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Substituent effects in ring-chain tautomerism of the condensation products of non-racemic 1,2-aminoalcohols with aromatic aldehydes

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ABSTRACT

The condensation of (*S*)-2-amino-2-phenylethanol or (*S*)-2-amino-3-phenylpropanol with substituted benzaldehydes in methanol or water led to crystalline products, which proved to exist in $CDCl_3$ at 300 K as three-component (ring^{cis}-open-ring^{trans}) tautomeric mixtures. The electronic effects of the 2-aryl substituents on the tautomeric equilibria were described by the Hammett equation. Good correlations were found between the equilibrium constants and the Hammett–Brown parameter (σ^+) of the substituent X on the 2-phenyl group.

1. Introduction

The synthesis and derivatization of 1,2- and 1,3-aminoalcohols are of both pharmaceutical and chemical interest. These difunctional moieties are frequently occurring structural motifs in biologically active compounds. Non-racemic 1,2- and 1,3-aminoalcohols are often utilized as resolving agents in the preparation of enantiopure substances or as chiral auxiliaries in various asymmetric transformations.[1]

Oxazolidine derivatives, obtained by the condensation of 1,2-aminoalcohols with oxo compounds, are also widely applied as intermediates or catalysts in asymmetric syntheses.[2] Excellent enantioselectivities have been achieved in the alkynylation of aldehydes,[3] in the Diels–Alder reactions of 1,2-dihydropyridines[4] and in a domino Michael–aldol reaction[5] through the use of chiral oxazolidine organocatalysts. Also, high yields and enantiomeric excesses have been attained in the bisoxazolidine-catalyzed nitroaldol reactions of different aliphatic and aromatic aldehydes.[6]

The structures of N-unsubstituted oxazolidines can be characterized by tautomeric equilibria of the cyclic and the corresponding Schiff base open-chain forms. Although Baldwin's rules suggest that ring closure of the open form is an unfavored 5-*endo-trig* process, a rapid equilibrium reaction has been observed to occur in solution.[7,8]

The ring-chain tautomeric character of oxazolidine derivatives provides these compounds with dual reactivity (substitution at the NH and/or addition at the C=N group), which is widely utilized in various synthetic transformations, for example the Reformatsky[9] and Ugi reactions[10] with the participation of the open tautomeric forms, or N-acetylation of the cyclic forms via iminium intermediates.[11]

The diastereoselective formation of bicyclic lactams in the domino ring-closure reactions of chiral phenylglycinols with γ-, δ- or ε-keto acids was earlier rationalized in terms of the differences in the rates of the acylation steps for the ring-chain tautomeric oxazolidine intermediates. These lactams are valuable building blocks in the enantioselective synthesis of structurally diverse piperidine-containing natural products and bioactive molecules.[12] Thanks to their ring-chain tautomeric character, oxazolidines have been applied as aldehyde sources in carbon-transfer reactions toward fused pyran and pyridine derivatives[13] and in the modified Pictet–Spengler synthesis of tetrahydro-β-carbolines.[14] Reductive aminations of oxo compounds with 1,2-aminoalcohols occur via oxazolidine intermediates,[15] and the ring-chain tautomeric character of oxazolidines also contributes to the development of prodrugs[16] or the creation of dynamic combinatorial libraries.[17]

As concerns the analogous N-unsubstituted 1,3-X,N-heterocycles (X = O, S, NR), the substituent dependence of the ring-chain tautomeric equilibria of oxazolidines was thoroughly studied earlier.[7,8,18,19] Investigations of a considerable number of 2-aryl-substituted derivatives led to the conclusion that the tautomeric ratios were substantially influenced by the electronic properties of the aryl substituents. For the tautomeric equilibria of 2-(X-phenyl)-substituted oxazolidines, a linear Hammett-type correlation was found between the log$K$ (K = [ring]/[chain]) values of the equilibria and the Hammett–Brown electronic parameter (σ^+) of substituent X on the 2-phenyl group (Eq. 1):[7,8,18,19]

$$\log K = \rho\sigma^+ + \log K_{X=H} \quad (1)$$

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In contrast with these earlier reports on ring-chain tautomerism, unusual results were presented in a recent paper.[20] Benzylideneamino derivatives were synthesized through the condensations of (*S*)-2-amino-2-phenylethanol or (*S*)-2-amino-3-phenylpropanol with substituted benzaldehydes, these reactions reportedly furnishing two-component ring-chain tautomeric mixtures.

Rather surprisingly, the amount of the Schiff base form in the tautomeric mixtures of the products formed in the reactions of (*S*)-2-amino-2-phenylethanol with substituted benzaldehydes varied from 92% to 99%. Interestingly, significant differences were not observed in the amounts of the open-chain form in the tautomeric mixtures of products formed in the reactions of (*S*)-2-amino-3-phenylpropanol with substituted benzaldehydes. For example, the amounts of (*S*)-2-(4-nitrobenzylideneamino)-3-phenylpropanol and (*S*)-2-(4-dimethylamino-benzylideneamino)-3-phenylpropanol in the tautomeric mixtures were 90% and 87%, respectively. Furthermore, for the ring-closed tautomer formed in the tautomeric mixture, a distinction of two epimers was not reported.[20]

In order to clarify this situation, we have re-examined the data presented in the paper of Wu et al.[20] We prepared the same (*S*)-2-benzylideneamino-2-phenylethanols and (*S*)-2-benzylideneamino-3-phenylpropanols and also additional model compounds.

2. Results and discussion

Harsh reaction conditions (e.g. long reflux times in high-boiling-point solvents, with the application of water traps or dehydrating agents) have at times been applied for the condensation of amino alcohols with aldehydes.[21] Wu et al. reacted (*S*)-2-amino-2-phenylethanol **1** or (*S*)-2-amino-3-phenylpropanol **2** with equivalent amounts of different benzaldehydes in anhydrous THF in the presence of $MgSO_4$ for 1 h.[20]

We earlier reported that 1,2- and 1,3-aminoalcohols react conveniently with aromatic aldehydes without any additive to yield the condensation products quantitatively within a few hours in MeOH or EtOH even at room temperature.[18,19] In the present study we followed this synthetic procedure. Moreover, in view of the emerging importance of water as a versatile solvent in organic synthesis,[22] including various condensations (e.g. the Ugi four-center three-component reaction,[23] or cyclocondensations of β-aminocarboxamides and various ketones[24]), the reactions of aminoalcohols **1** and **2** with aromatic aldehydes were also attempted in aqueous medium.

When **1** or **2** was reacted with an equivalent amount of the corresponding aldehyde in absolute MeOH, and the mixture was left to stand at room temperature for 1 h, condensations took place nearly quantitatively. After evaporation of the solution, each compound **3a–i**, **4a–i** was obtained as a stable crystalline product (Scheme 1). When the condensations of aminoalcohol **1** or **2** with the equivalent amounts of aldehydes were performed in distilled water, the mixtures were stirred vigorously at room temperature for 1 h and the precipitated products **3a–i**, **4a–i** were collected by filtration. The yields for the aqueous reactions proved to be somewhat higher than those for the condensations in MeOH.

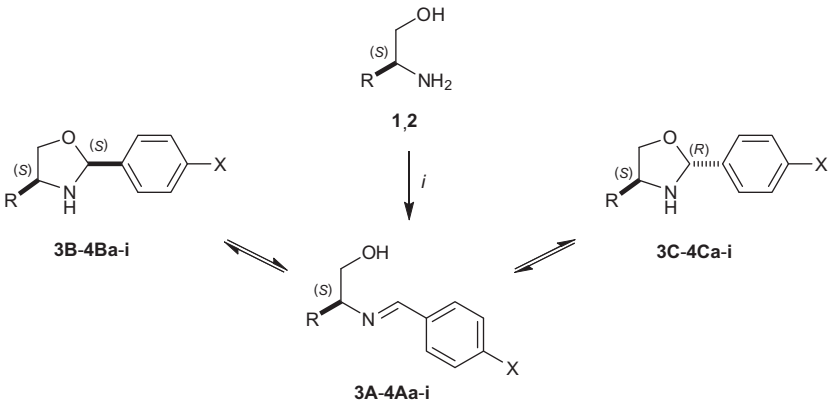
Since the compounds synthesized in MeOH and in H_2O are necessarily identical, we studied the tautomerism only on the compounds synthesized in MeOH. We found that in $CDCl_3$ solution at 300 K compounds **3** and **4** participated in three-component ring-chain tautomeric equilibria involving C-2 epimeric cyclic forms (**B** and **C**) besides the open tautomer (**A**) (Scheme 1). Since the NMR spectroscopic characterizations were very similar for **3a–i** and **4a–i**, only the data on **3a** and **4a** were chosen to illustrate the ^1H NMR spectra of the tautomeric compounds prepared and the relative configurations of the major and minor ring-closed tautomers (see Section 4). The NOE interaction observed between H-2 and H-4 in the NOESY spectra indicated that the major ring form had the *cis* configuration **B**. 2,4-Diaryl substituents did not change the sequence of the chemical shifts of the characteristic O–C*H*Ar–N and N=C*H*Ar protons.

In contrast with the three-component tautomeric equilibria detected in our work, Wu et al. reported only two components **A** and **B** in the tautomeric mixtures of the oxazolidines prepared. They did not describe the minor *trans* C-2 epimeric form **C**.[20]

Figures 1 and 2 show the 500 MHz ^1H NMR spectra of the products **3a**, and **4a** of the reactions of (*S*)-2-amino-2-phenylethanol or (*S*)-2-amino-3-phenylpropanol with *p*-nitrobenzaldehyde. In Figure 1, the singlets at 5.70 and 5.83 ppm are those of H-2 in the two ring-closed tautomers, while the azomethine singlet is at 8.48 ppm. In Figure 2, the corresponding singlets are shifted to lower values, with the H-2 singlets of the ring-closed tautomers at 5.55 and 5.70 ppm and the azomethine singlet at 8.02 ppm. Both spectra also contain the corresponding triplets or multiplets of H-4 of the epimeric ring forms of **3a** and **4a**.

In Figure 1, the well-separated triplets at 4.37 and 4.43 ppm correspond to H-4 in the major and minor ring forms of **3a**. In **4a**, multiplets appear at 3.73–3.81 ppm for H-4 of the major epimeric ring form, and overlapping multiplets are observed at 3.81–3.90 ppm for H-4 in the minor epimer (Fig. 2). The amounts of the tautomeric forms are also indicated in the spectra. Of the C-2 epimers, the major ring form in the tautomeric equilibria of **3a** and **4a** contains H-2 and H-4 in the *cis* position **B** (Tables 1 and 2).

The reported contents of the tautomeric forms in the tautomeric equilibria in the two studies differ drastically.[19] For instance, Wu



R = Ph: **1**, **3**; R= CH_2 Ph: **2**, **4**; X = **a**, NO_2; **b**, CN; **c**, Br; **d**, Cl; **e**, H; **f**, F; **g**, He; **h**, OMe; **i**, HMe_2.

Scheme 1. Reagents, conditions and yields: (i) XC_6H_4CHO, MeOH or H_2O, rt, 1 h, 61–99%.