/3.14–3.19	1.85	2.33	3.49/3.81
	s s	m m	s	s	s s
(*cis*)	4.68	2.69/3.04	1.85	2.37	3.72
	s	d, 12.6/d, 12.6	s	s	s
3 (*trans*)	4.95/5.05	2.62–3.09	1.88	2.36/2.43/2.51	3.51/3.90
	s s	m	s	s s s	s s
(*cis*)	4.69	2.65–2.78/2.99–3.13	1.88	2.36/2.43/2.51	3.72/3.79
	s	m m	s	s s s	s s
4	4.86/5.28/5.47	2.63–2.71/3.45–3.50	1.77/1.81	2.47/2.54	3.42/3.66
	s s s	m m	s s	s s	s s
5	5.04/5.33	2.80/3.12/3.17/3.75	2.12	2.29	3.49/3.99
	s s	d, 12.0/d, 12.0/d, 10.8/d, 10.8	s	s	s s
6	4.86/5.29/5.47	2.61–2.68/3.46–3.68	1.80/1.85	2.49/2.55	3.44
	s s s	m m	s s	s s	s
7	4.75	2.68–2.72/3.29–3.33	1.92/1.97	2.47/2.48	3.76
	s	m m	s	s s	s

Table 2 ^{13}C NMR data for the compounds **2**–**7**

Compound	C1/5	C2/4	C6/8	C9	C=O	-OCH$_3$	-NCH$_3$
2 (*trans*)	61.52/63.60	68.44/74.14	60.44/66.36	202.03	167.68/168.13	52.42/52.96	40.53/44.13
(*cis*)	62.73	71.83	59.72	202.34	167.37	52.73	43.31/44.56
3 (*trans*)	63.64/66.21	68.46/74.24	60.56/61.82	201.99	167.67/168.11	52.44/53.02	40.69/43.32/44.03
(*cis*)	62.91	71.56/72.03	59.76	202.37	167.47	52.67	43.32/44.15/44.34
4	62.44/64.14	65.72/66.25/76.47	60.53/61.09/61.40	202.17/202.53	167.03/167.34	52.38	43.18/43.90/44.59
5	62.25/62.64	70.52/73.17	61.97/66.22	200.86	169.46	52.30	40.75/44.30
6	62.83/63.28/64.94	66.41/66.90/77.68	60.95/61.40	203.76/204.28	167.85/168.13	52.07	42.66/42.83/ 43.82/44.59
7	63.95	72.81	60.10	204.12	168.21	52.30	43.10/43.34/44.42

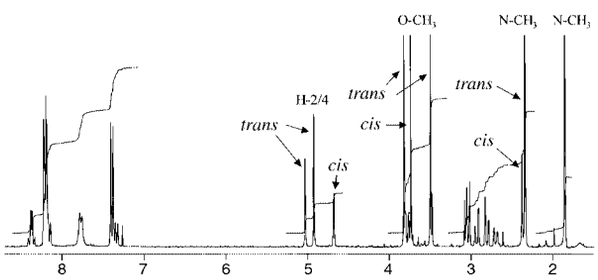


Fig. 1 ^{1}H NMR spectrum (300 MHz) of compound **2**.

glutarate, 1 mole of methylamine and 2 moles of the correspondingly substituted benzaldehyde were refluxed in ethanol to give the piperidone diester. Subsequent conversion of the thus obtained piperidones with formaldehyde and methylamine resulted in the 3,7-diazabicycles. NMR data of all compounds are displayed in Table 1 and Table 2.

From the simplicity of the NMR spectrum in the case of the 2,4-diphenyl substituted dimethyl 3,7-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate **1**, a symmetrical compound can be deduced.[9] In contrast, the NMR spectrum of the 4-nitrophenyl substituted compound **2**, obtained from the first fraction of crystals of the reaction solution, is characterised by a double set of signals (Fig. 1). Interestingly, for the hydrogens at positions 2 and 4, three singlets at $\delta = 4.68$, 4.92, and 5.03 ppm with an integration ratio of 1 : 2 : 2 were measured. The question arose whether either of the double set of signals belongs to rotational isomers as described for the 2,4-bis(3-chlorophenyl)-3,7-dimethyl-3,7-diazabicyclononanone[8] or to *cis–trans*-isomers as observed in the case of the 2,4-bis(2-pyridyl)-3,7-dimethyl-3,7-diazabicycle.[9] The following findings indicate that the two sets of NMR signals are caused by two configurational isomers rather than conformational isomerism. By means of fractional crystallisation, two different sorts of crystals were obtained, rhombic crystals characterised by a melting point of 215 °C and an R_f value of 0.6 on TLC, and amorphous crystals characterized by a melting point of 180 °C and a lower R_f value of 0.51. The amorphous powder could be converted into rhombic crystals by recrystallisation from methanol. The latter crystals gave a simple NMR spectrum which is characteristic of a symmetrically substituted diazabicycle with a *cis*-configuration of the phenyl rings. Logically, the second set of signals belongs to a diazabicycle with the phenyl rings *trans* to each other. Temperature-dependent NMR measurement of an isomeric mixture of **2** gave further evidence of *cis–trans*-isomerism. In DMSO-d$_6$ an increase in the signals of the *cis*-isomer was observed in connection with a simultaneous decrease in the other set of signals. The reaction was found to be irreversible. This observation indicates that the *cis*-isomer is thermodynamically more stable than the *trans*-isomer.

It is worth mentioning that in the case of the *cis*-isomer the *ortho*- and *meta*- hydrogens of either side of the phenyl ring gave two different AB systems: one system is located at 7.34 and 8.15 with a coupling constant of 8.7 Hz. NOE difference experiments showed these hydrogens to be positioned close to H2/4 of the bicyclic system. The signals of the second AB system are close together at $\delta = 8.35$ and 8.40 ppm, and can be assigned to the hydrogens which point to the "bottom" (*endo*) of the bicyclic skeleton. The results indicate that the phenyl ring takes a fixed, almost perpendicular position to the piperidone ring, which is in accordance with findings obtained *e.g.* for the 2,4-bis(3-chlorophenyl)-3,7-dimethyl-3,7-diazabicyclononanone.[8] Since no coalescence of the aryl signals was observed up to 90 °C, it was difficult to determine the rotational barrier by recording temperature-dependent NMR spectra.

However, in order to determine the activation barrier of the *trans–cis*-isomerisation, compound **2** was dissolved in methanol-d$_4$ and the solution was refluxed in the NMR tube.

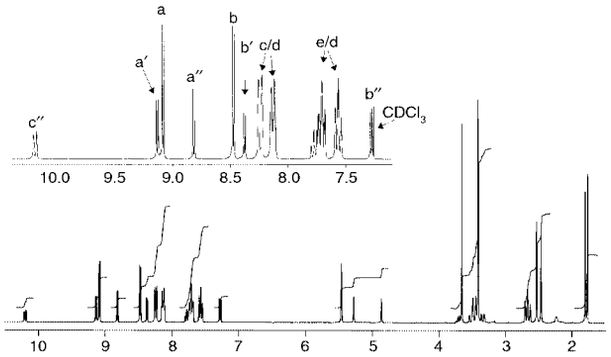


Fig. 2 ^{1}H NMR spectrum (300 MHz) of compound **4**.

NMR spectra were recorded every 16 min (after cooling to ambient temperature) and the ratio of the *trans*- and *cis*-isomers was determined from the integrals of the signals for H2/4. The ratio was plotted against the time. The rate constant k of the reaction was calculated from eqn. (1).[10] After 110 min

$$k(64.7\ ^\circ\mathrm{C}) = \frac{\ln 2}{t_{½}} = \frac{\ln 2}{2100\mathrm{s}} = 3.3 \times 10^{-4}\ \mathrm{s}^{-1} \qquad (1)$$

almost all *trans*-isomer was converted into the *cis*-isomer. The half-life of the reaction was found to be 2100 s, which resulted in a reaction constant $k(64.7\ ^\circ\mathrm{C}) = 3.3 \times 10^{-4}\ \mathrm{s}^{-1}$.

In order to calculate the activation barrier, the boiling point of methanol (64.7 °C) and the $t_{1/2}$ was subjected to the logarithmic form (3) of the EYRING equation (2), where $\Delta G^{‡}$

$$k = \frac{2T}{N_\mathrm{A} \times h}\, \mathrm{e}\, \frac{\Delta G^{‡}}{2T} \qquad (2)$$

is the free activation enthalpy, R is the universal gas constant (8.31 J K^{-1}), T is the absolute temperature (K), N_A is Avogadro's number (6.022×10^{23} mol^{-1}) and h is the Planck constant (6.6256×10^{-34} J s). From eqn. (3) the free activation

$$\Delta G^{‡} = 19.14\ T\left[10.32 - \log\left(\frac{k}{t}\right)\right] \qquad (3)$$

enthalpy was calculated to be 25 kcal mol^{-1}, indicating a rather high free activation barrier.

In the case of the 3-nitrophenyl substituted compound **3**, a similar *cis–trans*-isomerism was observed. From recrystallisation of a mixture of *cis–trans*-isomers in methanol, the pure *cis*-isomer was obtained. In contrast, in the case of 2-quinolyl substituted compound **5**, recrystallisation gave only the *trans*-isomer. Due to the asymmetry of the molecule, the NMR spectrum shows a "double" set of signals in comparison to the *cis*-isomers. The *trans*-configuration could be verified by the measurement of NOE experiments. Saturation of the signals of H2 and H4, respectively, showed only a very weak NOE effect for either hydrogen, whereas the saturation of the signal at $\delta = 5.04$ ppm resulted in a strong positive NOE with the signal at δ (H6/8) = 3.75 ppm and a negative NOE with the signal at δ (H6/8) = 3.17 ppm; the latter might be due to a three-spin effect (*cf*. ref. 11) and could only be observed where the signal belongs to a hydrogen (H2 or H4) in an axial position (*cf*. ref. 12). Logically, the saturation of the signal at $\delta = 5.33$ ppm, which has to be assigned to the hydrogen H2/4 in the equatorial position, does not show any NOE effect with signals belonging to H6/8.

The spectra of the 4-quinolyl **4** (Fig. 2) and 1-naphthyl derivative **6**, both having the aromatic system linked through the α-position to the diazabicycle, showed three signals at 4.86, 5.28, 5.47 ppm (ratio 1 : 1 : 2) and 4.86, 5.29, 5.47 ppm (ratio 1 : 1 : 3) for the protons H2/4, respectively. This ratio

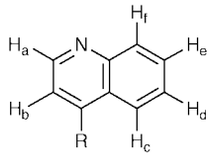


Fig. 3 Definition of hydrogens in the 4-quinoline residue.

was mirrored in the corresponding signals for the aromatic protons.

Again the question arose whether these different sets of signals belonged to configurational *cis–trans*-isomers or rotational isomers: according to the simple set of signals, one isomer seems to be symmetrical, whereas the double set of signals may belong to an asymmetrical isomer. Interestingly, in the spectra of the 4-quinolyl and 1-naphthyl derivatives **4** and **6**, a doublet of doublets could be found at $\delta = 10.2$ and $\delta = 10.4$ ppm, respectively. This rather strong downfield shift of a single aromatic proton might be caused by the ring current effect of either aromatic ring, which only seems to be possible where the aryl rings are in a *cis*-configuration. To prove this hypothesis, H,H-COSY and NOE experiments were performed to elucidate the spatial neighbourhood of this proton. First, the aromatic protons were assigned to the signals by the H,H-COSY experiment. From the results it was further hypothesized that both isomers are characterised by a *cis*-configuration of the aryl residues: according to the simple set of signals, one isomer has to be symmetrical (protons H_a, H_b, *etc*.) with both bicyclic aryl rings pointing to the outside (*exo*) of the skeleton. In the isomer with the double set of signals, one aryl ring seems to take an orientation similar to the symmetrical compound (protons $H_{a'}$, $H_{b'}$, *etc*.), and the other aryl ring is rotated by about 180° (protons $H_{a''}$, $H_{b''}$, *etc*., protons are defined in Fig. 3). The different orientation of the aryl rings creates the asymmetry; temperature dependent NMR measurements have shown that these apparent conformers do not interconvert at high temperatures. Thus, the isomerism can be denoted as an atropisomerism about a sp^2–sp^3 single bond.[13]

The NOE experiments support the hypothesis of symmetrical and asymmetrical *cis*-isomers (Fig. 4). On saturating the signal at 5.47 ppm which was assigned to H2/4 in the putative symmetrical compound, one positive NOE effect with the aromatic proton H_c was found. This is only possible in the above mentioned orientation of the 4-quinolyl ring of the symmetrical compound. Furthermore, a negative NOE effect could be detected, which can be explained as a three-spin-system between H2/4, the aromatic proton H_c and the aromatic proton H_d. Saturating the signals at 4.86 or 5.28 ppm which were supposed to belong to the protons H2/4 in the asymmetric compound led to a strong NOE effect at 5.28 or 4.86 ppm, respectively. This clearly demonstrates the spatial proximity of H2 and H4, realized in the *cis*-configuration. The signal at 5.28 ppm (H2) further showed an NOE effect to the aromatic proton $H_{c'}$ and negative effects to $H_{d'}$ (compared with the symmetrical compound) and $H_{b''}$. The signal at 4.86 ppm (H4) showed an NOE effect to $H_{b''}$ and a negative effect to $H_{a''}$. Taking the connecting pathways in the H,H-COSY into account, the proton showing the strong downfield shift could be assigned to the proton $H_{c''}$. It showed strong NOE effects to the protons $H_{d''}$ and $H_{b'}$ (not displayed). This strong downfield shift of $H_{c''}$ was likely to be caused by the spatial proximity of the phenyl rings in a way that the hydrogens of either ring feel the deshielding ring current effect of the other.

PM3 calculations of the diazabicycle **4** in the cc conformation and *cis*-configuration concerning the quinoline rings revealed two stable *cis*-geometries that differ in their heats of formation only by about 5 kcal mol^{-1}, one is the symmetrical arrangement of the aromatic rings ($\Delta H = -67.9$ kcal mol^{-1}) (Fig. 5), and the other one is an asymmetric arrangement with one quinolyl ring rotated by about 180° (Fig. 6) ($\Delta H = -63.2$

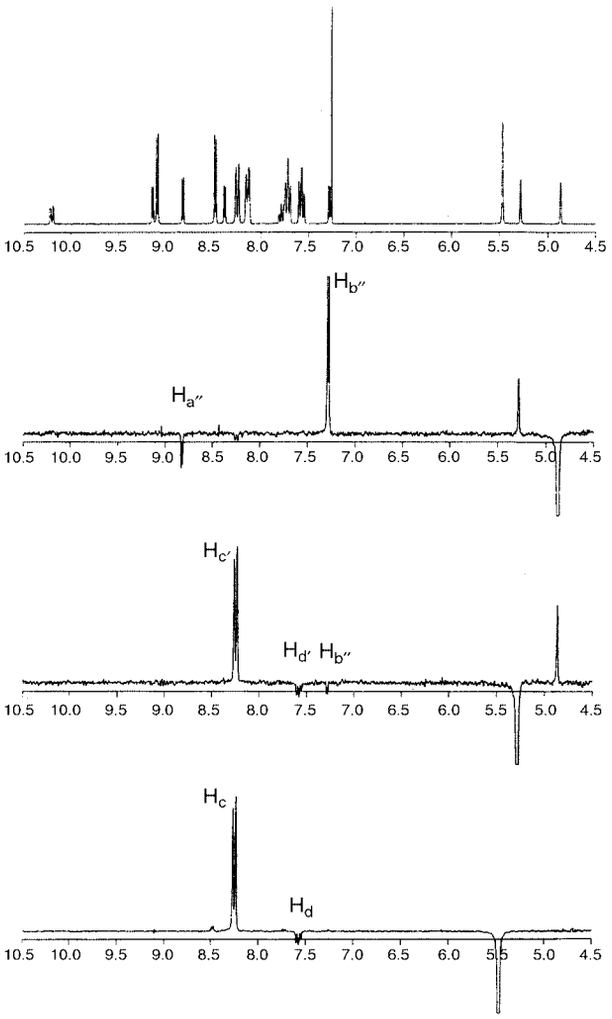


Fig. 4 NOE difference spectra of compound **4**.

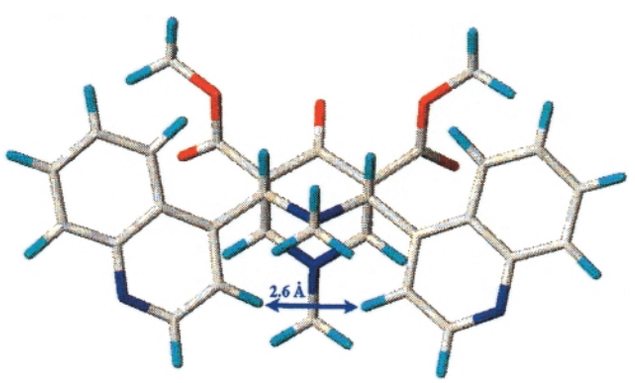


Fig. 5 Structure of the energetically stable symmetric *cis*-configuration of **4**, indicating the shortest distance between the quinoline substituents.

kcal mol^{-1}), both suggested by the NMR spectra. We analysed the possibility of interconverting the symmetric or the asymmetric arrangement into either form by rotation of the quinoline rings in steps of 5°. In each case, a strong spatial hindrance at least between the H_c proton of the quinoline rings and the protons of the N3 linked methyl group appeared. This finding nicely explains the stability of the isomers that was found experimentally. In Figs. 5 and 6 the short distances between the protons of both rings are marked. In the case of the symmetrical *cis*-conformation, such a short distance (2.6 Å) is observed between both $H_{b'}$ atoms. In the asymmetric *cis*-conformation an even shorter distance (2.4 Å) between $H_{b'}$ and $H_{c''}$ appeared. This explains the downfield shift of these hydrogens observed in the NMR spectra. In turn, if the distance between these protons is larger—as is the case with compound **1**—no such downfield shift can be observed.

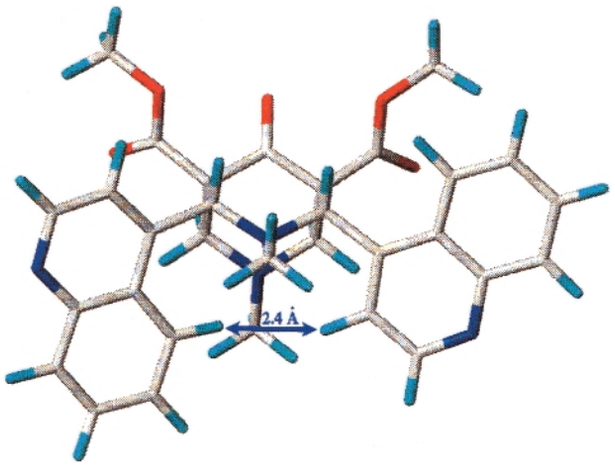


Fig. 6 Structure of the energetically stable asymmetric *cis*-configuration of **4**, indicating the shortest distance between the quinoline substituents.

Taking the results up to this point together, it can be stated that the quinolyl substituted compounds suffer from stereochemical overcrowding and, thus, form stable rotational isomers. Due to the high similarity in spatial properties between the naphthyl compound **6** (repulsions between $H_{c'}$ atoms and the N3 methyl group) and the quinolyl analogue **4**, stable rotational isomers can also be expected.

Theoretical calculations

In order to gain more insight into the stereochemical behaviour of the diazabicyclononanones, all conformations of the skeleton studied herein, chair-chair (cc), chair-boat(N7) (cb), boat(N3)-chair (bc) and boat-boat (bb) were subjected to force field and PM3 calculations. As expected from previously performed calculations for the analogous oxaazabicycles,[4] in each case the bc and bb conformations appeared to be energetically unfavourable. Comparing the energies of all the compounds and conformations, the cc conformations are slightly more stable than the cb conformations of the bicyclononanones; therefore, only the cc will be considered in the following discussions. Furthermore, an equatorial and axial orientation of the N3-methyl group to the piperidine ring were taken into consideration. In all cases the equatorial conformation appeared to be more stable than the axial orientation of the methyl group. The energies of the more stable conformations are listed in Table 3.

Thermodynamics of the *cis–trans*-equilibrium The conformations, *i.e.* the dihedral angles describing the orientation of the aromatic rings, obtained for the most stable conformations are very similar to the already published structures of **1**.[5] Comparing all compounds with regard to the *trans–cis* differences of the heats of formation, the aforementioned experimental findings can be partially understood: for **1** the $\Delta_{trans-cis}\Delta H$ value of 1.8 kcal mol^{-1} indicates a preference for a *cis*-conformation. The enthalpy differences between *trans*- and *cis*-configurations for **2** and **3** were found to be smaller (**2** $\Delta_{trans-cis}\Delta H = 1.0$ kcal mol^{-1}, **3** $\Delta_{trans-cis}\Delta H = 1.5$ kcal mol^{-1}; 1.0 kcal mol^{-1} in the case of the asymmetric forms). These differences in the heats of formation of the two alternative configurations cannot completely explain the experimentally measured *trans–cis*-ratios of **2** and **3** in comparison with **1**; however, they favour a *cis*-configuration which was obtained after recrystallisation.

For compound **4,** two structures with *cis*-configurations characterised by a symmetrical and an asymmetrical position

Table 3 Heats of formation (in kcal mol^{-1}) of low energy conformations of bicyclononanone derivatives

Compound	Thermodynamics		
	ΔH_{cis}	ΔH_{trans}	$\Delta_{trans-cis}\Delta H$
1	only *cis*		
sym	**−120.4**	−118.6	1.8
2	*cis*/*trans*	*cis* after recrystallisation	
sym	**−136.0**	−135.0	1.0
3	*cis*/*trans*		
sym	**−136.7**	−135.2	1.5
asym	−136.6	−135.6	1.0
4	only *cis*		
sym	**−67.9**	−62.7	5.2
asym	−63.2	−67.8	−4.6
5	*trans*		
sym	**−70.2**	−68.9	1.3
asym	−67.7	−69.3	−1.6
6	only *cis*		
sym	**−81.6**	−81.5	0.1
asym	−76.8	−74.8	2.0

of the 4-quinolyl ring were found in the experiments. For the sake of comparison, both conformations and their corresponding *trans*-configurations have been calculated. In the symmetric conformation, the *cis*-configuration appeared to be highly favoured over the *trans* (**4** $\Delta_{trans-cis}\Delta H = 5.2$ kcal mol^{-1}), whereas in the case of the "asymmetric" conformation (the aryl rings are rotated by 180° against each other), the opposite is true ($\Delta_{trans-cis}\Delta H = -4.6$ kcal mol^{-1}). However, the symmetric *cis*- and the "asymmetric" *trans*-isomer are energetically equivalent.

Nevertheless, experimentally only the *cis*-configuration of **4** was observed. The repulsion of the $H_{c'}$ hydrogen atom having a rather close contact of 2.5 Å to both nitrogen atoms of the bicycle skeleton is likely to be the reason for the thermodynamically unfavourable stability of the asymmetric *cis*-conformation. The *trans*-configuration lacks such a close spatial interaction. For the asymmetric compound, the clarification of this contradiction will be given in the kinetics part.

Similar contradictory results were obtained in the case of the 2-quinolyl substituted compound **5**, which could only be isolated in the *trans*-configuration. Both configurations were analysed. In agreement with the experiment, the heats of formation for the "asymmetric" compound predicted *trans* to be slightly more stable than *cis* ($\Delta_{trans-cis}\Delta H = -1.6$ kcal mol^{-1}). However, in the symmetrical conformation the *cis*-configuration is favoured ($\Delta_{trans-cis}\Delta H = 1.3$ kcal mol^{-1}) and is energetically comparable to both *trans*-conformations.

Since the thermodynamic examinations could not give satisfying explanations of all experimentally observed ratios of isomers, a subsequent kinetic study was performed.

Kinetics of the *trans–cis*-isomerisation mechanism. From the synthesis a mixture of *trans*/*cis* isomers of **2** was obtained. Heating a solution of the isomers up to 40 °C always results in a complete conversion of the *trans*-isomer into the *cis*-isomer of **2** which is in accordance with the NMR measurements mentioned above. It is not possible to isolate the pure *trans*-isomer.

The bicyclononanones are relatively rigid compounds. Two main mechanisms seem to be possible in principle. One is characterised by opening and closing of a covalent bond between C1/C2 and C4/5, respectively, corresponding to a retro-Mannich reaction. In order to switch from one to the other configuration, in the ring-opened form a rotation of the H–C2(C4) bond around the N(3)–C2(C4) bond has to occur and seems to be possible. At first glance, a second mechanism might be possible: it is characterised by a temporary deprotonation of C2 or C4, leading to a planar sp^2 carbon atom. Reprotonation from the backside would lead to the isomerism. If the latter mechanism were to take place, a

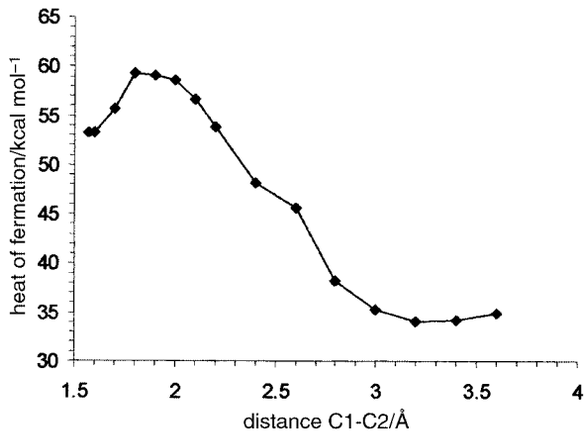
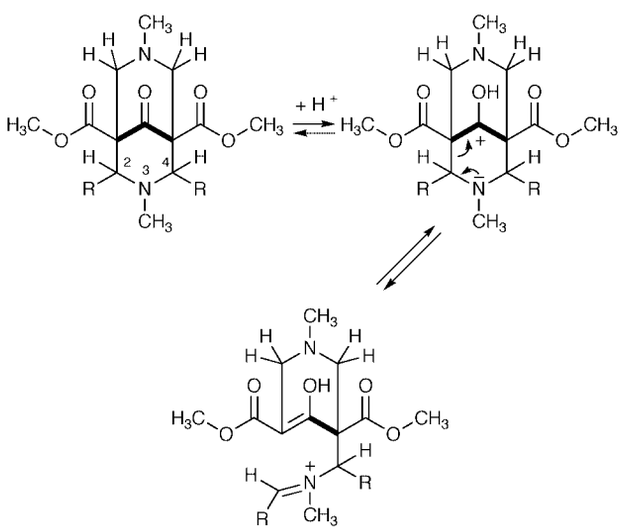


Fig. 7 Diagram representing the dependence of the length of the C1–C2 bond on the heat of formation (PM3 calculations) of **2**.

hydrogen/deuterium exchange should be observed in deuterated solvent. However, an NMR study of the isomerisation (see above) performed in methanol-d_4 did not show a H/D exchange. Therefore, only a retro-Mannich reaction needs to be discussed in order to explain the observed isomerism.

As the initial step of the retro-Mannich reaction, a protonation of the keto carbonyl group is a prerequisite to stabilise the resulting ring-opened product by formation of an enol (see Scheme 2). To gain an insight into the probability for such a



Scheme 2 Cleavage of the C1–C2 or C4–C5 bond and theoretical mesomeric stabilisation of the resulting anion.

carbonyl protonation, the heats of formation of the keto-protonated structures were compared with the corresponding N3-protonated compounds (Table 4). As is expected from chemical understanding, in each case the N3-protonated compounds are more stable than those with a hydroxy group. Interestingly, the differences of the heats of formation are in the range (about 16 to 33 kcal mol^{-1}) of the experimentally observed activation barrier for a *trans–cis* isomerisation.

Starting from the carbonyl protonated forms, reaction coordinate calculations to lengthen the C1–C2 bond in steps of 0.1 Å to a distance of 3.7 Å were performed. As an example, the resulting energy pathway is schematically shown for **2** in Fig. 7. After overcoming a transition state at 1.8 Å with an energy effort of 6.1 kcal mol^{-1} the bond cleaves with energy gain. A comparison of the heats of formation of the optimised ring-opened forms of all compounds with the ones of the ring-closed form is listed in Table 5. All possible conformations have been calculated including two asymmetric forms for the *cis*- and

Table 4 Comparison of the proton affinities of the N3-nitrogen atom and the carbonyl oxygen atom

	cis			*trans*		
	ΔH_f N3-prot	ΔH_f *enol*	$\Delta\Delta H_{f,enol\text{-}N3\text{-}prot}$	ΔH_f N3-prot	ΔH_f *enol*	$\Delta\Delta H_{f,enol\text{-}N3\text{-}prot}$
1						
sym	25.8	53.8	28.0	28.1	51.7	23.6
2						
sym	25.4	48.0	22.6	27.1	47.5	20.4
3						
sym	21.4	45.6	24.2	23.9	45.7	30.8
asym	22.1	45.6	23.5	24.8	43.2	18.4
4						
sym	82.5	108.8	26.3	92.6	113.4	20.8
asym	88.4	108.5	25.7	84.4	106.6	22.2
5						
sym	72.6	101.6	29.0	74.7	92.9	18.2
asym	73.7	103.2	29.5	72.9	98.3	25.4
6						
sym	61.8	90.4	28.6	64.0	93.9	29.9
asym	67.9	95.8	27.9	72.2	88.1	15.9

Table 5 Enol-forms of several bicyclononanone derivatives corresponding to the Mannich or retro-Mannich reaction, respectively

	cis			*trans*			
	ΔH_f open	ΔH_f closed	$\Delta\Delta H_f$, closed–open	ΔH_f open	ΔH_f closed	$\Delta\Delta H_f$, closed–open	$\Delta\Delta\Delta H_f$, *cis–trans*
1		25.8			28.1		
sym	31.7	53.8	22.1	32.8	51.7	18.9	3.2
2							
sym	34.3	48.0	13.7	34.2	47.5	13.3	0.4
3							
sym	29.6	45.6	16.0	29.8	45.7	15.9	0.1
asym	30.5	45.6	15.1	30.2	43.2	13.0	2.1
4							
sym	90.5	108.8	18.3	89.3	113.4	24.1	−5.8
asym	91.4	108.5	17.1	92.5	106.6	14.1	3.0
5							
sym	81.2	101.6	20.4	81.3	92.9	11.6	8.8
asym	80.2	103.2	23.0	81.9	98.3	16.4	6.6
6							
sym	69.2	90.4	21.2	71.2	93.9	22.7	−1.5
asym	71.3	95.8	24.5	70.3	88.1	17.8	6.7

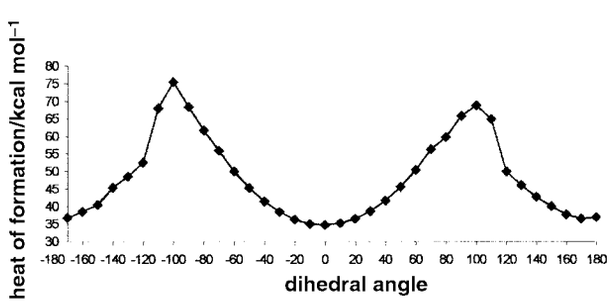


Fig. 8 Diagram representing the dependence of the rotation of the dihedral angle C4–N3–C2–H (see Fig. 9) on the heat of formation (PM3 calculations) of **2**.

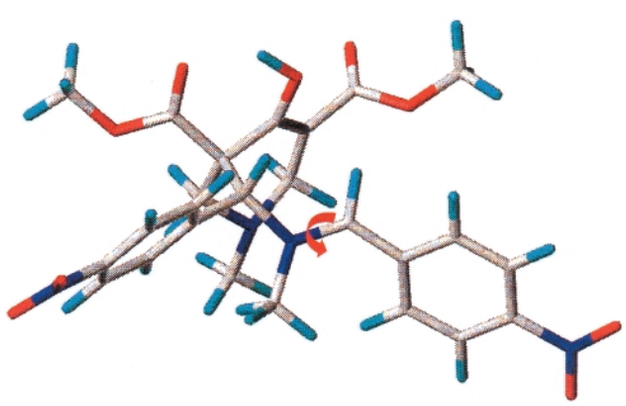


Fig. 9 The structure of the open enol-form of compound **2** in a quasi *cis*-configuration. The arrow indicates the rotation of the bond to switch from a *cis*- to a *trans*-configuration.

four for the *trans*-configuration. In Table 5, however, only those structures are considered which appeared more stable in the neutral compounds and which may be relevant for the mechanistic analysis.

In addition, the process of isomerisation *per se*, that is the rotation of the C2(C4)–H bond, needs to be discussed. For this purpose the dihedral angle C4–N3–C2–H was rotated in steps of 10° (see Fig. 8). Two barriers were observed, each characterised by an almost perpendicular orientation of the C–H bond to the plane of C4–N3–C2 whereby the rotation passing a repulsion with the N3-methyl group is slightly lower (ΔH_f = 34.1 kcal mol^{-1}) than in the direction of the former C1–C2 bond (ΔH_f = 40.7 kcal mol^{-1}).

Taking the energy efforts and gains of each step together the retro-Mannich reaction is probably the mechanism of the *trans–cis* or *cis–trans* isomerisation. Even though the entropy contributions or the solvent stabilisation influences were not considered (polar solute supports polar transition states), the barrier for the isomerisation is in the range of the experi-

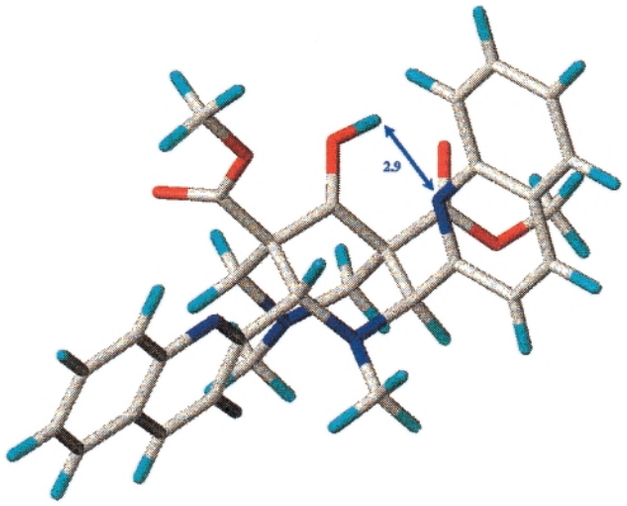


Fig. 10 Attractive electrostatic interactions between the hydroxy group and the nitrogen atom of the 2-quinolyl ring of the symmetric *trans*-form of **5**.

mentally determined value. Two contradictions remain to be answered: firstly, even though in the case of the 4-quinolyl compound (**4**) the symmetric *cis*-form and "asymmetric" *trans*-configuration were found to be energetically equivalent, only the *cis*-conformation was observed. Secondly, what, in turn, is the reason for the stabilisation of the *trans*-configuration of the 2-quinolyl analogue (**5**), exclusively isolated from the synthesis.

Compound **5** will be discussed first. Analogously to the energetically more stable *cis*-configurations of the neutral bicyclic system, the ring-opened enol forms are also slightly more stable than the structures related to the *trans*-configuration. In the following discussion, only the differences in the heats of formation of the optimised closed and open enol forms were considered as the barrier, keeping in mind that an additional barrier of about 6 kcal mol^{-1} (Scheme 2) has to be added. Interestingly, the activation barrier which has to be overcome in order to form the closed bicycle is, in the case of the *cis*-configuration, considerably disfavoured in comparison to the formation of a *trans*-configuration for **5**: by far the lowest activation barrier to form the symmetric *trans*-configuration is found to be only 11.6 kcal mol^{-1} in comparison to 20.4 or 23.0 kcal mol^{-1} for the *cis*-configuration, respectively. This effect is caused by a stabilisation of the enol *trans* structure by attractive electrostatic interactions between the hydrogen atom of the hydroxy group and the nitrogen atom of the 2-quinolyl ring due to the relatively short distance of 2.9 Å (see Fig. 10). No such stabilisation could be found for the symmetrical *cis*-form. In addition, if the differences of heats of formation between the open and closed enolic *cis*- and *trans*-configurations ($\Delta\Delta\Delta H_f$ (*cis*–*trans*)) were compared with all other compounds (Table 5), such a large difference cannot be observed. Thus, for kinetic reasons, the conclusion can be drawn that the symmetric *trans*-configuration has to be formed in the case of **5**.

However, if the proton is removed from the hydroxy group in the *trans*-form and the stable bicyclononanone with the 9-keto group is rebuilt, the above-mentioned attractive interaction will change to repulsive interactions which are due to the strong negative partial charge of the carbonyl oxygen atom and the negative charge of the nitrogen of the 2-quinolyl ring. Thus, the *trans*-form becomes thermodynamically less stable than the *cis*-configuration.

Taking the thermodynamic and kinetic discussions together, it can be concluded that the preferred formation of the *trans* configuration of **5** is kinetically controlled. For the 4-quinolyl substituted compound **4**, a mixture of symmetrical and asymmetrical *cis*-configurations was found experimentally. It is difficult to explain the additional formation of the asymmetric *cis*-form. Comparing the heats of formation of the ring-opened enol-forms, the asymmetric *cis*-structure is 1.1 kcal mol^{-1} favoured over the corresponding *trans*-configuration, which would explain the experimental result. However, in contradiction to this, the difference of the heats of formation between the closed and open compound is 3 kcal mol^{-1} higher for the *cis*- than for the *trans*-configuration. Maybe these somewhat contradictory results illustrate the limitations of semiempirical PM3 calculations performed in the gas phase. Nevertheless, the thermodynamic preference of the open asymmetric *cis*- over the *trans*-form of **4** seems to be responsible for the formation of the corresponding neutral bicyclononanone with an asymmetric *cis*-configuration.

Overall, a retro-Mannich reaction is very probably the mechanism responsible for *trans*–*cis*- and *cis*–*trans*-isomerisations. By means of semiempirical PM3 calculations we could show that thermodynamic as well as kinetic aspects play an important role in the formation of stable bicyclononanones. In addition, it can be concluded that all isomers for each compound are stable enough for pharmacological studies. No isomerisation should be expected. However, the complex stereochemical behaviour has to be taken into account when analysing structure–activity relationships of these compounds as κ-selective opioids. Preliminary pharmacological screening has shown the 2-quinolyl derivative to have high affinity for the κ-receptors.

Experimental

Chemicals and materials

Melting points were determined with a Dr Tottoli melting point apparatus (Büchi, Switzerland) and were not corrected. IR spectra, recorded as KBr discs, were obtained using a Perkin-Elmer 298 spectrometer. Analysis indicated by the symbols of the elements was within ±0.4% of the theoretical value. TLC was carried out using silica gel 60 F_{254} (Merck No. 5554). As eluent a mixture of cyclohexane–ethyl acetate–methanol (10 : 4 : 1) was used. Dry solvents were used throughout.

General procedure for the synthesis of the 2,6-diaryl substituted piperidones

Dimethyl 3-oxoglutarate (0.02 mol) dissolved in 10 ml methanol is added dropwise to a solution of 0.04 mol arylaldehyde and 0.02 mol aqueous methylamine (40%) in 20 ml methanol at 0 °C. After 12 hours at 5 °C the product is obtained. It is recrystallised from ethanol.

General procedure for the synthesis of dimethyl 2,4-diphenyl-3,7-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate 1, dimethyl 2,4-bis(4-nitrophenyl)-3,7-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate 2, dimethyl 2,4-bis(3-nitrophenyl)-3,7-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate 3 and dimethyl 2,4-bis(2-quinolyl)-3,7-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate 5

Piperidone (0.0025 mol) is dissolved in 20 ml methanol under reflux. Aqueous formaldehyde (0.6 ml, 35%) and 0.4 ml aqueous methylamine (40%) are added and the solution is refluxed for 10 minutes. After 3 hours at room temperature the solvent is evaporated. The remaining oil is dissolved in ethanol and ether. The product crystallises after 1–2 days. It is recrystallised from ethanol. Analytical data of compounds **2**–**7** are described in Table 6.

Preparation of the dimethyl 2,4-bis(4-quinolyl)-3,7-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate 4

Piperidone (0.0025 mol) is dissolved in 20 ml methanol under reflux. Aqueous formaldehyde (1.2 ml, 35%) and 0.8 ml

Table 6 Analytical data for the compounds **2**–**7**

Compound (Formula)	Yield[a] (%)	Mp/°C	Found (%) (Required) C	H	N
2 ($C_{25}H_{26}N_4O_9$)	90	180 (*trans*), 215 (*cis*)	56.80 (57.02)	5.14 (4.98)	10.47 (10.65)
3 ($C_{25}H_{26}N_4O_9$)	67	215 (decomp.)	56.90 (57.02)	4.99 (4.98)	10.57 (10.65)
4 ($C_{31}H_{30}N_4O_5$)	23	202 (decomp.)	68.99 (69.12)	5.75 (5.62)	10.24 (10.41)
5 ($C_{31}H_{30}N_4O_5$)	98	145 (decomp.)	68.87 (69.12)	5.42 (5.62)	10.32 (10.41)
6 ($C_{33}H_{32}N_2O_5$)	22	197 (decomp.)	73.68 (73.85)	6.10 (6.01)	5.22 (5.22)
7 ($C_{33}H_{32}N_2O_5$)	26	171–173	73.63 (73.85)	6.08 (6.01)	5.22 (5.22)

[a] Yields were not optimised.

aqueous methylamine (40%) are added and the solution is refluxed for 20 minutes. After 3 hours at room temperature the solvent is evaporated. The remaining oil is dissolved in ethanol. The solvent is allowed to evaporate from the open beaker at room temperature. It is recrystallised from ethanol in the same manner (for analytical data see Table 6).

Preparation of the dimethyl 2,4-bis(1-naphthyl)-3,7-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate 6

Piperidone (0.0025 mol) is dissolved in 40 ml methanol under reflux. Aqueous formaldehyde (1.2 ml, 35%) and 0.8 ml aqueous methylamine (40%) are added after 5, 20, 40 and 60 minutes. After 90 minutes the reaction is interrupted. The product crystallises at room temperature. It is recrystallised from ethanol (for analytical data see Table 6).

Preparation of the dimethyl 2,4-bis(2-naphthyl)-3,7-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate 7

Piperidone (0.0025 mol) is dissolved in 40 ml methanol under reflux. Aqueous formaldehyde (1.2 ml, 35%) and 0.8 ml aqueous methylamine (40%) are added and the solution is refluxed for 30 minutes. The product crystallises after 3–4 days at room temperature. It is recrystallised from ethanol (for analytical data see Table 6).

NMR measurements

All ^{1}H and ^{13}C NMR experiments spectra were performed on a Varian XL 300 FT NMR spectrometer operating at 299.956 MHz (^{1}H) and 75 MHz (^{13}C) with a sample temperature of 30 °C. In the case of the ^{1}H NMR spectra, a varying number of scans (depending on the experiment) with a frequency range of 2200 Hz were collected into 65 000 data points, giving a digital resolution of 0.33 Hz point^{-1}. An appropriate Gaussian function was applied before Fourier transformation to enhance the spectra resolution. Abbreviations for data quoted are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. ^{1}H and ^{13}C NMR assignments given for each compound were confirmed by randomly running HETCOR and H,H-COSY experiments.

Theoretical methods

All molecules were constructed with the molecular modelling program SYBYL 6.4[14] on Silicon Graphics Workstations. Each flexible molecule was subjected to an extensive conformational search by systematically rotating each rotatable bond by 30° increments. An energy cut-off of 7 kcal mol^{-1} above the energy minimum was applied. All conformations obtained from the search were grouped into families based on similarities of their dihedral angles (±30°). Using the TRIPOS force field[15] and the Powell minimizer contained in SYBYL/MAXIMIN, the lowest energy member of each conformational family was then extensively minimized. The Gasteiger method (PEOE) was used to calculate the partial charge distribution of the molecules.[16,17] Electrostatic interactions were taken into consideration by using a relative permittivity of $\varepsilon = 4r$ with a distance dependent function which, in our experience, gives relevant conformations in agreement with solution conformations obtained by NMR spectroscopy. The semiempirical calculations were carried out using the PM3[18] hamiltonian as implemented within the MOPAC 7.0 program in SYBYL. For comparison we also used AM1 sometimes. The differences in heats of formations which are of importance to the conclusions to be drawn in the paper are in the same range as obtained with PM3. However, the rather high deviations from experimental values of the heats of formations of some nitro substituted benzene rings (nitrobenzene, 3-nitrotoluene, 4-nitrotoluene) in the case of AM1 (9.78 kcal mol^{-1} to 13.37 kcal mol^{-1}) in comparison to only 0.86 kcal mol^{-1} to −2.83 kcal mol^{-1} using PM3 led to the preference of PM3. The most stable conformations obtained from the force field calculations were optimised with PM3 using the keywords PRECISE, SCFCRT = 1.D-12, EF, NOINTER, GEO-OK and GNORM = 0.1.

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