JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 11, 411–418 (1998)

NMR and semi-empirical study of the tautomerism of 2,2′-bisbenzimidazolyl

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Received 16 April 1997; revised 25 August 1997; accepted 15 September 1997

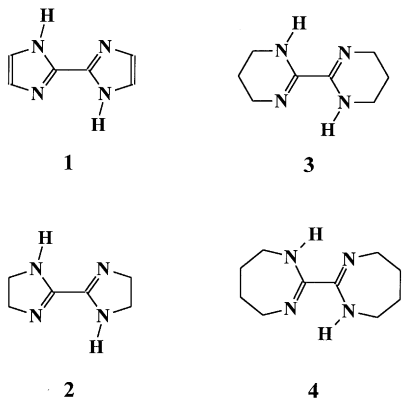
ABSTRACT: A dynamic NMR study of the tautomerism of 2,2′-bisbenzimidazolyl in DMSO-d_6 and a mechanistic interpretation of the process, based on a stepwise, single-proton transfer and formation of a zwitterionic intermediate, are presented. This interpretation is substantiated by semi-empirical calculations of the postulated intermediate and transition state, that yield results which are compared with previous studies on related aliphatic systems. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: 2,2′-bisbenzimidazolyl; tautomerism; NMR; semi-empirical calculations

INTRODUCTION

The tautomerism of nitrogen-containing heterocycles via proton transfer has been the subject of a variety of publications. Investigated systems include porphyrins,[1] azophenine[2] and oxalamidines.[3–5] From kinetic isotope effects and dynamic NMR studies a common mechanism for the interconversion of these tautomeric species has emerged, based on a stepwise, single-proton transfer with formation of zwitterionic intermediates. The rate of these processes depends to some extent on the solvent, but mainly on the structure of the nitrogen-containing heterocycle. Thus, for the series of oxalamidines bisimidazolyl (**1**), 2,2′-bis(4,5-dihydro-1,3-diazole) (**2**), 2,2′-bis(3,4,5,6-tetrahydro-1,3-diazine) (**3**) and 2,2′-bis(4,5,6,7-tetrahydro-1,3-diazepine) (**4**) only for the latter compound was an intramolecular double proton transfer detected at *ca* 350 K. By contrast, **2**, for example, did not exhibit any tautomerism arising from an intra- or intermolecular proton-transfer processes in the temperature range 280 – 410 K.[5] This difference in behaviour was rationalized by the influence of heavy-atom reorganization processes during the single-proton shift, which contributed to varying extents to the energy barriers of tautomerism for each substrate.

In this paper we present a dynamic NMR study of the tautomerism of 2,2′-bisbenzimidazolyl (**5**) in DMSO-d_6. The choice of this system was motivated by the hope that, in contrast to the bisimidazolyl **1**, compound **5** might prove a more convenient substrate for tautomeric studies. We hoped that the greater acidity of the protons-in-flight in **5** might compensate for the large, unfavourable energetic barrier due to the heavy-atom reorganization involved in the tautomeric process. Our results are rationalized theoretically by a semi-empirical study of the postulated intermediate and transition state, employing the PM3 hamiltonian. We therefore test the hypothesis of a stepwise, single-proton transfer as a probable mechanism for the tautomerism of **5**, in agreement with all previous reports on related oxalamidines. In addition, although our theoretical calculations lead to values of energy barriers which differ substantially from the experimental results, an observation which was also true for systems **1**–**4**,[4] they allow a direct comparison of **5**



Scheme 1.

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E-mail address: czucco@cfm.ufsc.br
Contract/grant sponsor: CAPES.
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CCC 0894–3230/98/060411–08 $17.50

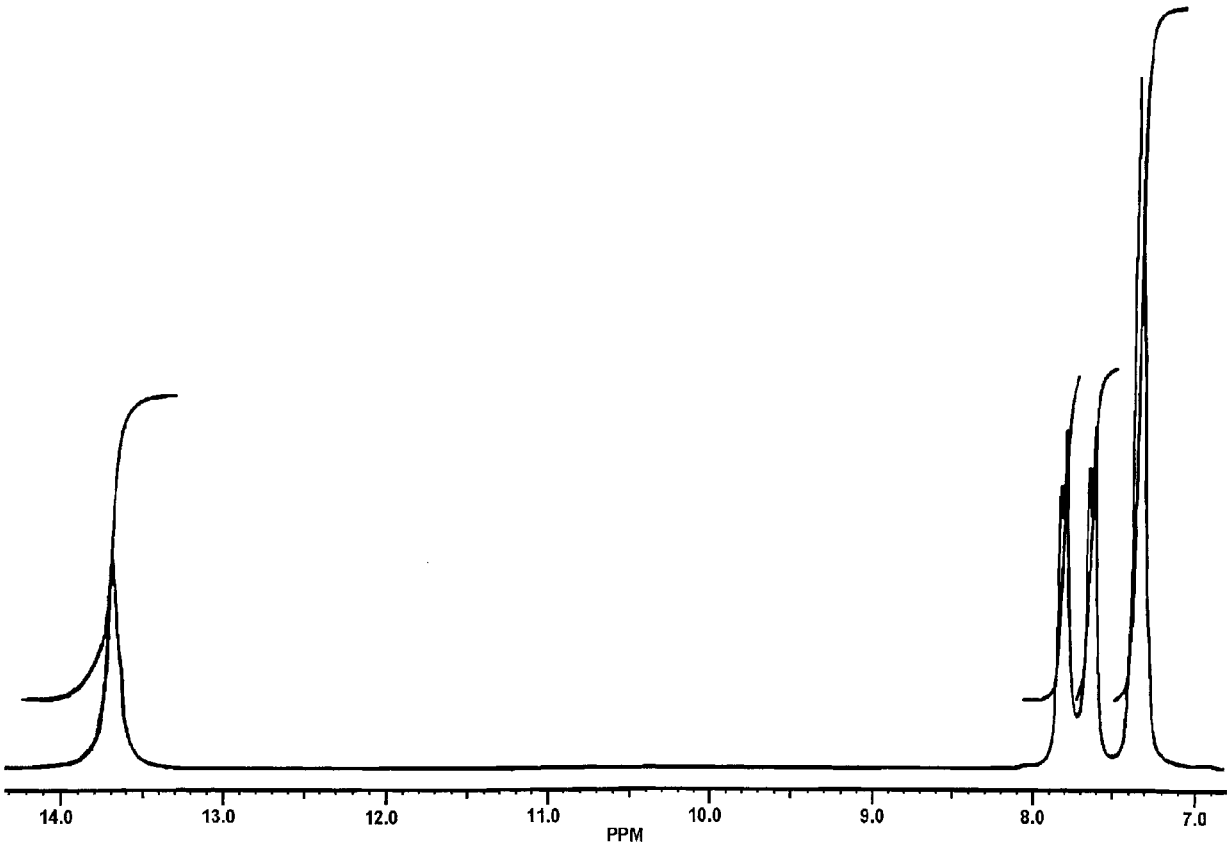


Figure 1. ^{1}H NMR spectrum of **5** in DMSO-d_6 at 20 °C

with the aliphatic heterocyclic systems studied previously by the same method.

EXPERIMENTAL

The 2,2′-bisbenzimidazolyl (**5**) was prepared by reaction of *o*-phenylenediamine and hexachloracetone.[6]

The ^{13}C and ^{1}H NMR spectra of **5** were recorded with a Bruker AC 200 MHz spectrometer, employing tetramethylsilane as internal standard.

Semi-empirical calculations were performed with the MOPAC 6.0 package,[7] utilizing the PM3 hamiltonian. Heats of formation for **5**, the transition state (**TS**) and the zwitterionic intermediate (**I**) were determined after full geometrical optimizations, employing the PRECISE mode as a criterion for convergence. Optimization of the transition state was attained following the eigenvector-following routine, calculating the hessian matrix every five steps in the optimization (MOPAC keywords TS and RECALC = 5). The optimization started from two different geometries, one symmetrical and the other non-symmetrical, both of which yielded the same end structure. The confirmation that the stationary point obtained was a transition state was achieved by subjecting the structure to a force calculation (keyword FORCE), which yielded one and only one negative vibration frequency, associated with the N—H bond of the proton-in-flight. The alternative activation energy for a hypothetical concerted process was estimated through a single-point calculation on the symmetrical structure **S**, obtained as described in the Discussion.

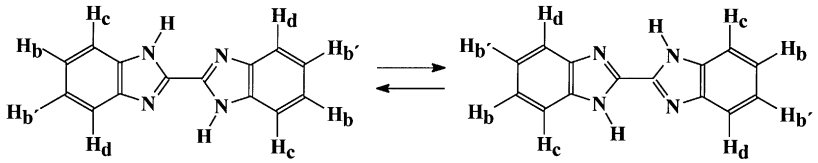
RESULTS AND DISCUSSION

The ^{1}H NMR spectrum of 2,2′-bisbenzimidazolyl (**5**) in DMSO-d_6 at 20 °C is shown in Fig. 1. Figure 2 shows the 13C NMR spectrum of **5** under the same conditions.

As can be seen from the ^{1}H NMR spectrum, the rate of tautomerism of **5** by proton transfer of the NH hydrogens is small enough at 20 °C to yield a clear non-equivalence of the aromatic protons *ortho* to the nitrogen atoms.

These protons (H_c and H_d) appear as two doublets at δ 7.85 and 7.63, coupled to the neighbouring hydrogens H_b and $H_{b'}$ with a coupling constant J = 6 Hz. These latter hydrogens, being further away from the NH groups, appear almost equivalent, as an AB system at δ 7.30.

The ^{13}C NMR spectrum of **5** at 20 °C shows even more



5 5

Scheme 2.

clearly the absence of any detectable tautomerism at this temperature. The signals, corresponding to seven non-equivalent carbon atoms, are easily assignable to the more deshielded C-1/C-1′ (143.9 ppm) and C-5/C-5′ (143.6 ppm), and to the other benzo carbon atoms C-4/C-4′ (134.9 ppm), C-9/C-9′ (123.7 ppm), C-8/C-8′ (122.3 ppm), C-7/C-7′ (119.3 ppm) and C-6/C-6′ (112.2 ppm).

Figure 3 shows the ^{1}H NMR spectra of 2,2′-bisbenzimidazolyl at 50, 80, 110 and 130 °C. Two features are clearly discernible as the temperature is raised: the NH singlet around 13.7 ppm at 20 °C becomes gradually broader, until it practically disappears at 110 °C, and the two doublets at 7.85 and 7.63 ppm, coalesce to a broad signal at 50 °C, becoming sharper again as a doublet of doublets at 110 °C.

The corresponding uncoupled ^{13}C NMR spectra of **5** are shown in Fig. 4. As the temperature is raised, the signals corresponding to the seven non-equivalent carbon atoms of 2,2′-bisbenzimidazolyl gradually coalesce and disappear, and the spectrum is simplified at 130 °C to four signals, two quaternary carbons at 143.2 (C-1/C-1′) and 138.7 ppm (C-4/C-4′ and C-5/C-5′), and two tertiary carbons at 121.9 (C-8/C-8′ and C-9/C-9′) and 114.8 ppm (C-6/C-6′ and C-7/C-7′).

The spectra shown in Figs 3 and 4 allow us to estimate the free energy of activation for the tautomeric process, by the equation

$$\Delta G^{\neq} = 1.914 \times 10^{-2} T_c (9.972 + \log T_c/\Delta\nu_c) \quad (1)$$

which relates this energy to the coalescence temperature

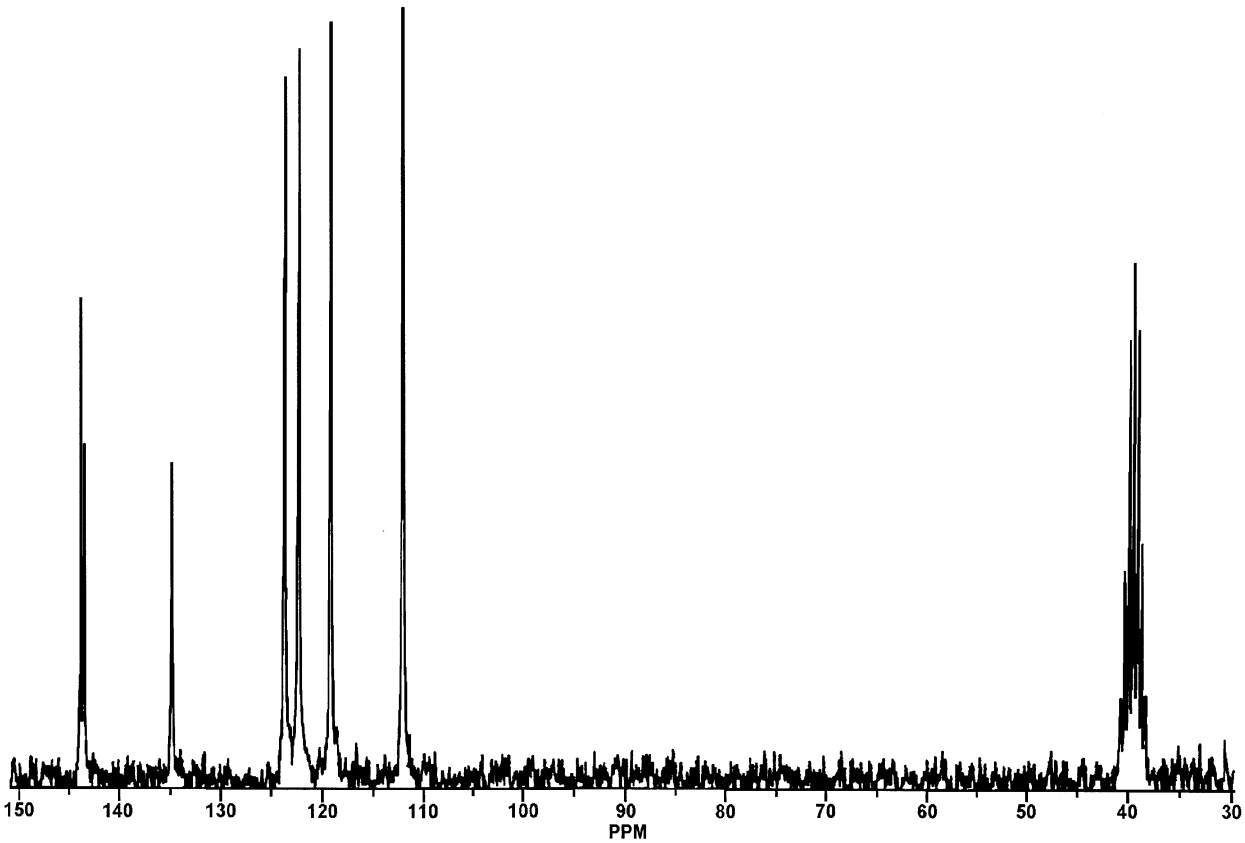
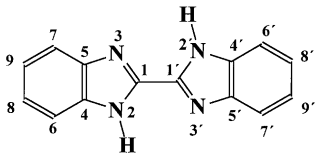
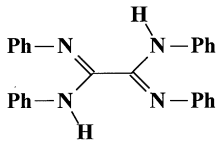


Figure 2. ^{13}C NMR spectrum of **5** in DMSO-d_6 at 20 °C



5

Scheme 3.



6

Scheme 4.

T_c of two given signals absorbing with a frequency difference $\Delta\nu_c$.[8]

Application of this equation to the two proton doublets at 7.85 and 7.63 ppm, which are assumed to coalesce at 323 K (Fig. 2), yields a free energy of activation of 67 kJ mol^{-1}. Estimates based on the ^{13}C NMR spectra in Fig. 4 yield similar values. As an example, the signals at 112.2 and 119.3 ppm, which are assumed to coalesce at 383 K, yield an activation energy of 69 kJ mol^{-1}. Our estimated activation energy of 67–69 kJ mol^{-1} may be compared with that of systems **3** (>90 kJ mol^{-1}), **4** (56–58 kJ mol^{-1})[5] and **6** (43.0 kJ mol^{-1}).[9]

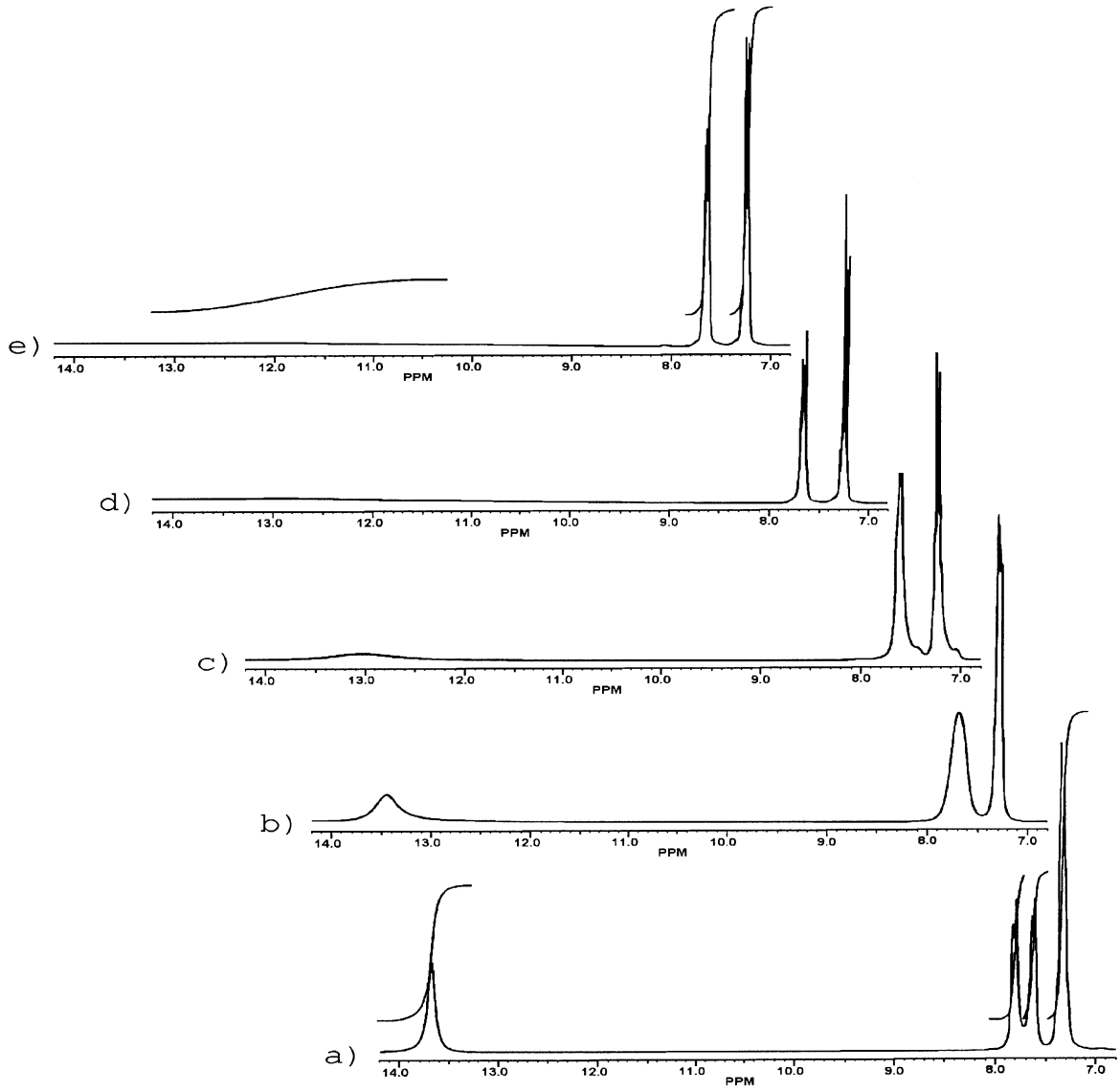


Figure 3. ^{1}H NMR spectra of **5** in DMSO-d_6 at 50, 80, 110 and 130°C

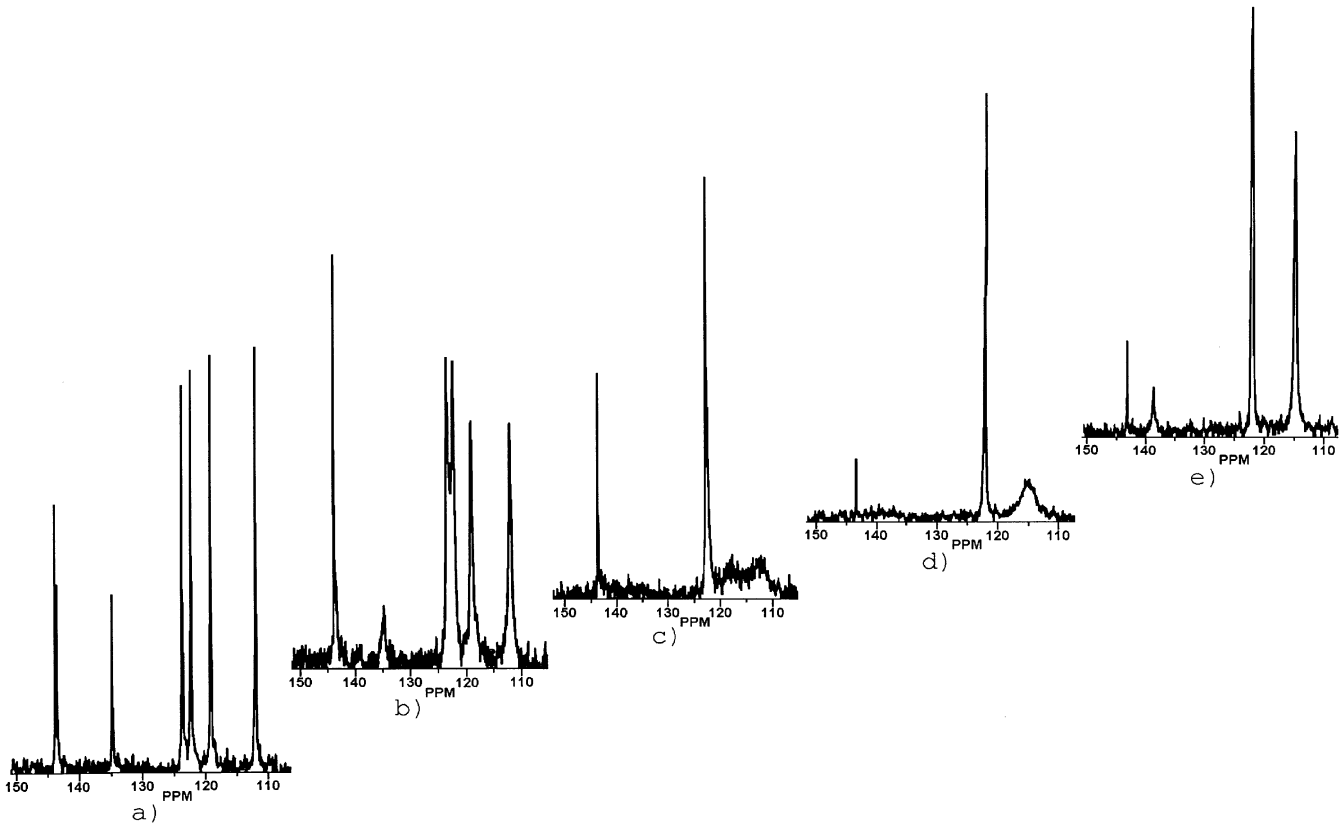


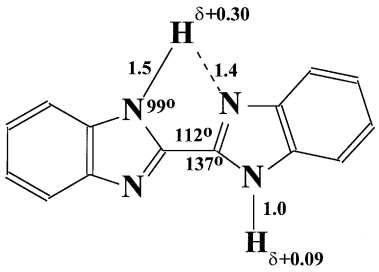
Figure 4. ^{13}C NMR spectra of (5) in DMSO-d_6 at 50,80, 110 and 130°C

It is seen that the proton transfer in the 2,2′-bisbenzimidazolyl system (**5**) takes place at an intermediate rate between that of systems **4 – 6** and that of the aliphatic molecule **3.**

It has been proposed that systems **1 – 4** and compound **6** do not tautomerize via a concerted, symmetrical process, but through a stepwise, single-proton transfer mechanism, with the formation of a zwitterionic intermediate.[3–5] It seems reasonable to assume a similar mechanism for the tautomerism of 2,2′-bisbenzimidazolyl (**5**). A theoretical investigation of the two possible mechanistic alternatives for **5** might corroborate this assumption, in addition to shedding light on the relative behaviour of our system, as compared with the other previously studied oxalamidines.

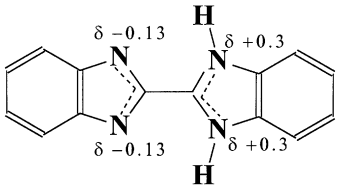
We therefore decided to perform semi-empirical calculations at the PM3 level on the 2,2′-bisbenzimidazolyl molecule and to compare our results with those for other similarly studied systems.

The optimization of a transition state for the tautomerism of **5** was carried out starting from two different geometries. The first was a symmetrical one, where the ground-state bisbenzimidazolyl had two protons-in-flight at an equal distance from the two nitrogen termini, in a geometrical arrangement fairly close to an eventual transition state of a concerted process. The second initial arrangement assumed an asymmetric transition state, with a single-proton transfer from one nitrogen atom (N-2) to another (N-3′). Both initial geometries converged to the same transition state structure **TS** depicted here, shown with some pertinent bond lengths, angles and charges on the H atoms. In order to confirm that this stationary point was indeed a transition state we performed a force calculation on this structure and determined its vibrational frequencies. As expected for a transition state, we obtained one and only one imaginary frequency, corresponding to the NH vibration involving the proton-in-flight. This result confirmed the assumption



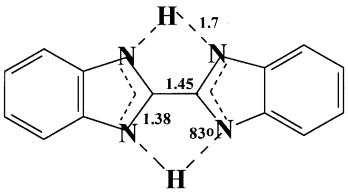
TS

Scheme 5.



I

Scheme 6.



S

Scheme 7.

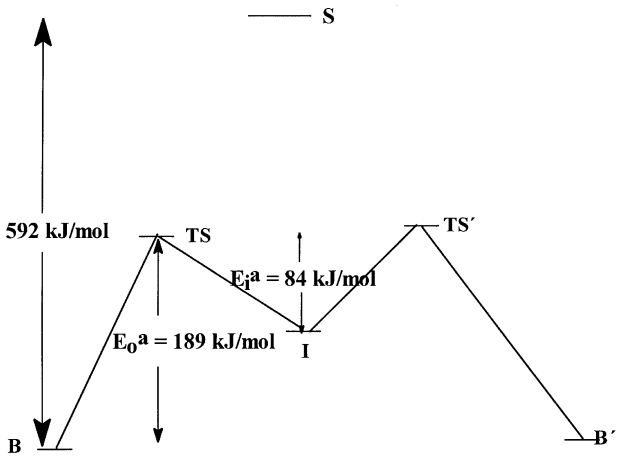


Figure 5. Energy profile for the tautomeric interconversion of the equivalent bisbenzimidazolyl forms **B** and **B′**, through intermediate **I** and the equivalent transition states **TS** and **TS′**. The position of a hypothetical symmetrical concerted transition state **S** is also shown (the drawings are not to scale)

of a stepwise, single-proton transfer for the tautomerism of **5**.

As for compound **2** studied previously,[4] the proton transfer in **5** is accompanied by a heavy-atom reorganization of the whole molecule. The two N atoms involved in the single-proton transfer approach each other and reduce their distance from 3.0 Å in the stable bisbenzimidazolyl molecule to 2.45 Å in the transition state. This is the result of an angular deformation between the two initially symmetrical benzimidazolyl moieties, which has the effect of pushing the other two nitrogen atoms apart, from a distance of 3.0 Å in the stable molecule to 3.4 Å in the transition state. Relaxation of the transition state with full proton transfer to the N-3′ leads to the zwitterionic intermediate **I**, shown here with the calculated charges on all nitrogen atoms.

We next proceeded to compare the two possible pathways, by estimating the activation energy for a hypothetical symmetrical transition state, taking place in a concerted way.

As stated before, in our search for a transition state our calculations never converged to any stationary point which might correspond to a concerted transition state. However, in order to rule out the possibility of such a mechanism, we decided to perform a single-point calculation on a hypothetical symmetrical structure and compare it with our obtained transition state structure **TS.** Since our choice of this hypothetical structure had to be arbitrary, we started from the optimized geometry of the dianion of **5.** We then added two protons to this structure, one at the bottom and the other at the top, positioning them at variable distances from it, along the C_{2v} axis of the symmetrical dianion. We assumed for all single-point calculations a constant bond distance of 1.45 Å between the two rings (a mean value between the distances of 1.44 Å, calculated for bisbenzimidazolyl, and 1.46 Å , calculated for its dianion), and a C-1—N-2 distance of 1.38 Å, a mean of the values for the calculated C—N (1.41 Å) and C═N (1.35 Å) bonds of bisbenzimidazolyl. Employing these parameters, we arrived at the structure **S** as the best symmetrical arrangement (with minimum energy) of the two protons-in-flight.

Our calculations predicted for this hypothetical symmetrical transition state an activation energy of 592

Table 1. Activation energies for the tautomerism of systems **2**–**6**

Compound	E^a (exp.) (kJ mol^{-1})	E_o^a (calc.) (kJ mol^{-1})	E_i^a (calc.) (kJ mol^{-1})
2[a]	—	220	102
3[a]	>90	172	112
4[a]	56.2	123	118
5	67–69	189	84
6[a]	43.0	143	114

[a] Experimental and calculated values from Ref. 4.

kJ mol^{-1}, well above the value of 189 kJ mol^{-1} calculated for the stepwise, single-proton transfer mechanism. A graphical comparison of these two processes is given in Fig. 5.

Table 1 compares the calculated activation energies E_o^a and E_i^a for **5** with those of systems **2**–**4** and **6**.[4]

In all cases the calculated activation energies E_o^a are much larger than the experimental values. Nevertheless, the calculated values reproduce the experimental trends reasonably well. Thus, the bisbenzimidazolyl system **5** is expected to tautomerize more easily than the bisimidazolyl system **2**, for which this process could not be detected,[5] but less readily than systems **4** and **6.** Also, formation of the zwitterionic intermediate **I** from the transition state **TS** is least exergonic for the bisbenzimidazolyl compound **5.** The value of E_i^a in the series closest to that of the aromatic compound **5** (84 kJ mol^{-1}) is of the analogous, equally aromatic bisimidazolyl system **2** (102 kJ mol^{-1}), which is intermediate between that of **5** and the non-aromatic oxalamidines **3, 4** and **6.**

Although we may find some correlation between the theoretical and experimental energy values in Table 1, the above analysis is in many respects limited. For example, the theoretical activation energy for **3** would predict it to tautomerize more easily than **5.** In fact, no proton-transfer process was detected for **3** between 280 and 410 K,[5] in contrast to **5**, for which this process could already be observed by 330 K. Solvent effects may possibly account for such discrepancies.

In fact, in all our preceding discussion we assumed only intramolecular pathways for the tautomeric process. We followed in our discussion the thorough approach and the resulting conclusions on systems **2**–**4** that provided us with a solid ground upon which to build our own analysis. However, the exclusion of solvent-assisted intermolecular pathways in the tautomerism of **3** in an inert solvent such as methylcyclohexane[5] seems much more reasonable than in our case, where tautomerism of **5** takes place in DMSO. In this more polar milieu the role of the solvent should not be negligible, with the result that theoretical calculations, which apply to a hypothetical process in the gas phase, may divert significantly from the experimental observations.

Both intramolecular and solvent-assisted intermolecular processes may take place in the tautomerism of **5** in DMSO.

In the first case, we would expect the polar solvent to favour the stepwise mechanism, which involves a zwitterionic intermediate **I**, rather than the concerted pathway. Increased stabilization of species **I** by the solvent, compared with the bisbenzimidazolyl substrate, would reduce the values of both E_o^a and E_i^a in Fig. 5. This could well explain the fact that **5** tautomerizes more easily in DMSO than **3** in methylcyclohexane, in spite of exhibiting a higher calculated activation energy in the gas phase (189 kJ mol^{-1}) than **3** (172 kJ mol^{-1}).

A solvent-assisted intermolecular proton transfer in the tautomerism of **5** should also be facilitated in DMSO. The strong donor solvent might reasonably act as a general base catalyst in this process, helping to abstract a proton from the imidazolic NH. The low-field shift of this hydrogen atom in DMSO is indicative of some degree of hydrogen bonding with the solvent, a fact which points in that direction.

Therefore, neither the spectroscopic data nor the theoretical calculations presented in this work allow us to decide safely between an intramolecular or a solvent-assisted intermolecular tautomeric process for the bisbenzimidazolyl molecule in DMSO. The fact that the experimental activation energy reported by us falls in the range of the E^a values obtained for systems **3, 4** and **6** in an inert medium, where this choice seems more certain, suggests that **5** also tautomerizes via an intramolecular stepwise process. However, we cannot rule out some degree of solvent participation in this tautomerism, and even the existence of a parallel intermolecular proton transfer, facilitated by the basic DMSO solvating molecules.

In conclusion, ^{1}H and ^{13}C NMR spectra of 2,2′-bisbenzimidazolyl in DMSO-d_6, recorded in a range of temperatures between 293 and 383 K, were used to study the tautomerism of this compound. An activation energy of 67–69 kJ mol^{-1} was estimated for the process. The experimental data do not allow us to decide safely between an intramolecular and a solvent-assisted intermolecular pathway for the tautomerization. Nevertheless, our activation energy falls in the range of values for the tautomerization of other oxalamidines, where the intramolecular mechanism seems more certain. This suggests that a similar mechanism should also be operating for **5** in DMSO, which would tautomerize via a stepwise, single-proton transfer, with the formation of a zwitterionic intermediate. Semi-empirical calculations at the PM3 level reinforced this assumption, showing that the rate-determining proton transfer is accompanied by a deformation of the whole molecule, thus bringing the nitrogen termini of the N—H···N proton-transferring group closer in the transition state.

Acknowledgements

The authors thank CAPES, CNPq and PRONEX for financial support.

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