JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 10, 525–530 (1997)

FOLDED CONFORMATIONS OF *N*-(AMINOALKYL)-9-PHENANTHRENECARBOXAMIDES IN THE CRYSTAL AND SOLUTION†

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The molecular structures of three tertiary *N*-(aminoalkyl)-9-phenanthrenecarboxamides were investigated in solution and the solid state by means of ^{1}H NMR spectroscopy and x-ray crystallography. The tertiary amides exist as a mixture of *E* and *Z* isomers in solution and the aminoalkyl groups exist as a mixture extended and folded conformers. A crystalline *N*-(aminoethyl)amide was obtained as the pure *Z* isomer in which the phenanthrene and amide planes are nearly perpendicular and the aminoethyl group is folded over the less hindered face of the amide group. Rotation about the Ar–C(O) bond is slow in resolution rendering these molecules chiral on the NMR time-scale. As a consequence, the α-methylene protons display large diasterotopic splittings when the aminoalkyl group is *syn* to the amide carbonyl. Folded conformations place the *Z* and *E* aminoalkyl groups in the deshielding and shielding regions, respectively, of the phenanthrene rings, resulting in large differences in chemical shifts. © 1997 John Wiley & Sons, Ltd.

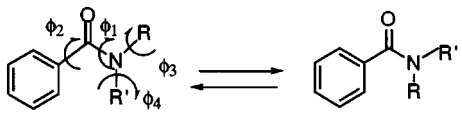
J. Phys. Org. Chem. **10**, 525–530 (1997) No. of Figures: 10 No. of Tables: 2 No. of References: 21

Keywords: N-(aminoalkyl)-9-phenanthrenecarboxamides; molecular structures; folded conformations

Received 11 September 1996; revised 11 December 1996; accepted 16 December 1996

INTRODUCTION

The conformational analysis of tertiary benzamides has proved to be a fertile area for NMR investigations.[1] Four dihedral angles define the conformation of the amide group [equation (1)]. The barrier for rotation about the amide C–N bond (ϕ_1) has been most extensively investigated and is known to be dependent upon both steric and electronic effects. Benzamides possessing two *ortho* substituents can have sufficiently high barriers [>20 kcal mol) (1 kcal = 4·184 kJ)] to permit the separation of *E* and *Z* atropisomers.[1] Tertiary benzamides bearing two *ortho* substituents possess large Ar—C(O) dihedral angles (ϕ_2) and may also have large barriers for rotation about the Ar—C(O) bonds (>10 kcal mol^{-1}).[2] Barriers for rotation about the N—C bonds of tertiary amides (ϕ_3 and ϕ_4) are too low for measurement by NMR methods; however, there is a distinct preference for conformations in which the β-carbon of both the *syn* and *anti N*-alkyl groups are perpendicular to the amide plane.[3,4]



(1)

The NMR spectra of tertiary benzamides have revealed two interesting phenomena. First, the geminal methylenes of the *N*-alkyl or benzyl groups can display large diasterotopic splittings when the benzamide has either one *ortho* substituent or two dissimilar *ortho* substituents (R≠R′) and the methylene is *syn* to the amide oxygen.[2,5,6] This phenomenon was originally attributed to the effect of the *ortho* substituent on the rotamer populations of the *N*-alkyl group,[5] but later shown to result from slow rotation about the Ar—C(O) bond.[2,6] Such molecules have perpendicular dissymmetric planes and thus are chiral on the NMR time-scale. Second, the aminomethyl resonances of the *Z* isomers of *N,N*-[(dimethylamino)alkyl]benzamides [(R = $(CH_2)_n$ NMe_2, R′ = H, equation (1)] are shifted downfield compared to those of the *E* isomers.[7] This phenomenon was attributed to conformational preferences of an unspecified nature.

We have recently investigated the effects of the amide ground-state conformation upon intramolecular photoinduced electron transfer in a family of *N*-(aminoalkyl)-9-phenanthrenecarboxamides.[8] More rapid electron transfer for *E* vs *Z* aminoalkyl groups was attributed to differences in the spatial overlap between the singlet phenanthrene (electron acceptor) and trialkylamine

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†Dedicated to Frederick G. Bordwell in recognition of his achievements as a scientist and in appreciation of an exemplary colleague.

CCC 0894–3230/97/070525–06 $17.50

Table 1. ^{1}H NMR chemical shift data for **1**–**4**[a]

Compound	CH_3 (amide)	α-CH_2	β-CH_2	γ-CH_2	CH_3(amine)
(Z)-**1**	2·83	3·67, 3·78[b]	1·78	1·51	1·05[c]
(E)-**1**	3·25	3·13	1·52	1·10	0·67[c]
Δδ*(ppm)*	−0·42	0·58	0·27	0·41	0·38
(Z)-**2**	2·87	3·62, 4·01[b]	2·72		2·41
(E)-**2**	3·29	3·25	2·37		1·90
Δδ(ppm)	−0·42	0·57	0·35		0·51
(Z)-**3**	2·85	3·71, 3·78[b]	1·99	2·48	2·32
(E)-**3**	3·27	3·20	1·61	1·99	1·98
Δδ(ppm)	−0·42	0·56	0·38	0·49	0·36
(Z)-**4**	3·10	3·77, 4·05[b]	3·36		2·84
(E)-**4**	3·35	3·80	3·31		2·64
Δδ(ppm)	−0·25	0·11	0·05		0·20

[a] Chemical shift in $CDCl_3$ solution vs TMS.
[b] Diasterotopic protons.
[c] Terminal methyl group.

(electron donor) for the *E* vs *Z* conformers. In the course of characterization of these molecules by NMR spectroscopy, it was found that they display both of the phenomena described above. In addition one of the aminoalkyl phenanthrenes was found to crystallize as a single conformer. We report here the results of our investigation of the solution and crystal structures of these molecules which serve to establish the importance of folded conformers in solution as well as in the crystal.

RESULTS

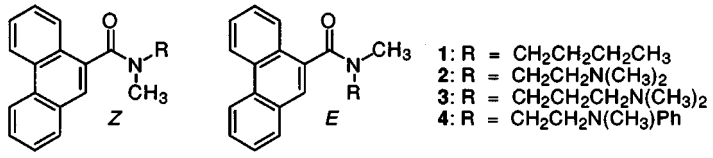
NMR Spectra

The synthesis of *N*-butyl-*N*-methyl-9-phenanthrenecarboxamide (**1**) and the *N*-(aminoalkyl)-9-phenanthrenecarboxamides **2**–**4** have been reported previously.[8] ^{1}H NMR chemical shifts for the alkyl hydrogens of **1**–**4** are reported in Table 1 and data for alkyl and selected aromatic hydrogens of **4** and *N*,*N*-dimethylaniline are reported in Chart. 1. The spectra of **1**–**4** display two sets of resonances attributed to the *Z* and *E* isomers. In each case the upfield amide *N*-methyl resonance and downfield methylene resonance is assigned to the *Z* isomer. These assignments are consistent with published assignments for tertiary benzamides and have been confirmed in the case of **1** by a benzene dilution shift study.[9] The remaining methylene resonances were assigned on the basis of spin decoupling studies. The *Z*/*E* isomer ratios for **1**–**4** can be determined by integration of the amide and amine *N*-methyl singlets. The *Z* isomer contents in $CDCl_3$ solution all are between 50 and 59% (Table 2). These values are independent of temperature (233–293 K) and solvent ($CDCl_3$, C_6D_6 or CD_3CN).

Table 2. Equilibrium isomer content and coalescence temperature

Amide	*Z* isomer (%)	T_c (K)
1	50	295
2	59	322
3	51	297
4	56	303

Large diasterotopic splittings are observed for the α-methylene hydrogens of (*Z*)-**1**–**4** (Table 1). The magnitude of the splitting decreases in the order **2**>**4**>**1**≈**3**. Diasterotopic splitting was not observed for (*E*)**1**–**4** or for either the *E* or *Z* isomer of the 9-anthrenececarboxamide analog of **4**. Coalescence of the diasterotopic α-protons was observed at temperatures ranging from 295 to 322 K (Table 2). No coalescence of the amide or amine *N*-methyl resonances was observed for temperatures as high as 333 K. Large differences in chemical shifts (Δδ, Table 1) are observed for the amide alkyl and aminoalkyl groups of the *Z* vs *E* isomers



Structures 1–4

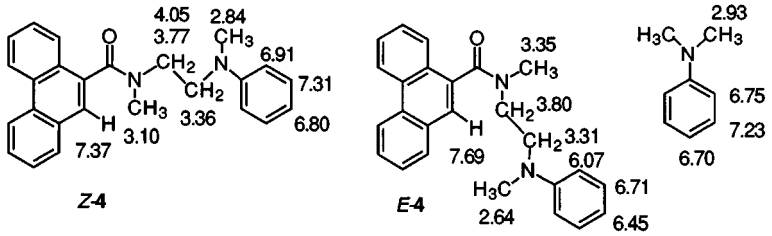


Chart 1

of **1**–**4**. Compared with the *N*-methyl chemical shift of *N*,*N*-dimethylethylamine (δ 2·33 in $CDCl_3$), the amine *N*-methyl resonances of (*Z*)-**2** and **3** are downfield while those of (*E*)-**2** and **3** are shifted upfield. An analogous difference in chemical shift is seen for the terminal methyl of the butyl group in (*Z*)-**1** and (*E*)-**1**. The aniline *N*-methyl chemical shifts for (*Z*)-**4** and (*E*)-**4** are both upfield of that for *N*,*N*-dimethylaniline (δ 2·93 in $CDCl_3$) and have smaller $\Delta\delta$ values than those of **1**–**3**.

Based on the absence of deshielding of H(8) and H(10) by the amide group, the phenanthrene and amide groups of **1**–**4** are most likely orthogonal in solution, as previously observed for *N*,*N*-dimethyl-9-phenanthrenecarboxamide.[10] The H(10) resonance in (*Z*)-**4** (δ 7·37) is substantially upfield from that of unsubstituted phenanthrene (δ 7·82). In comparison with the *N*-phenyl protons of *N*,*N*-dimethylaniline, those of (*Z*)-**4** and (*E*)-**4** are shifted downfield and upfield, respectively (Chart 1).

Crystal structure

The ORTEP drawing of the crystal structure of (*Z*)-**4**, obtained by crystallization of **4** from benzene–diethyl ether mixed solvent, is shown in Figure 1. The crystal is monoclinic and belongs to the space group *Ia*(#9). Repeated attempts to grow crystals from other solvents were either unsuccessful or produced crystals unsuitable for diffraction. The phenanthrene and amide groups of (*Z*)-**4** are planar and nearly orthogonal (86° dihedral angle). The β-methylene is perpendicular to the amide plane and the amide and amine nitrogens are *gauche* (67·4° dihedral angle). The aniline nitrogen geometry is flattened pyramidal with the lone pair directed away from the amide group. The planes of the phenanthrene and aniline are edge-to-face with a dihedral angle of 82° and a 5·24 Å distance between the centroids of the aniline and phenanthrene BC rings. The planes of the amide and aniline groups diverge at an angle of 37° and the closest contact between the aniline plane and the carbonyl carbon is 3·68 Å.

DISCUSSION

The tertiary 9-phenanthrenecarboxamides **1**–**4** all exist as a mixture of *E* and *Z* isomers in solution.[8] The slight preference for the *Z* isomers in the case of **2** and **4** (Table 1) may be a consequence of the slightly greater steric demands

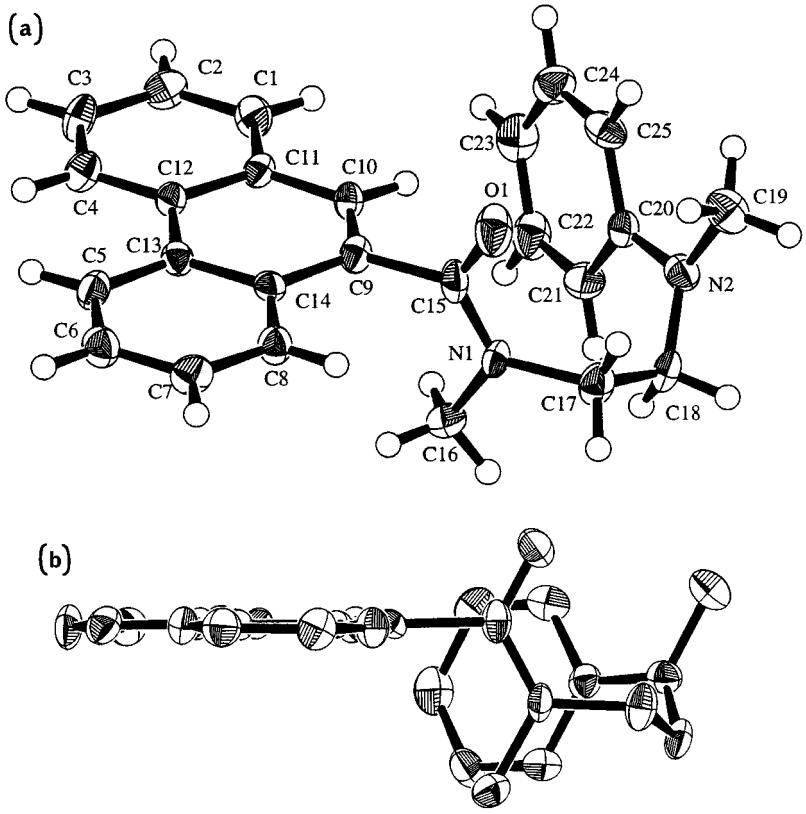


Figure 1. ORTEP drawing of *(Z)*-**4** viewed (a) from above the phenanthrene plane and (b) from the C(7) edge of the phenanthrene plane with hydrogen atoms deleted.

of their β-aminoalkyl groups when compared with the *N*-butyl group of **1** or the γ-aminoalkyl group of **3**. The isomer ratios are independent of temperature and solvent. Crystallization of **4** from benzene–diethyl ether mixed solvent provided a crystal of (*Z*)-**4**. The *E* and *Z* isomers of several tertiary 2,6-disubstituted benzamides have previously been separated by fractional crystallization.[11] These benzamides have barriers for amide C–N rotation (>22 kcal mol^{-1}) which are substantially larger than that for *N*,*N*-dimethylbenzamide (16 kcal mol^{-1}).[1a] The barriers for amide rotation have not been determined for **1**–**4**; however, they are estimated to be ≥ 24 kcal mol^{-1} based both on the failure to observe coalescence of the amide *N*-methyl protons below 333 K and by analogy with an *N*,*N*-dialkyl-1-naphthylenecarboxamide, for which a barrier of this magnitude has been reported.[2b]

We have previously suggested that the Ar—C(O) dihedral angle in tertiary phenanthrene carboxamides is *ca.* 90° on the basis of MM2 calculations and the absence of deshielding of the phenanthrene H(8) or H(10) by the carbonyl group.[8,10] The 86° dihedral angle observed for the crystal of (*Z*)-**4** is consistent with this suggestion. This dihedral angle is significantly larger than the 45° reported for *N*,*N*-dimethyl-*p*-bromobenzamide.[12] The potential energy surface for twisting about the Ar—C(O) bond is shallow between 45° and 135° and thus could be determined by crystal packing forces in the solid state.[10b] However, the larger dihedral angle and larger rotational barrier for phenanthrenecarboxamides vs benzamides are consistent with the greater steric demand of the phenanthrene.

In the crystal structure of (*Z*)-**4** the amide group is planar and the β-methylene is perpendicular to the amide plane, as is generally the case for both secondary and tertiary amides.[3,4] The most interesting feature of the structure of (*Z*)-**4** is the folding of the aniline over the less hindered face of the amide, toward phenanthrene H(10). This results in a *gauche* interaction between the amide and amine nitrogens and an edge-to-face interaction between the phenanthrene and aniline rings. A preference for *gauche* conformations has been observed for second-row electronegative elements ('*gauche* effect'),[13] but we are unaware of evidence for such an effect involving amine and amide nitrogens. Transannular interactions have been observed between tertiary amines and ketone carbonyl groups in medium-sized rings and attributed to bonding between nitrogen and carbonyl carbon.[14] Such interactions have not been observed for acyclic aminoalkyl ketones and there is no close contact between amine nitrogen and carbonyl carbon in the crystal structure of (*Z*)-**4** (Figure 1). The observation of charge-transfer absorption spectra for *N*-(anilinoalkyl)phthalmides has been attributed to a ground-state interaction between the aniline donor and phthalimide acceptor.[15] It is possible that a weak intramolecular charge-transfer interaction may help stabilize the folded conformation of (*Z*)-**4**. No charge-transfer absorption is observed for (*Z*)-**4**; however, charge-transfer fluorescence is observed for (*Z*)-**4** but not for (*E*)-**4**.[8b]

The edge-to-face phenanthrene–aniline interaction may also help stabilize the folded conformation of (*Z*)-**4**. The centroid–centroid distance for the aniline and phenanthrene BC rings is 5·24 Å, similar to the distance for arenes which have edge-to-face or herringbone crystal packing motifs[16] as well as the calculated distance for the benzene dimer in the vapor phase.[17] The 82° dihedral angle for the aniline and phenanthrene planes is also typical of edge-to-face arenes. The upfield shift of phenanthrene H(10) and downfield shifts of the aniline protons in the solution NMR spectrum of (*Z*)-**4** (Chart 1) suggest that the folded conformation is populated in solution. MM2 calculations for (*Z*)-**2** and (*E*)-**2** indicate that the *gauche* conformations for the C_α—C_β bond are *ca* 1 kcal mol^{-} less stable than the *anti* conformations, which are the calculated gas-phase global minima.[8b] We expect that both the *E* and *Z* isomers of **1**–**4** exist as mixtures of *gauche* and *anti* C_α—C_β rotamers in solution. However, it is possible that the edge-to-face arene–arene interaction in (*Z*)-**4** results in an enhanced population of folded conformations. Even if a folded conformation is not the solution minimum for (*Z*)-**4**, it is not uncommon for conformationally mobile molecules to crystallize in higher energy folded conformations. In fact, there have been several reports of molecules which have random conformations in solution but folded conformations with edge-to-face[18] or face-to-face[19] arene–arene interactions in the solid state.

The solulution NMR spectra of the *Z* isomers of **1**–**4** have non-equivalent geminal α-methylene protons. Simlar results have been reported for several *ortho*-substituted tertiary benzamides.[2,5,6] The presence of perpendicular dissymmetric planes in these molecules renders them chiral on the NMR time-scale and hence the geminal protons are diasterotopic. Heating of **1**–**4** results in coalescence of the α-methylene protons (Table 2), but not the amide or amine *N*-methyl. Thus coalescence must result from rotation about the Ar—C(O) bond. The estimated barrier heights are 18–19 kcal mol^{-1} for **1**–**4** (calculated from the coalescence temperature and chemical shifts using the method of Oki[20]). A large barrier alone is not sufficient for the observation of diasterotopic splitting. Thus splitting is not observed for the α-methylene protons of (aminoalkyl)-9-anthrenecarboxamide analogs of **4**, which presumably have a higher barrier for Ar—C(O) rotation than **1**–**4** but do not possess perpendicular dissymmetric planes.

Diasterotopic splitting is not observed for the *E* isomers of **1**–**4**. Lewin and Frucht[6] previously observed much larger splitting for the *Z* vs *E* α-methylene protons of *ortho*-substituted *N*,*N*-dibenzylbenzamides. This difference, like the large difference in chemical shifts for *Z* vs *E* amide methyl or methylene protons, probably reflects the highly anisotropic electrostatic potential in the vicinity of the amide nitrogen.[21] As seen in Figure 1(a), the two α-methylene protons of (*Z*)-**4** are pseudo-axial and pseudo-equatorial in the folded conformation and thus should have very different electronic environments. Rotation about the amide N–C_α bond would average the

environment of these protons; however, the aminoalkyl group may prefer to occupy the face of the amide toward phenanthrene H(10) vs H(8) for steric reasons. The difference in diasterotopic splitting for the *Z* isomers of **1**–**4** (Table 1) may also reflect differences in the conformer populations for the different alkyl or aminoalkyl groups. The difference in electronic environment should be much smaller for the α-methylene protons of the *E* vs *Z* isomers since neither proton is oriented toward the amide oxygen.

A second unusual feature of the solution NMR spectra of **1**–**4** is the large difference in chemical shift for the *Z* vs *E* aminoalkyl protons on carbons remote from the amide nitrogen (Table 1). A similar difference was observed by Budzikiewicz *et al.*[7] for the terminal methyl groups of *N*-methyl-*N*-alkylbenzamides and aminomethyl groups of *N*-methyl-*N*-(dimethylaminoalkyl)benzamides; however, no such effect was observed for the corresponding acetamides. They found that the $\Delta\delta$ value decreased from 0·20 to 0·08 ppm for the terminal methyls of an *N*-butyl and an *N*-hexyl group and from 0·28 to 0·06 for the amine methyls of a dimethylaminoethyl and a dimethylaminopentyl group. They did not report data for the intervening methylene protons; however, the data in Table 1 establish that large $\Delta\delta$ values are observed for the entire butyl group in **1** and aminoalkyl groups in **2**–**4**.

The large $\Delta\delta$ values observed of the amide *N*-methyl and α-methylene protons of both alkyl and aryl tertiary carboxamides can be attributed to the effects of the highly anisotropic electrostatic potential in the victinity of the amide nitrogen.[21] However, it seems highly unlikely that this effect could be transmitted to protons many atoms removed from the amide nitrogen. Since large $\Delta\delta$ values are observed for aryl- but not alkylcarboxamides, it seems likely that this effect is a consequence of the anisotropy of the aromatic ring rather than the amide group. Comparison of the proton chemical shifts for the *E* and *Z* isomers of **1**–**4** with those of the model compounds butane, *N*,*N*-dimethylethylamine and *N*,*N*-dimethylaniline (Chart 1) indicate that the protons of *Z* alkyl or aminoalkyl groups are shifted downfield and those of the *E* groups are shifted upfield. This is consistent with the population of folded conformations in which the alkyl or aminoalkyl groups in the *Z* and *E* isomers are located, respectively, near the edge (deshielding region) and the face (shielding region) of the phenanthrene. The larger $\Delta\delta$ values for the phenanthrenecarboxamides vs benzamides may simply result from the larger Ar—C(O) dihedral angle or the larger size of the former arene.

In summary, we find that the tertiary 9-phenanthrenecarboxamide **4** crystallizes as the *Z* isomer in which the *N*-aminoalkyl substituent is folded over the face of the amide group and the phenanthrene and aniline rings adopt an edge-to-face geometry. In solution **1**–**4** exist as mixtures of *E* and *Z* isomers. Folded conformations of their *N*-alkyl or *N*-aminoalkyl substituents can account for the large differences in chemical shift for the *Z* vs *E* isomers. Large barriers for rotation about the Ar—C(O) bond render these molecules chiral on the NMR time-scale, resulting in diastereotopic splitting of the α-methylene protons of the *Z* isomers. Further studies of the structure and photochemical behaviour of *N*-aminoalkylamides are in progress.

EXPERIMENTAL

The synthesis of **1**–**4** has been described previously.[8b] ^{1}H NMR spectra were recorded using a Varian Gemini 300 or Varian XLA 400 spectrometer with TMS as an internal standard. Data for the x-ray structure was recorded using an Enraf-Nonius CAD4 diffractometer with graphite monomchormated Mo Kα radiation ($\lambda = 0{\cdot}71069$ Å) at 153 ± 1 K.

SUPPLEMENTARY MATERIAL

Tables of bond distances, angles, fractional atom coordinates and anisotropic thermal parameters for (*Z*)-**4** (12 pages) are available from the author on request.

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