Controlling the ring-chain tautomeric equilibrium of a tetrahydroquinazoline/imine system by steric hindrance

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Abstract

We have explored the use of steric hindrance on controlling the ring-chain tautomeric equilibrium of a tetrahydroquinazoline/imine system. Two imines, one of them having a bulky group (E)-N-(3-((2-((4-methylphenylsulfonamido)methyl)phenylimino)methyl)pyridin-2-yl)pivalamide ($H_2L^1_{SB}$) and the other one without bulky group (*E*)-*N*-(2-(2,3-dihydroxybenzylideneamino)-benzyl)-4-methylbenzenesulfonamide ($H_2L^2_{SB}$) have been synthetised and spectroscopically studied by ^{1}H NMR. Besides, the formation of the corresponding 1,2,3,4-tetrahydroquinazolines ($H_2L^1_{TQ}$ and $H_2L^2_{TQ}$) was tested.

Keywords

Tetrahydroquinazoline / Imine / Pivalamide / Fenol / Tautomerism

Introduction

Apart from its biological relevance, tetrahydroquinazolines [1-10] are attractive systems for constitutional dynamic chemistry [11] because they can easily undergo ring-chain tautomerism by reversible cyclisation of imines, thus acquiring a great academic importance. It has been reported [8] that the preference for the chain tautomeric form (imine) can be explained by an intramolecular hydrogen bond between -NH_2 and -HC=N- groups (Fig. 1).

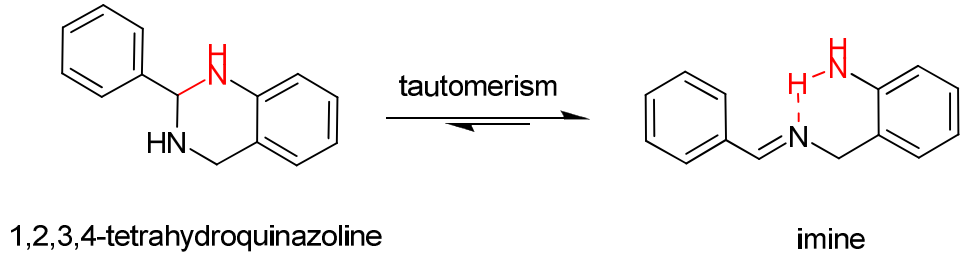

Fig. 1. Ring-chain tautomerism in 2-aryl-1,2,3,4-tetrahydroquinazolines showing the intramolecular hydrogen bond between -NH_2 and -N=HC- groups in the imine.

For the last few years we have focused our attention on controlling the tautomeric equilibrium between tetrahydroquinazolines (TQ) and imines (SB) using metal coordination [9,10], but in this work we have explored the use of steric hindrance for the same purpose. Thus, we will attempt the synthesis of two imines (Fig. 2), one of them having a pivalamide group (E)-N-(3-((2-((4-methylphenylsulfonamido)methyl)phenylimino)methyl)pyridin-2-yl)pivalamide and the other one a hydroxy group (*E*)-*N*-(2-(2,3-dihydroxybenzylideneamino)-benzyl)-4-methylbenzenesulfonamide ($H_2L^1_{SB}$ and $H_2L^2_{SB}$,

respectively). Both imines have the ability to form intramolecular hydrogen bonds (O-H···N or N-H···N), but the bulky group of $H_2L^1{}_{SB}$ could prevent the N-H···N interaction.

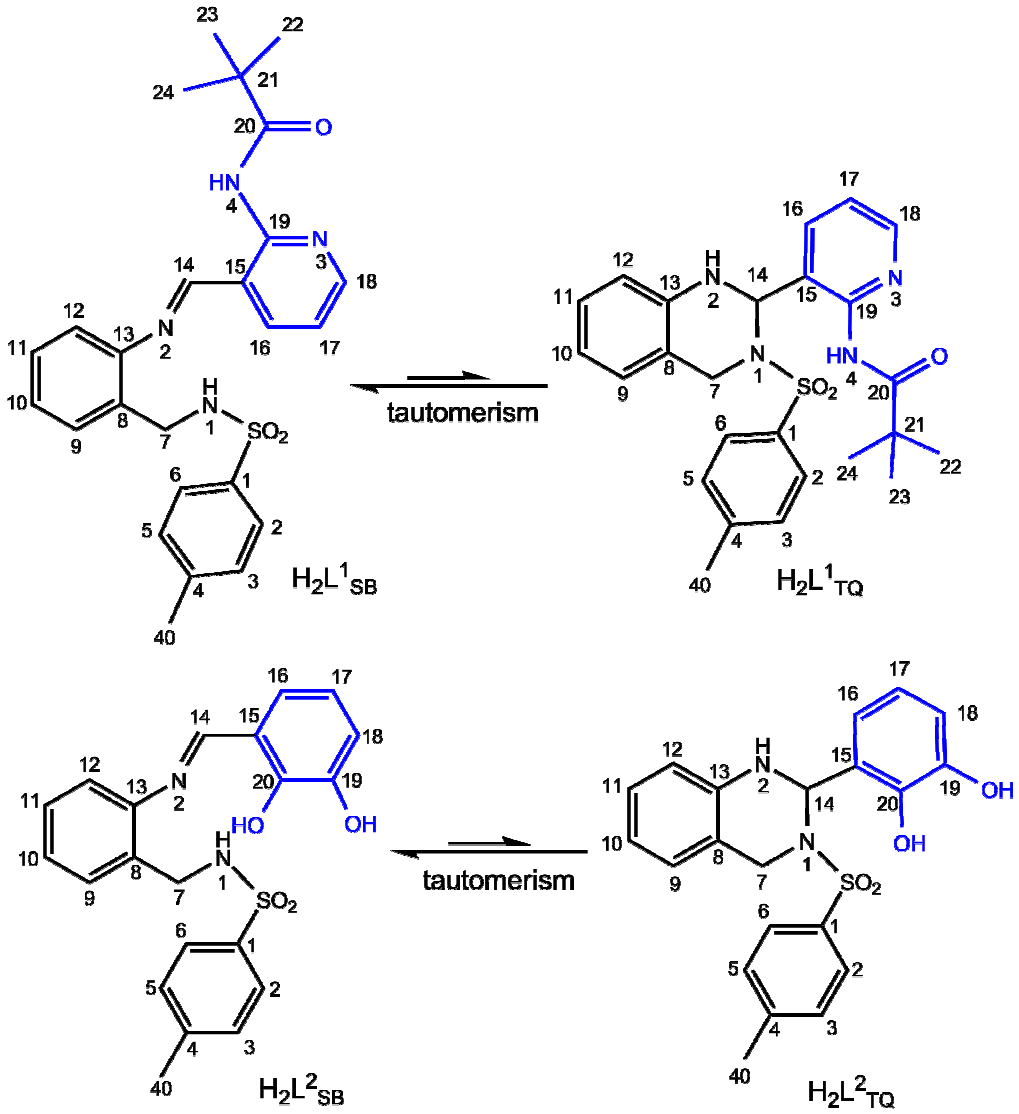

Fig. 2. Schematic representation of $H_2L^1{}_{SB}$ and $H_2L^2{}_{SB}$ (chain tautomeric forms) showing the corresponding ring tautomeric forms ($H_2L^1{}_{TQ}$ and $H_2L^2{}_{TQ}$, respectively) and the numbering scheme for NMR.

Experimental

$H_2L^1{}_{SB}$. *N*-(3-formylpyridin-2-yl)pivalamide (0.30 g, 1.45 mmol) was added to a ethanol solution (40 mL) of 2-tosylaminomethylaniline (0.40 g, 1.45 mmol). The resulting solution was refluxed for 3 h. After cooling, it was filtrated upon celite, and the resulting solution was concentrated to obtain a solid. ^{1}H NMR (500 MHz, DMSO-d_6, δ in ppm): 10.61 (s, 1H, HN-4), 8.53 (d, 1H, H-18), 8.24 (d, 1H, H-16), 8.15 (s, 1H,H-14) , 7.86 (t, 1H, HN-1), 6.75 (t, 1H, H-11), 7.59 (d, 2H, H-2 + H-6), 7.40 (d, 1H,H-9), 7.38 (t, 1H, H-17), 7.37 (t, 1H, H-11), 7.24 (d,2H, H-3 + H-5), 7.23 (t, 1H, H-10), 6.95 (d, 1H, H-12), 4.07 (d, 2H, H-7), 2.33 (s, 3H, H-40), 1.18 (s, 9H, H-22 + H-23 + H-24.

$H_2L^2{}_{SB}$. 2,3-dihydroxybenzaldehyde (0,15 g, 0,73 mmol) was added to a ethanol solution (40 mL) of 2-tosylaminomethylaniline (0.20 g, 0.73 mmol). The resulting solution was refluxed for 3 h. After cooling, it was filtrated upon celite, and the resulting solution was

concentrated to obtain an orange solid. ^{1}H NMR (500 MHz, DMSO-d_6, δ in ppm): 12.56 (s, 1H, HO-20), 9.28 (s, 1H, HO-19), 8.70 (s, 1H, H-14), 8.30 (d, 2H, H-3 + H-5; d, 1H H-18), 8.06 (t, J = 5.9 Hz, 1H, HN), 7.64 (d, J = 8.5 Hz, 2H, H-2 + H-6), 7.36 (d, 1H, H-16; t, 1H, H-17), 7.23 (t, J = 7.7 and 1.4 Hz, 1H, H-10), 7,10 (d, J = 7.7 and 1.4 Hz, 1H, H-12), 6.96 (d, J = 7.7 and 1.4 Hz, 1H, H-9), 6.79 (t, J = 7.7 Hz, 1H, H-11), 4.10 (d, J = 5.3 Hz, 2H, H-7), 2.34 (s, 3H, H-40).

$H_2L^1_{TQ}$. *N*-(3-formylpyridin-2-yl)pivalamide (0.15 g, 0.73 mmol) was added to a chloroform solution (40 mL) of 2-tosylaminomethylaniline (0.20 g, 0.73 mmol). The resulting solution was refluxed for 14 h. After cooling, it was filtrated upon celite, and the resulting solution was concentrated to obtain a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.63 (s, 1H, HN-4), 8.37 (d, 1H, H-18), 7.52 (d, 1H, H-16), 7.51 (d, 2H, H-6 + H-2), 7.19 (t, 1H, H-17), 6.99 (d, 2H, H-3 + H-5), 6.75 (t, 1H, H-11), 6.74 (d, 1H, HN-2), 6.64 (d, 1H, H-9), 6.50 (d, 1H, H-14), 6.37 (t, 1H, H-10), 6.23 (d, 1H, H-12), 4.35 (d, 1H, H-7$_{eq}$), 3.61 (d, 1H, H-7$_{ax}$), 2.18 (s, 3H, H-40), 1.30 (s, 9H, H-22, H-23, H-24).

Results and discussion

With the aim of investigating the use of steric hindrance to control the ring-chain tautomeric equilibrium of a tetrahydroquinazoline/imine system, we have synthesised and characterised *N*-(3-(3-tosyl-1,2,3,4-tetrahydroquinazolin-2-yl)pyridin-2-yl)pivalamide and (*E*)-*N*-(2-(2,3-dihydroxybenzylideneamino)-benzyl)-4-methylbenzenesulfonamide. Besides, the formation of the corresponding 1,2,3,4-tetrahydroquinazolines ($H_2L^1_{TQ}$ and $H_2L^2_{TQ}$) was tested resulting that only $H_2L^1_{TQ}$ was formed.

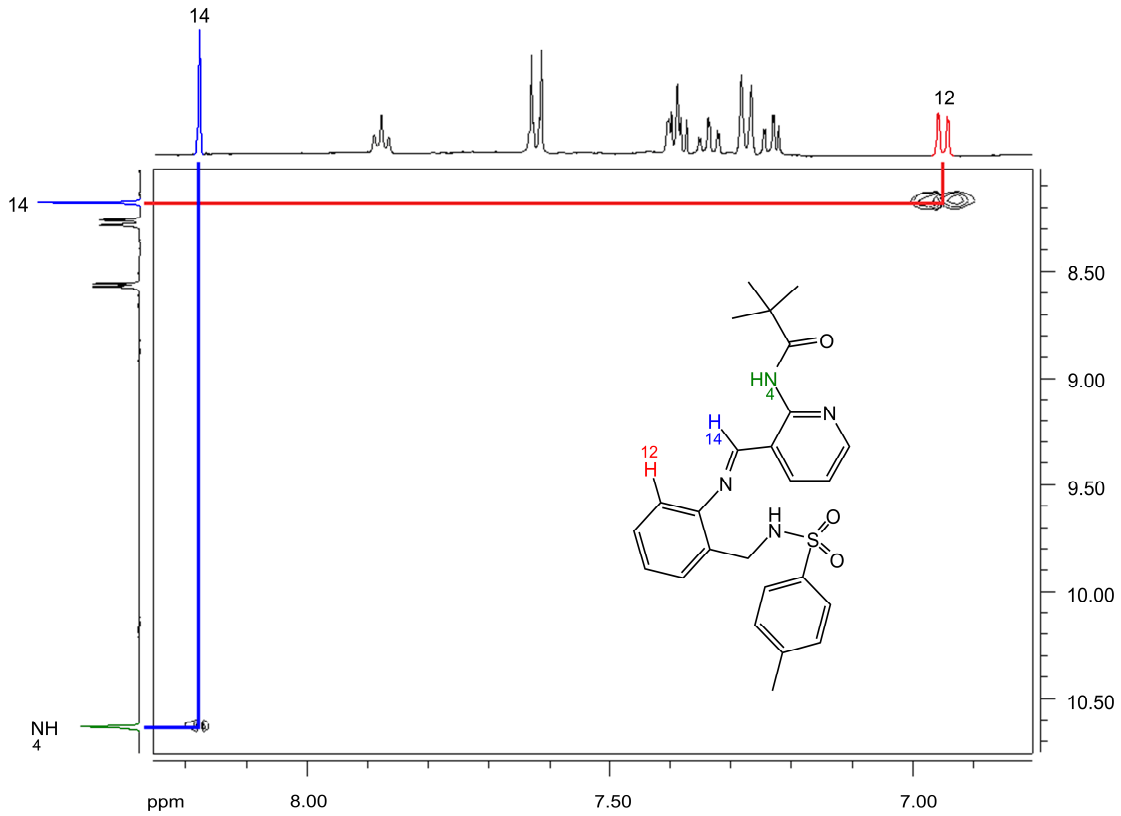

Fig. 3. Partial view of the NOESY spectrum of $H_2L^1_{SB}$ showing the cross peaks due to the H12···H14···HN4 coupling. The steric hindrance due to the pivalamide group prevents the conformation stabilised by N4-H···N2 intramolecular interaction.

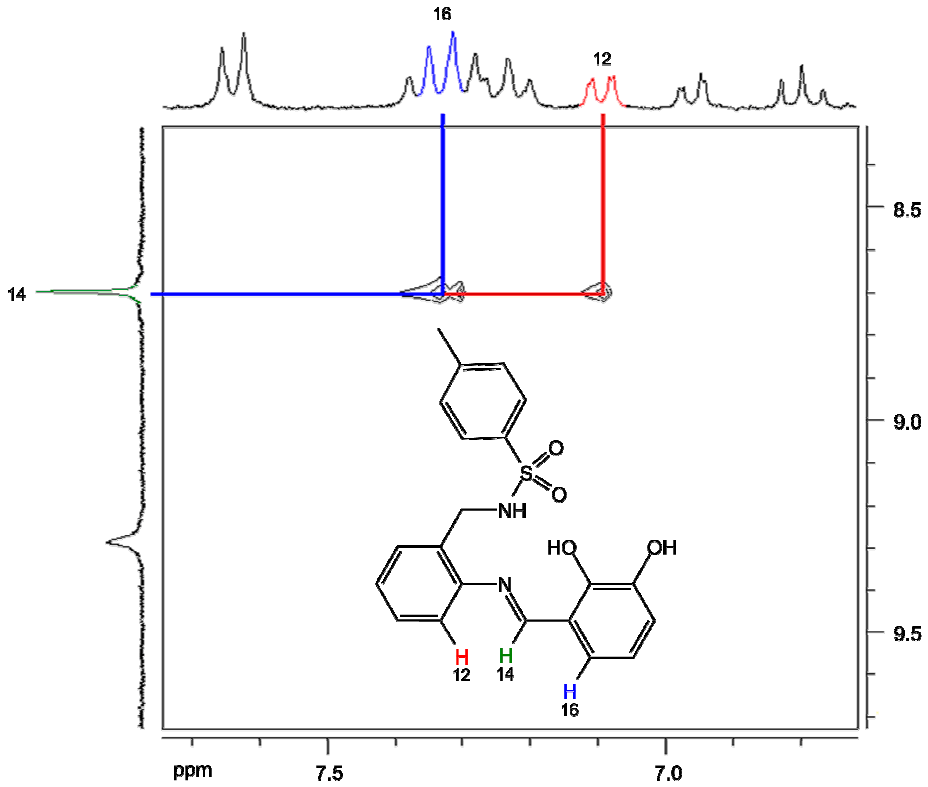

Fig. 4. Partial view of the NOESY spectrum of $H_2L^2_{SB}$ showing the cross peaks due to the H12···H14···H16 coupling. The absence of a bulky group allows the O-H···N intramolecular interaction, which stabilises the chain taumeric form (imine).

Two-dimensional H-H (COSY and NOESY experiments) and H–C (HSQC and HMBC experiments) NMR correlation spectra have been used to a complete assignment of the spectra of $H_2L^1_{SB}$, $H_2L^2_{SB}$ and $H_2L^1_{TQ}$ revealing their conformations. The NOESY spectrum of $H_2L^1_{SB}$ (Fig. 3) showed the cross peaks due to the H12···H14···HN4 coupling, which is the expected for a conformation influenced by steric hindrance. The steric hindrance due to the pivalamide group prevents the N4-H···N2 intramolecular interaction. In contrast, the NOESY spectrum of $H_2L^2_{SB}$ (Fig. 4) revealed the cross peaks due to the H12···H14···H16 coupling, which is the expected for hydrogen bonding between -NH_2 and -N=HC- groups. This is supported by the molecular structure of $H_2L^2_{SB}$, which is shown in Fig. 5.

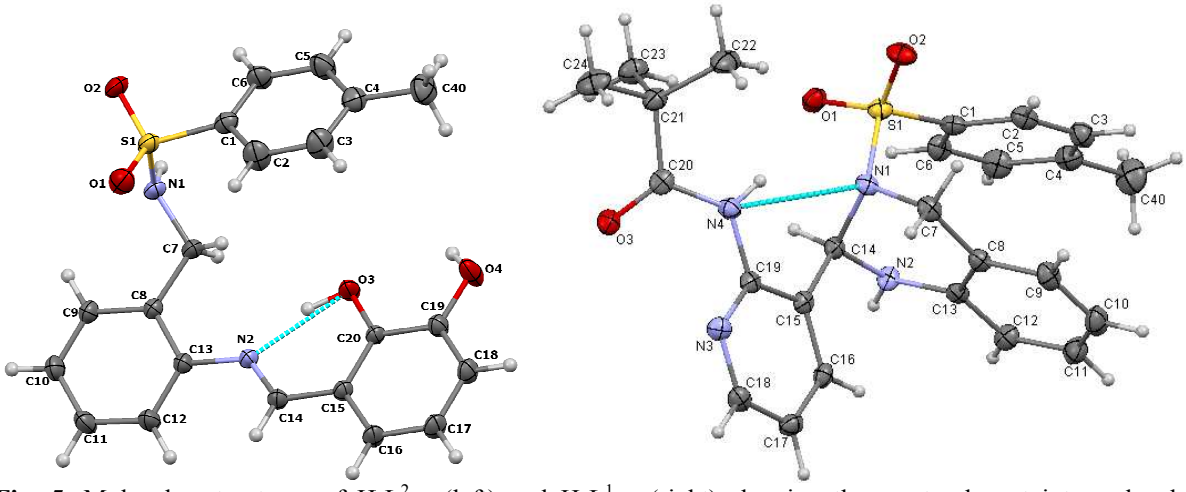

Fig. 5. Molecular structures of $H_2L^2_{SB}$ (left) and $H_2L^1_{TQ}$ (right) showing the most relevant intramolecular hydrogen bonds.

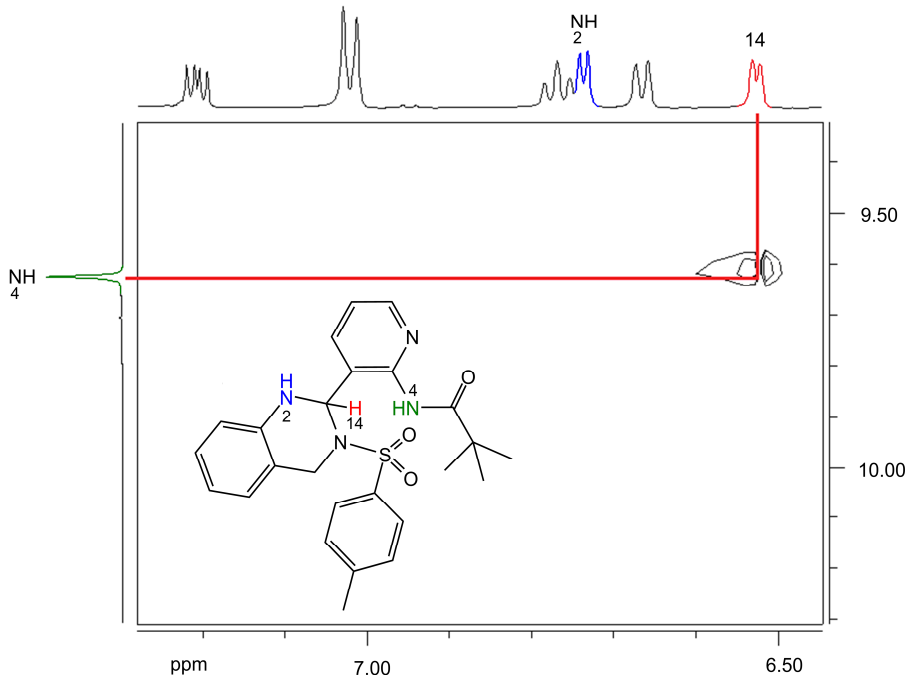

Fig. 6. Partial view of the NOESY spectrum of $H_2L^1_{TQ}$ showing the existence of cross peaks due to the H14···HN4 coupling. The absence of HN2···HN4 coupling is also shown. The conformation is stabilised by the existence of an N4-H···N1 intramolecular interaction

The NOESY spectrum of $H_2L^1_{TQ}$ (Fig. 6) showed the cross peaks due to the H14···HN4 coupling, which is the expected for a conformation stabilised by the existence of an N4-H···N1 intramolecular interaction. This is supported by the molecular structure of $H_2L^1_{TQ}$, which is shown in Fig. 5.

Conclusions

We have demonstrated that the ring-chain tautomeric equilibrium of a tetrahydroquinazoline/imine system can be controlled by steric hindrance. The strong intramolecular interaction O-H···N prevents the tautomerism and therefore the formation of the 1,2,3,4-tetrahydroquinazoline in the system $H_2L^2_{SB}/H_2L^2_{TQ}$, while the steric hindrance due to the pivalamide group prevents the intramolecular interaction N4-H···N2 and therefore the formation of the 1,2,3,4-tetrahydroquinazoline is possible in the system $H_2L^1_{SB}/H_2L^1_{TQ}$.

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