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Conformational isomers in the photocyclodimerization of *N*-acylated dibenz[b,f]azepine derivatives

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Abstract

The benzophenone-sensitised photodimerizations of *N*-acetyl- and *N*-propionyldibenz[e,f]azepine were investigated in acetone as the solvent. In both the systems, the ^{1}H NMR analysis of the products revealed two isomeric photodimers differing in the chemical shifts and coupling constants of the cyclobutane protons, aromatic protons and the protons of the acetyl or propionyl group. Upon raising the temperature to ca. 70 °C the signals merge. The findings can be ascribed to a single thermally restricted conformational process such as the rotation about the C–N amide bond. The process exhibits free activation energies: $\Delta G^{\#} = (74 \pm 2)\,\mathrm{kJ\,mol^{-1}}$ (*N*-acetyl) and $\Delta G^{\#} = (70 \pm 2)\,\mathrm{kJ\,mol^{-1}}$ (*N*-propionyl).

Keywords: Conformational isomers; Photodimerizations; *N*-Acylated dibenz[b,f]azepine

1. Introduction

The photochemical dimerization of unsaturated organic molecules is a well-known process in organic photochemistry [1]. In stilbene and stilbene derivatives, this type of photoreaction prevails if the central stilbene double bond is fixed in a ring system. In this case, the two competing photoreactions *cis–trans* isomerization and dihydrophenanthrene formation cannot take place.

It is well known [2] that a number of *N*-acyl derivatives of iminostilbene (dibenz[b,f]azepine) photochemically react in the presence of a triplet sensitizer such as benzophenone via the excited triplet state of the dibenz[b,f]azepine to form cyclobutane derivatives **2** as shown in Fig. 1. The pharmaceutically active "carbamazepine" (**1**, R = NH_2), a drug used in the therapy of epilepsy [3], is among the compounds investigated. Direct irradiation of **1** does not lead to photodimers. In this respect, the dibenz[b,f]azepines do not behave like stilbenes, which form dimers from the singlet excited state [4].

Kricka et al. [2,5] found only one type of dimer in their experiments and were led to the assumption that the more stable *anti*-configuration of the cyclodimers **2** was formed exclusively. According to crystal investigations by Harding [6], the photodimer **2a** in an anhydrous crystal exhibits an *anti*-configuration at the cyclobutane ring. Taga et al. [7] reported the same result a few years later for the hydrated crystals of **2a**. A dimer with a *syn*-configuration at the central cyclobutane ring has not been reported in the literature and there are no indications published for the presence of further isomers in this cyclodimerization reaction: in 1984, Robson and Sharples [8] published NMR data showing a singlet signal at $\delta = 4.0$ ppm for the cyclobutyl protons (indicating a single isomer) in accord with the findings of Ashikaga et al. [9,10] in 1987 and Alimoglu et al. [11] in 1992.

In this paper, we present NMR spectroscopic data of the photodimers **2a** and **2b**, which clearly prove the presence of two isomers in solution after photodimerization.

2. Results

Upon benzophenone-sensitised irradiation of **1a** and **1b** in acetone solution, the dimers **2a** and **2b** were formed as crystalline precipitates. The ^{1}H NMR spectrum of the photoproduct **2a** is shown in Fig. 2. It exhibits three characteristic absorption ranges: the CH_3 groups at $\delta = 2.39$ ppm, the cyclobutyl protons (H-10, H-10′, H-11, H-11′) at $\delta = 3.89$–4.11 ppm and the aromatic protons (H-1–H-4, H-1′–H-4′, H-6–H-9, and H-6′–H-9′) at $\delta = 6.85$–7.47 ppm. The fact that all signals are doubled in the spectrum suggests the existence of two non-equivalent isomers I and II in the solution with a product ratio of 2:3 as determined by

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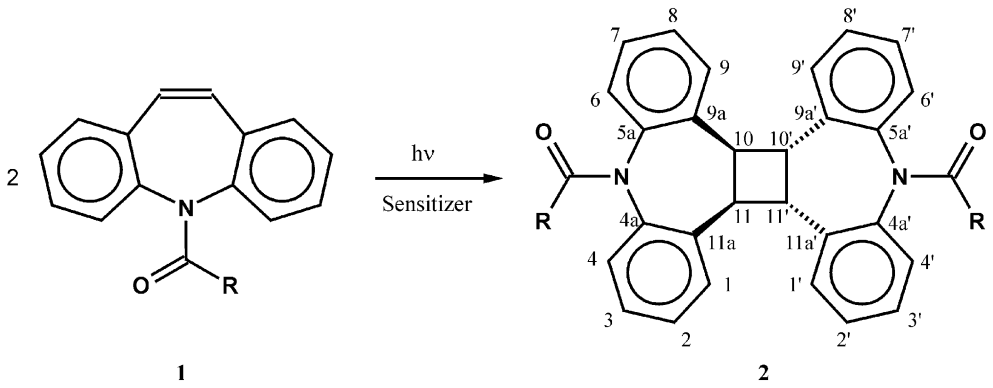

Fig. 1. Photochemical dimerization of *N*-acyl dibenz[b,f]azepines with R = CH_3 (**a**), C_2H_5 (**b**).

evaluating the corresponding integrals. This ratio was independent of the irradiated compound as well as the degree of photoconversion (20–50%), i.e. of the irradiation time, which was varied between 4 and 12 h. In Fig. 3, cuts of NMR spectra showing the sections of the cyclobutyl protons in **2a** and **2b** are shown. The four cyclobutyl protons generally appear as two AA′BB′ spin systems: In **2a** one is formed by the symmetrical pattern centered at $\delta = 3.91$ and 4.09 ppm and the other one by the symmetric pattern at $\delta = 3.99$ and 4.01 ppm. Both of the spectra may be completely analyzed, using the standard rules for this spin system. At least three couplings between the four protons are expected. The analysis was carried out using the program WINDAISY and provides values for the coupling constants $^3J_{HH}$ and $^4J_{HH}$ of the four cyclobutane protons. In Tables 1 and 2 and in Fig. 4, the results of simulations are shown.

Table 1
Chemical shifts δ (ppm) of **2a** from simulation for isomers I and II

Isomer	δ_{H10}	$\delta_{H\text{-}10'}$	$\delta_{H\text{-}11}$	$\delta_{H\text{-}11'}$
I	3.98	3.98	4.02	4.02
II	3.91	4.09	4.09	3.91

Table 2
Coupling constants J (Hz) of **2a** from simulation for isomers I and II

Isomer	$^3J_{10,10'}$	$^3J_{11,11'}$	$^3J_{10,11}$	$^3J_{10',11'}$	$^4J_{10',11}$	$^4J_{10,11'}$
I	7.4	7.4	11.1	11.1	−1.3	−1.3
II	11.2	11.2	7.4	7.4	−1.2	−1.2

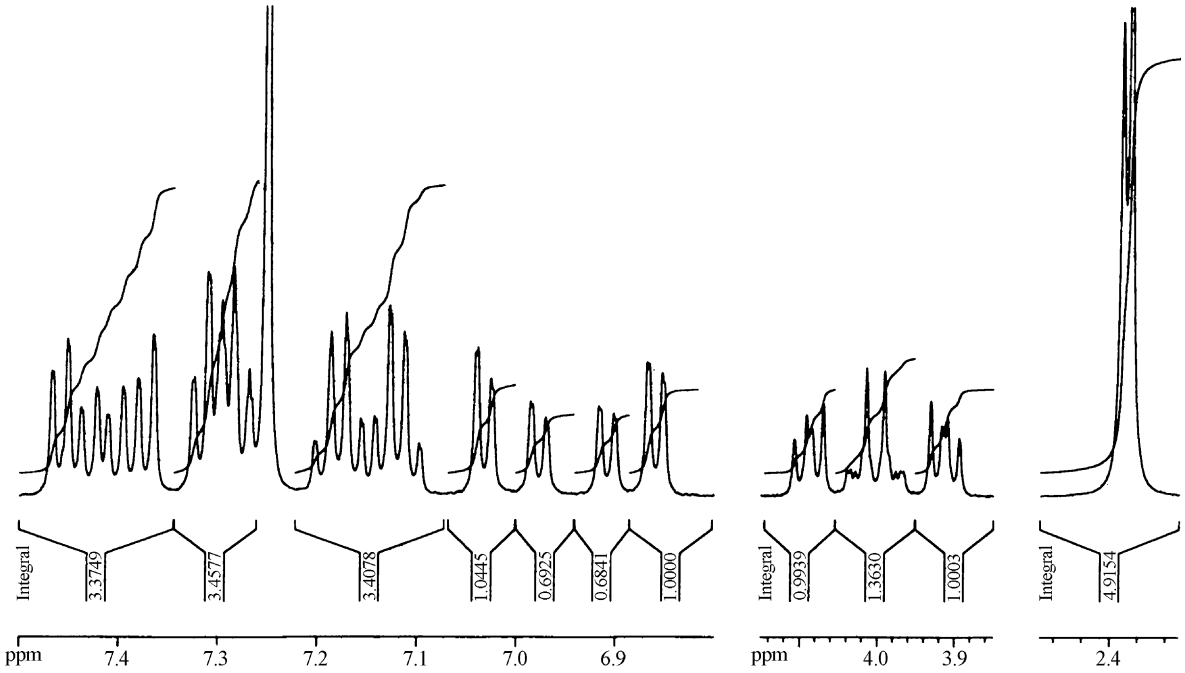

Fig. 2. ^{1}H NMR spectrum of **2a** in $CDCl_3$.

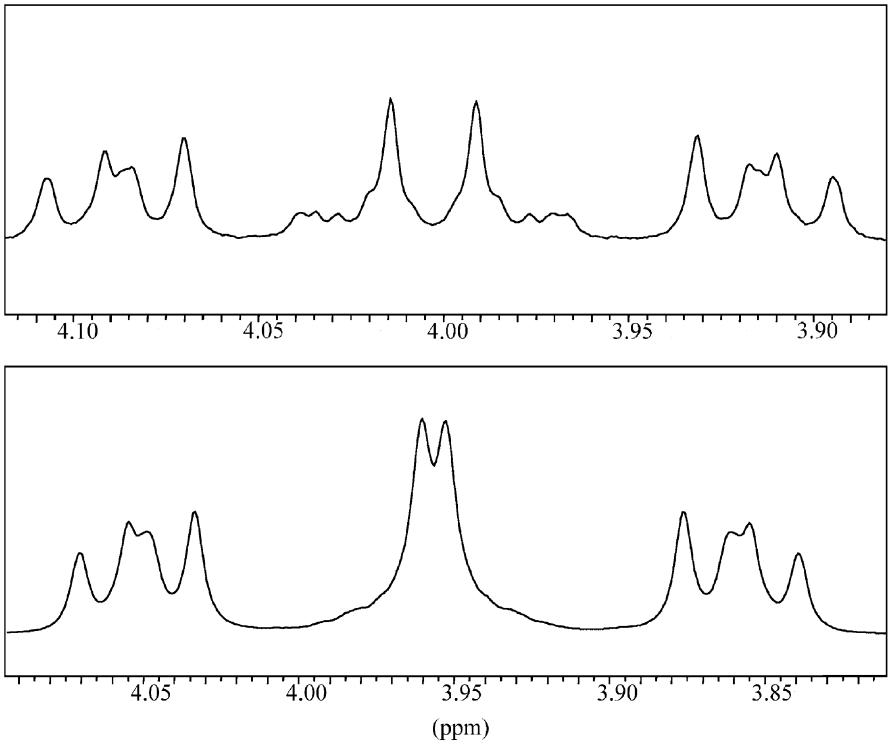

Fig. 3. Cut of the ^{1}H NMR spectrum of **2a** (top) and **2b** (bottom) in $CDCl_3$ showing the cyclobutane region.

In fact, two independent AA′BB′ spin systems were obtained from the simulation which perfectly agree with the two spin systems in the experimental spectrum (Fig. 4). The differences in the coupling constants of the cyclobutyl protons between the isomers I and II reflect different geometries of these two isomers.

To find out the origin of the presence of two isomers, further NMR experiments were carried out. NMR spectra of **2a** in toluene solution measured at different temperatures reveal an elucidating temperature dependence, as shown in Fig. 5: the two AA′BB′ spin systems of the cyclobutyl signals observed at room temperature (Fig. 3) merge at a coalescence temperature of about $T_c = 75\,^{\circ}\mathrm{C}$ (348 K). Above this temperature, an A_4 spin system appears in the spectrum exhibiting a singlet at $\delta = 3.95$ ppm. An analogous effect is shown for the aromatic protons at ca. $T_c = 70\,^{\circ}\mathrm{C}$ (343 K). They take the shape of a spectrum of an *ortho*-substituted aromatic compound consisting of two doublets and two triplets. The doublet assigned to the methyl group changes to one singlet at ca. $T_c = 60\,^{\circ}\mathrm{C}$ (333 K) with a chemical shift of $\delta = 2.19$ ppm. The experimental values for the coalescence processes could be analyzed using a modified Eyring equation, cf. [12]

$$\Delta G^{\#} = RT_c\left(22.96 + \ln\left(\frac{T_c\,\mathrm{Hz}}{\Delta\delta\,\mathrm{K}}\right)\right)$$

to obtain values for the free energy of activation $\Delta G^{\#}$. The three slightly different coalescence temperatures observed lead to a common mean value for the free energy of activation of $\Delta G^{\#} = (74 \pm 2)\,\mathrm{kJ\,mol^{-1}}$ for the coalescence in the different spectral regions, indicating a single motional process. The NMR spectra of compound **2b** showed temperature dependence similar to that of **2a**. The free energy of activation for the process in **2b** was determined to be $\Delta G^{\#} = (70 \pm 2)\,\mathrm{kJ\,mol^{-1}}$.

3. Discussion

The presence of *syn*- and *anti*-configurated isomers in the irradiated solution is ruled out by the observation that a singlet NMR signal is found for the cyclobutane protons above the coalescence temperature. On the basis of previously published results [6,7], we have to assume that both the isomers I and II are *anti*-dimers. Further, the fact that the product ratio is independent of the irradiation time excludes secondary photolysis (or secondary sensitization) as the origin of the second product.

We may rationalize our observation in that we consider a thermally restricted conformational change for these compounds. According to previous studies [13–15] on 10,11-dihydrodibenz[b,f]azepines (i.e. substituted derivatives of **1** with the double bond saturated), three conformational processes must be discussed: (i) rotation about the C–N amide bond; (ii) inversion of the seven membered azepine ring; and (iii) twisting of the bond between the C-atoms 10 and 11. The last process (for an illustration see [15]) is unlikely in our systems, since the bond is incorporated in the cyclobutane ring.

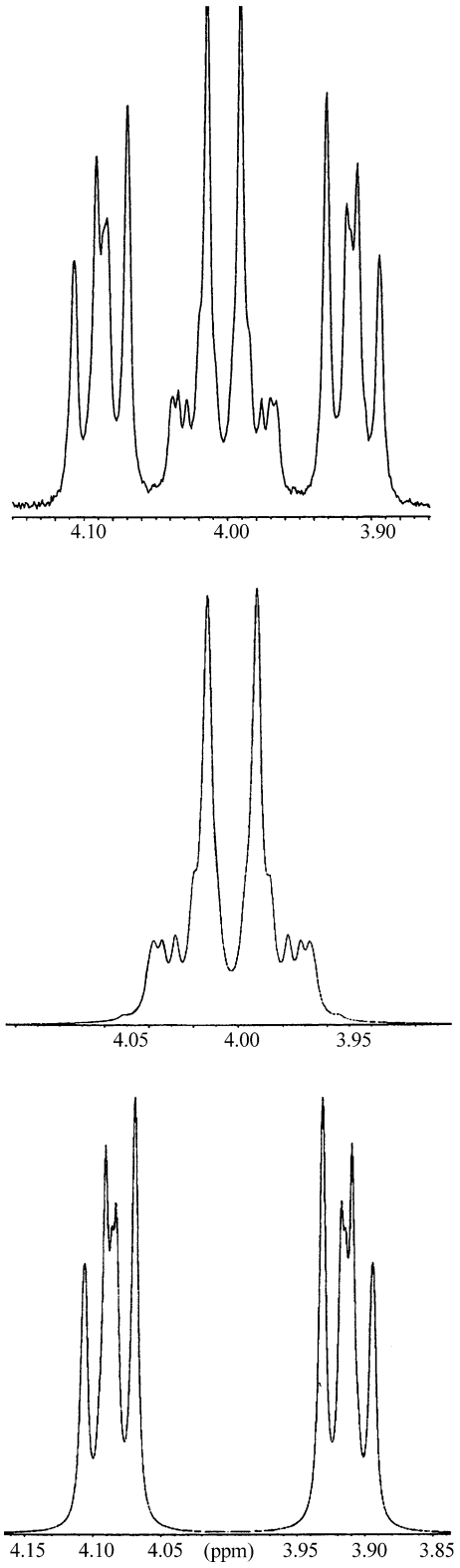

Fig. 4. Spectra of **2a** measured (top) and simulated (isomers I and II; bottom).

As to (i), the free rotation about the amide C–N amide bond is hindered due to its partial double bond character. Thus two conformational isomers might exist at room temperature as shown in Fig. 6. Simple molecular modeling shows that the conformation of the seven membered ring results in a spatial vicinity of the substituent R of one azepine amide moiety and the cyclobutyl protons belonging the other seven membered ring. This might explain the significant influence which the conformation of the amide group has on the chemical shift of the cyclobutyl protons.

Taking these facts into account one is tempted to assign the *Z* form to isomer I in Table 1 and the *E* form to isomer II on the basis of the following consideration: in the *Z* isomer (cf. Fig. 1) the protons 10 and 10′ as well as 11 and 11′ are equivalent; in the *E* isomer the protons 10 and 11′ as well as 10′ and 11 show chemical equivalence. Coupling therefore occurs between vicinal protons in the *trans*-configuration ($^3J_{10,10'}$ and $^3J_{11,11'}$, respectively) in the *E* isomer, while the coupling vincinal protons in the *Z* isomer exhibit *cis*-configuration ($^3J_{10,11}$ and $^3J_{10',11'}$, respectively). According to the Karplus–Conroy relationship [12], the latter (*cis*-configurated) protons should exhibit the larger coupling constants as found in our systems. The observed difference in coupling constants (3.8 Hz, see Table 1), however, is too small for an unequivocal assignment, since the cyclobutane systems may be quite flexible [12].

The inversion of the seven membered azepine ring (case (ii), cf. Fig. 7) constitutes another motion, which in our systems might be hindered due to steric interactions between the alkyl substituents of the planar amide group and the aromatic protons at the 4- and 6- or 4′- and 6′-positions. Upon inversion the cyclobutyl protons may assume non-equivalent equatorial (e) or axial (a) positions with respect to the azepine ring. For the resulting coupling constants, we can expect the following order: $^3J_{aa} > {}^3J_{ae} \approx {}^3J_{ee}$.

Abraham et al. [13,14] as well as Ellefson et al. [15] reported on NMR investigations of other (related but distinct) seven membered azepine systems, i.e. *N*-acetyl-10-cyano-10,11-dihydro-2H-dibenz[b,f]azepine and further N-substituted dihydrobenzazepines. While Ellefson et al. discussed their results widely in terms of hindered ring inversion and twisting of the C-10–C-11 ethene bridge, Abraham et al. proposed that both ring inversion and amide bond rotation freeze in a concerted process. The latter seems reasonable, since the ring inversion can be fast only if the amide substituents arrange perpendicular to the mean ring plane, i.e. if rotation about the C–N bond is allowed.

In our systems, however, we had to expect more than two isomers if both, amide and ring conformers, were formed. Since we find two isomers only, we have to assume either that one of the possible motional processes is equilibrated at room temperature or that only one sort of ring conformer is capable of photodimerization. In keeping with the assumption of only one conformational process is the fact that a common value for the free energy of activation is determined for the process in all regions of the NMR spectrum.

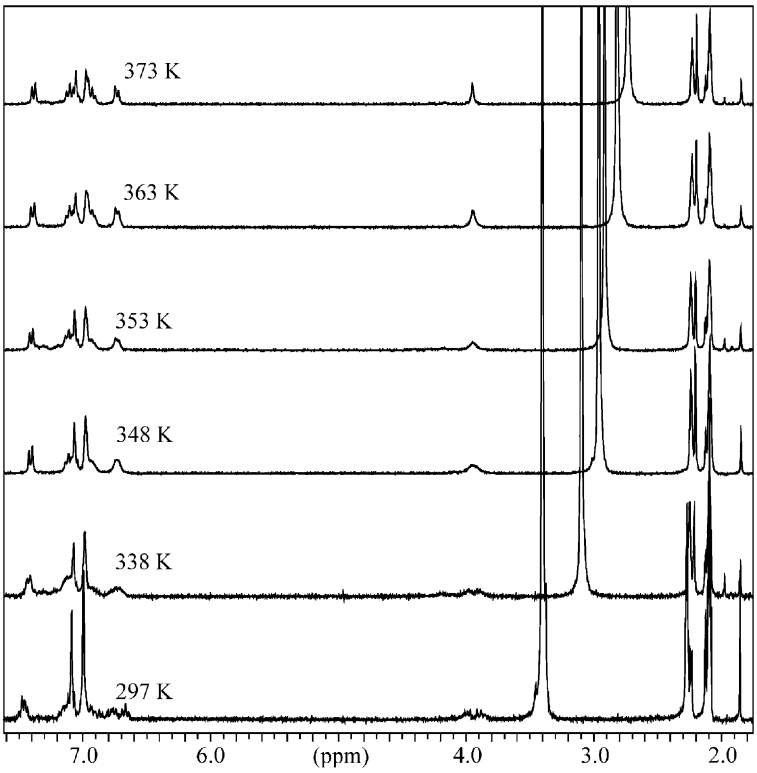

Fig. 5. ^{1}H NMR spectra of **2a** as a function of temperature.

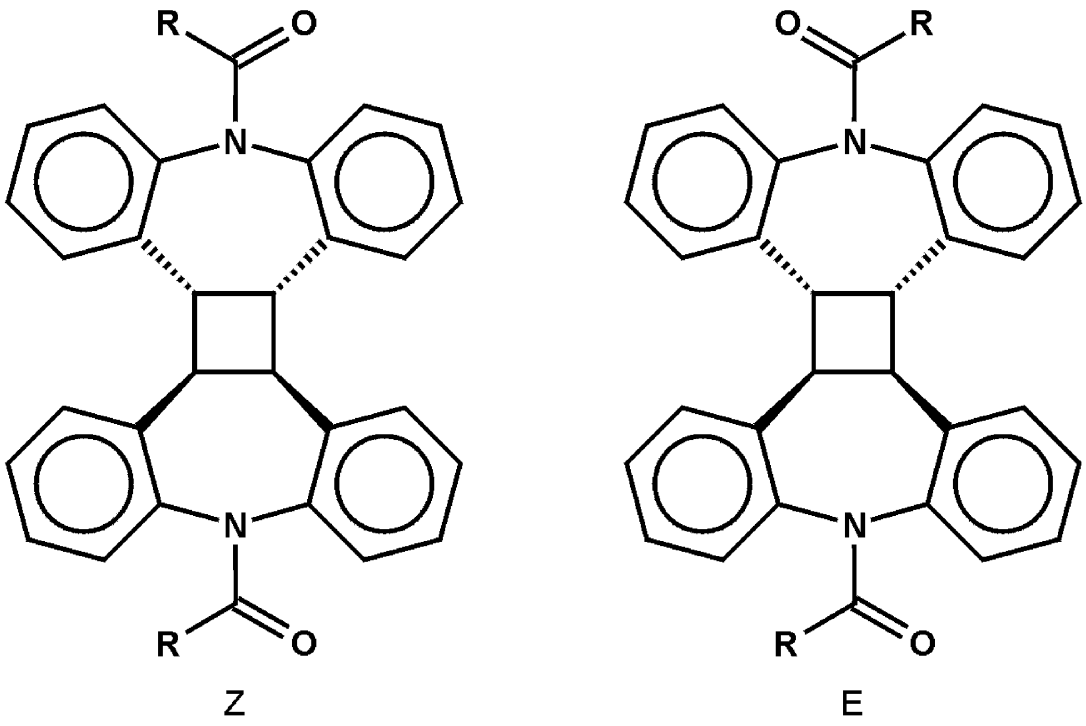

Fig. 6. Isomers of **2**.

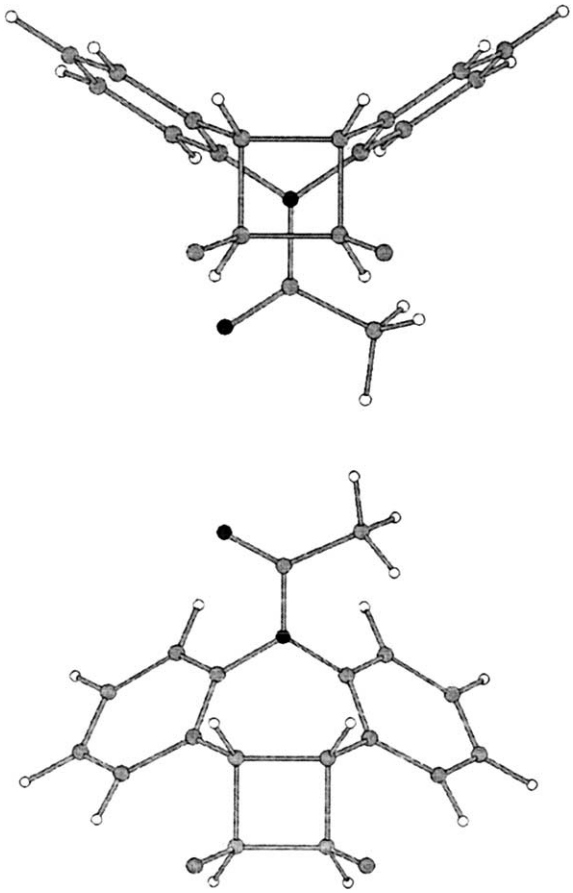

Fig. 7. Illustration of the inversion of the seven-membered ring, case (ii).

The obtained values of $\Delta G^{\#}$ (ca. 72 kJ mol^{-1}) are in the order of what can be expected for the rotation of amide bonds [12]. This rotation, therefore, is the most likely cause of the appearance of two isomers such as represented in Fig. 6.

4. Conclusion and outlook

Two isomeric photodimers of *N*-acetyl- and of *N*-propionyl-dibenz[b,f]azepine are formed upon benzophenone-sensitized photodimerization. Their existence can be ascribed to thermally restricted conformational changes in these compounds, probably the constrained rotation about the C–N amide bond. Future work will concentrate on investigating dibenz[b,f]azepines bearing larger substituents R, which may allow the separation and isolation of the conformers due to higher barriers.

5. Experimental

5-Acetyldibenz[b,f]azepine (**1a**) and 5-propionyldibenz-[b,f]azepine (**1b**) were prepared via a literature procedure [6] from iminostilbene (Aldrich) and acetylchloride or propionylchloride (from stocks of the TU Dresden), respectively, and showed the physical and spectroscopic properties reported there. Benzophenone was recrystallized three times from an ethanol solution. Acetone and toluene were purchased from Baker in UV spectroscopic quality and used without further purification.

Photodimer **2a**: a stirred solution of 0.85 g (3.6 mmol) of 5-acetyldibenz[b,f]azepine (**1a**) and 0.73 g (4 mmol) of benzophenone in 100 ml acetone was irradiated for 5 h at 20 °C under an argon atmosphere through the gas–liquid interface. A high pressure mercury lamp (OSRAM HBO 100 W) with a cut-off filter ($\lambda > 335$ nm) was used. The filter assured that the sensitizer was excited exclusively. The product **2a** precipitated after ca. 4 h from the solution as a white crystalline substance. The solid was filtered off and washed several times with water and acetone. Drying in vacuo gave a white powder. Yield: 0.31 g (36%); m.p. 341–343 °C (Ref. [5]: 342–345 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.47$–7.36 (4d, $^3J = 7.7$ Hz, 4H, Ar-H), 7.32–7.26 (m, 4H, Ar-H), 7.20–7.09 (m, 4H, Ar-H), 7.04 (d, $^3J = 7.5$ Hz, 1H, Ar-H), 6.97 (d, $^3J = 7.5$ Hz, 1H, Ar-H), 6.91 (d, $^3J = 7.5$ Hz, 1H, Ar-H), 6.85 (d, $^3J = 7.5$ Hz, 1H, Ar-H), 4.10–3.89 (m, 2 AA′BB′-spin system, 4H, cyclobutan-H), 2.39–2.38 (2s, 6H, $-CH_3$). ^{13}C NMR ($CDCl_3$, 126 MHz): $\delta = 170.5$, 170.3 (C-12, C-12′), 141.8, 141.5, 140.7, 140.4 (C-4a, C-4a′, C-5a, C-5a′), 138.2, 138.1, 137.5, 137.4 (C-9a, C-9a′, C-11a, C-11a′), 131.9, 131.5, 131.2, 130.7, 128.9, 128.7, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9 (Ar-C), 48.5, 48.4, 48.3, 48.2 (C-10, C-10′, C-11, C-11′), 22.7, 22.9 (C-13, C-13′). MS (ESI), *m*/*z* (%B): 471.3 (100) [$(M + H)^+$], 295.2 (9) [$(M + H)^+ - 176.2$], 236.1 (9) [$(M + H)^+ - 235.3$].

Photodimer **2b**: a stirred solution of 0.99 g (4 mmol) 5-propionyldibenz[b,f]azepine (**1b**) and 0.73 g (4 mmol) of benzophenone in 100 ml acetone was irradiated for 6 h at 20 °C under an argon atmosphere through the gas–liquid interface. A 100 W high pressure mercury lamp (OSRAM HBO) was used. A cut-off filter transparent at $\lambda > 335$ nm ensured selective irradiation of the sensitizer. After 4.5 h, the product **2b** started to precipitate from the solution as a white crystalline substance. The solid was filtered off and was washed several times with water and acetone. Drying in vacuo gave a white powder. Yield: 0.29 g (29%); m.p. 324–326 °C (Ref. [5]: 323–325 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.44$ (2d, 2H, Ar-H), 7.37 (2d, 2H, Ar-H), 7.31–7.24 (m, 4H, Ar-H), 7.19–7.10 (m, 4H, Ar-H), 7.04 (d, $^3J = 7.4$ Hz, 1H, Ar-H), 6.97 (d, $^3J = 7.4$ Hz, 1H, Ar-H), 6.89 (d, $^3J = 7.4$ Hz, 1H, Ar-H), 6.84 (d, $^3J = 7.4$ Hz, 1H, Ar-H), 4.08–3.85 (m, 2 AA′BB′-spin system, 4H, cyclobutan-H), 2.76–2.68 (dq, $^3J = 7.3$ Hz, 2H, NCO–C$H_{\alpha 1}$–H$_{\alpha 2}$), 2.56–2.48 (dq, $^3J = 7.3$ Hz, 2H, NCO–CH$_{\alpha 1}$–$H_{\alpha 2}$), 1.35 (t, $^3J = 7.3$ Hz, 6H, $-CH_3$). ^{13}C NMR ($CDCl_3$, 126 MHz): $\delta = 173.8$, 173.6 (C-12, C-12′), 141.5, 141.1, 140.9, 140.5 (C-4a, C-4a′, C-5a, C-5a′), 138.2, 137.5, 137.5 (C-9a, C-9a′, C-11a, C-11a′), 132.0, 131.4, 131.2, 130.6, 129.0, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8 (Ar-C), 48.3, 48.2, 48.2, 48.1 (C-10, C-10′, C-11, C-11′), 27.7, 27.6 (C-13,

C-13′), 9.8 (C-14, C-14′). MS: ESI, *m*/*z* (%B): 557.2 (7) [$(M + H)^+ + 57.9$], 499.3 (100) [$(M + H)^+$], 250.2 (6) [$(M + H)^+ - 249.1$].

Analysis: ^{1}H NMR spectra of samples dissolved in d-chloroform were run at 500 MHz on a Bruker spectrometer (model DRX 500). For the temperature variation experiments on a Bruker spectrometer (model ACP 300) at 300 MHz, the photodimers were dissolved in a mixture of d_8-toluene and d_6-DMSO (9:1 ratio). For spectrum analysis and simulation the WINDAISY program (Bruker) was used.

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