π-Selectivities of *trans*-2-heterobicyclo[4.4.0]decan-5-ones in reductions with NaBH$_4$ and Na(CN)BH$_3$

Rengarajan Balamurugan, Vardhineedi Sriramurthy & Veejendra K Yadav*

Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India

E-mail: vijendra@iitk.ac.in

The axial selectivities of 2-heterobicyclo[4.4.0]decan-5-ones decrease from the N-benzyl-2-aza- to 2-oxa- to 2-thia-species. This does not follow the earlier proposed Cieplak's hypothesis of $n_{heteroatom} \rightarrow \sigma^{*\#}$ interaction. It is rather dependent on the differential electron withdrawing abilities of the heteroatoms that translate further into differential $\sigma_{vicinal} \rightarrow \pi^*_{C=O}$ interactions in the ground states of the molecules. The heightened axial selectivity of the aza-species is probably due to hydrogen bonding of nitrogen with the solvent that enhances its electron withdrawing ability further.

Keywords: 2-Heterobicyclo[4.4.0]decan-5-ones, π-selectivity, $n_{heteroatom} \rightarrow \sigma^{*\#}$ interaction, $\sigma_{vicinal} \rightarrow \pi^*_{C=O}$ interactions, hydrogen bonding

Geneste *et al*. have reported enhancement in reaction rate on replacement of C4 in cyclohexanone by N or S and attributed it to the through-space effect of dipole-dipole interactions[1]. Cieplak hypothesised $n_{heteroatom} \rightarrow \sigma^{*\#}$ (hereafter $n \rightarrow \sigma^{*\#}$, $\sigma\#$ is the incipient bond in the TS) overlap and argued that it was more effective throughout the reaction pathway in the axial approach of a nucleophile than in the equatorial approach as shown in **Figure 1**[2]. Cieplak used this premise to explain the observed increase in the absolute rate constants of nucleophilic additions to 4-hetero-cyclohexanones in the order of increasing electron donor ability of the heteroatom lone pair that was considered to be the smallest for oxygen and the largest for sulfur. The $n \rightarrow \sigma^{*\#}$ premise was also used to predict higher relative yields of the axial approach in metal hydride reductions of 4-heterocyclo-hexanones than the corresponding carbon-analog. This was found to corroborate with the experimental results even though the differences were very small[2a]. Cieplak noted lack of systematic study of the reduction stereochemistry of tetrahydro-*4H*-thiapyran-4-one. This did not allow excluding a decrease in electron density of the ring σ bonds as the major factor leading to the observed shift in the reduction stereochemistry.

Whereas the said decrease in the electron densities of the ring σ bonds would appear to be a genuine possibility in the aza- and oxa-species for the electron-withdrawing characters of σ_{C-N} and σ_{C-O}, leading therefore to enhanced axial selectivities, there must actually be an increase in the electron densities of the ring σ_{C-C} bonds in the thia-species for the electron-donating character of σ_{C-S}[2b], leading to a decrease in the axial selectivity. It is to be noted that the equatorial attack is stabilized by the participation of the ring σ_{C-C} bonds and, likewise, the axial attack is stabilized by the participation of the σ_{C-Hax} bonds on the carbons adjacent to the carbonyl function through their interactions with (a) $\sigma^{*\#}$ in the respective TSs, according to the Cieplak model, and (b) $\pi^*_{C=O}$, according to the antiperiplanar effects[3]. Thus, Cieplak's speculation of the relative selectivity based on the changes in the electron densities of the ring σ_{C-C} bonds due to different heteroatoms does not explain why the thia-species was at all expected to exhibit the highest rate constant and also the highest axial selectivity among the three heterocycles examined.

The $n \rightarrow \sigma^{*\#}$ premise was shown to find support from the relative rate constants of NaBH$_4$ reduction of N-alkyl-4-piperidones[2]. Modification of the electron donating power of nitrogen lone pair through substitution resulted in predictable changes in the reduction rate constant. N-Methylation, for instance, increased the reduction rate because it lowered the
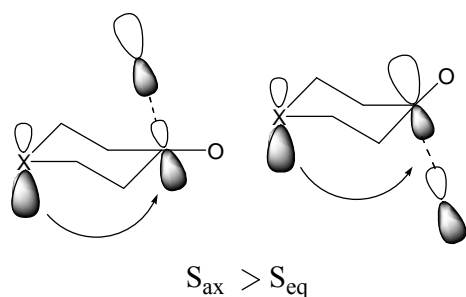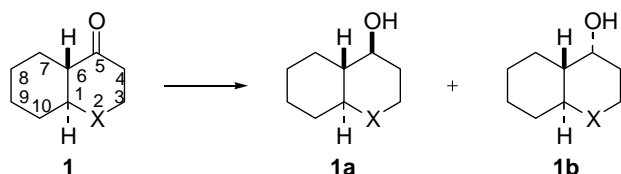
$$S_{ax} > S_{eq}$$

Figure 1 — Cieplak's hypothesis on n→σ*# overlap control in 4-heterocyclohexanones

Table I — Experimental π-selectivities of the substrates **1**, X = NBn/O/S

Substrate	Hydride	Temperature (°C)	Time (min)	Attack (ax:eq)
1, X = NBn	NaBH$_4$	0	60	>30:1
	Na(CN)BH$_3$	25	60	>34:1
1, X = O	NaBH$_4$	0	30	6.3:1
	Na(CN)BH$_3$	25	60	13:1
1, X = S	NaBH$_4$	0	40	3.9:1
	Na(CN)BH$_3$	25	60	9.5:1

Scheme I — Reduction of **1** (X = NBn, O, S)

ionization potential of aliphatic amines[4] and the resultant decrease in energy separation between n_N and σ*# improved the two-electron stabilization of the axial TS[2]. Further, branching of the N-alkyl group reversed the above effect because it allowed delocalization of the nitrogen lone pair into the σ$_{C-C}$ of the substituent, leading to an increased energy gap between n_N and σ*# and, thus, the less efficient stabilization of the axial TS. The rate constant for NaBH$_4$ reduction of N-*tert*-butyl-4-piperidone was almost one-half the rate constant of N-methyl-4-piperidone.

We were concerned primarily with the predicted profile of the axial selectivity and, thus, the reduction of the title substrates with NaBH$_4$ and Na(CN)BH$_3$ was examined (**Scheme I**). These substrates are conformationally rigid to allow a rapid analysis of product distribution. The ratios of the isomers were calculated from the relative C*H*OH integrals. The eq-C*H*OH resonated at a lower magnetic field than the corresponding ax-C*H*OH. The observed relative selectivity contrasted what was predicted by the n→σ*# hypothesis. It has been discovered that the n→σ*# interactions are absent from the Natural Bond Orbital (NBO) analysis[5] of the TS structures formed from LiH. Each TS located in the present study was characterized by a single imaginary frequency. The calculations were performed using the Gaussian 98 suit of programs[6]. It has been demonstrated previously that calculations of the TSs with LiH for ketone reduction reproduced the trends observed experimentally in reduction with NaBH$_4$[7]. Herein are presented the results of this study.

Results and Discussion

The alcohols were separated by column chromatography over silica gel and the relative stereochemistry of the major alcohol in each instance was secured by a single crystal X-ray structure analysis of the corresponding *p*-bromobenzoate[8]. The ratios of the axial and equatorial attacks are collected in **Table I**. The ratio varied considerably with the change in the heteroatom. While aza-**1**, X = NBn exhibited the highest axial selectivity (> 30:1), thia-**1**, X = S exhibited the lowest axial selectivity (3.9:1). The selectivity of oxa-**1**, X = O was in between those of aza-**1** and thia-**1**. Na(CN)BH$_3$ exhibited significantly higher axial selectivity than NaBH$_4$. The observed selectivity profile does not corroborate with the predictions based on the n→σ*# hypothesis.

If it were indeed for the n→σ*# interaction as proposed by Cieplak, the relative level of the observed axial selectivity will be expected to be different. In particular, the axial selectivity of thia-**1** must have be the highest among the three substrates examined. The lowest axial selectivity of thia-**1** raised doubts about the existence of the n→σ*# interaction. This has led to the investigation of the same from the NBO analysis of the TSs formed from **1** and LiH.

The NBO analysis is based on optimally transforming a given wave function into localized forms that correspond to one-center (lone pair) and two-center (bond) elements in the Lewis structure regime. Donor-acceptor interactions related to hyperconjugation in the TS are estimated by the Second Order Perturbation Theory analysis implemented in the NBO 5.0 program[5]. Lewis resonance structures that have a forming bond are chosen for the analysis.

The *ax*-aza-**1**-LiH, *ax*-oxa-**1**-LiH and *ax*-thia-**1**-LiH TSs were calculated at HF/6-31G* and HF/6-31+G* levels. The n→σ*# interaction was absent in each instance. The corresponding equatorial TSs were also

calculated. The n→σ*# interaction was absent, again, in each instance.

The energy differences of the above axial and equatorial TSs are collected in **Table II**. The HF/6-31G* and HF/6-31+G* energy profiles suggest the poorest axial selectivity from thia-**1** and the highest axial selectivity from oxa-**1**. The axial selectivity of aza-**1** (**Figure 2**)will be predicted to be intermediate to the other two. This contrasts the experimental finding. It was actually aza-**1** that exhibited the highest axial selectivity and not oxa-**1**.

Electrostatic attractions bring the two reactants together to allow the subsequent manoeuvres through the TS to result in the product formation. A substrate prone to axial attack must have larger electrostatic attraction for the other reactant on the axial face than on the equatorial face. The kinetic facial selectivity of a given substrate must therefore be a function of its ground state geometry, the interactions of $\pi^*_{C=O}$ with other molecular orbitals, in particular. In the event, $\sigma_{C\alpha\text{-Hax}} \to \pi^*_{C=O}$ and $\sigma_{C\alpha\text{-C}\beta} \to \pi^*_{C=O}$ interactions are inherently destined to be important in determining the selectivity in the absence of other control elements such as steric interactions and chelation effects.

The steric interactions will enlarge as a nucleophile moves closer to the carbonyl group to form the TS. This is in consequence of (a) the closeness of the two reactants to each other, and (b) the ensued changes in hybridization of the carbonyl carbon from sp^2 to sp^3. In reactions with large nucleophiles, the steric

interactions may outsmart the electronic effects in select instances[9]. It is therefore necessary to avoid such effects by selecting substrates that are devoid of large substituents near the reaction site and by allowing them to react with small nucleophiles in the investigations of electronic effects alone. In the absence of steric and chelation effects, the TS will represent a true measure of the electronic effects.

The inductively electron withdrawing N and O atoms are expected to reduce the electron densities of the ring bonds $\sigma_{C1\text{-}C6}$ and $\sigma_{C3\text{-}C4}$. This will reduce $\sigma_{C1\text{-}C6} \to \pi^*_{C=O}$ and $\sigma_{C3\text{-}C4} \to \pi^*_{C=O}$ interactions and result in higher axial selectivity. On the contrary, $\sigma_{C\text{-}S}$ is electron donating[10]. The consequent increase in the electron densities of $\sigma_{C1\text{-}C6}$ and $\sigma_{C3\text{-}C4}$ will result in increased $\sigma_{C1\text{-}C6} \to \pi^*_{C=O}$ and $\sigma_{C3\text{-}C4} \to \pi^*_{C=O}$ interactions and, thus, a loss in the axial selectivity. The higher axial selectivity of aza-**1** in comparison to oxa-**1** is likely to be due to the hydrogen bonding of the nitrogen with the reaction medium that renders the nitrogen more electron withdrawing than oxygen. The prospect of such a hydrogen bonding and its analogous effect has previously been suggested by le Noble to explain the predominant syn selectivity of 5-aza-2-adamantanone[11].

The changes in the relative electron densities of the ring bonds $\sigma_{C1\text{-}C6}$ and $\sigma_{C3\text{-}C4}$ due to different heteroatoms must also be reflected in their interactions with $\pi^*_{C=O}$[12]. In keeping with the experimental results, the sum of $\sigma_{C1\text{-}C6} \to \pi^*_{C=O}$ and $\sigma_{C3\text{-}C4} \to \pi^*_{C=O}$ interactions in thia-**1** must be larger than those in the aza- and oxa-species. Alternatively, the sum of $\sigma_{C4\text{-}Hax} \to \pi^*_{C=O}$ and $\sigma_{C6\text{-}Hax} \to \pi^*_{C=O}$ interactions must be smaller in thia-**1** than those in the aza- and oxa-species. These interactions are collected in **Table III**. The sum of $\sigma_{C1\text{-}C6} \to \pi^*_{C=O}$ and $\sigma_{C3\text{-}C4} \to \pi^*_{C=O}$ interactions changed from 5.85 kcal/mol and 4.71 kcal/mol in **1**, X = NBn to 5.90 kcal/mol and

Table II — Energy differences of the axial and equatorial LiH-TSs

Substrate	$-[E_{ax\text{-}TS} - E_{eq\text{-}TS}]$ kcal/mol	
	HF/6-31G*	HF/6-31+G*
1-LiH, X = NMe	1.26	1.10
1-LiH, X = O	1.58	1.47
1-LiH, X = S	1.07	0.83

Table III — The $\sigma \to \pi^*_{C=O}$ interactions (kcal/mol) in **1**, *trans*-decalone and **1**-H_2O, X = NMe

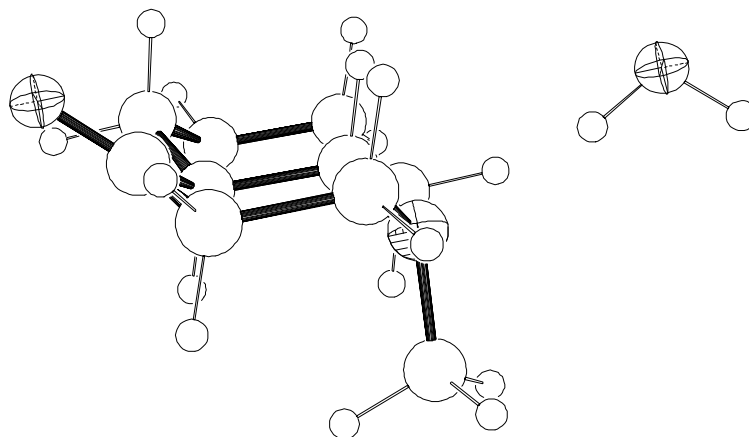| Substrate	HF/6-31G* (B3LYP/6-31G*)			
	$\sigma_{C1\text{-}C6}\text{-}\pi^*_{C=O}$	$\sigma_{C3\text{-}C4}\text{-}\pi^*_{C=O}$	$\sigma_{C4\text{-}Hax}\text{-}\pi^*_{C=O}$	$\sigma_{C6\text{-}Xax}\text{-}\pi^*_{C=O}$
1, X = NMe	2.91 (2.35)	2.99 (2.38)	7.63 (5.62)	7.73 (5.74)
1, X = NBn	2.83 (2.28)	3.02 (2.43)	7.67 (5.63)	7.77 (5.75)
1, X = O	3.08 (2.63)	2.82 (2.14)	7.67 (5.46)	7.60 (5.40)
1, X = S	3.00 (2.41)	3.11 (2.43)	6.42 (4.85)	6.46 (4.86)
1, X = CH₂	3.11 (2.54)	3.05 (2.43)	7.21 (5.35)	7.12 (5.26)
1-H_2O, X = NMe	2.69	2.83	7.45	7.66

Figure 2 — aza-**1**-H$_2$O (N...H = 2.076 Å, HF/6-31G*)

4.77 kcal/mol in **1**, X = O and 6.11 kcal/mol and 4.84 kcal/mol in **1**, X = S at the HF/6-31G* and B3LYP/6-31G* levels, respectively. Alternatively, the sum of $\sigma_{C4-Hax} \rightarrow \pi^*_{C=O}$ and $\sigma_{C6-Hax} \rightarrow \pi^*_{C=O}$ interactions changed from 15.44 kcal/mol and 11.38 kcal/mol in **1**, X = NBn to 15.27 kcal/mol and 10.86 kcal/mol in **1**, X = O and 12.88 kcal/mol and 9.71 kcal/mol in **1**, X = S. Indeed, the changes in the electron densities of the ring bonds σ_{C1-C6} and σ_{C3-C4} due to different heteroatoms reflect reasonably well in the $\sigma_{vicinal} \rightarrow \pi^*_{C=O}$ interactions and, further, the $\sigma_{vicinal} \rightarrow \pi^*_{C=O}$ interactions predict the correct order of π- selectivity.

To demonstrate the electron withdrawing effect of hydrogen bonding and the above-predicted effect on the π-selectivity through the related $\sigma_{vicinal} \rightarrow \pi^*_{C=O}$ interactions, aza-**1**–H$_2$O, wherein H$_2$O is hydrogen bonded to the nitrogen[13], was calculated. The orbital interactions are collected in **Table III**. It is clear that the said hydrogen bonding has electron withdrawing effect on the ring bonds that leads to reduction in $\sigma_{C1-C6} \rightarrow \pi^*_{C=O}$ and $\sigma_{C3-C4} \rightarrow \pi^*_{C=O}$ interactions. The sum of these interactions in aza-**1**-H$_2$O is lower than those in oxa-**1** and thia-**1**. Further, the difference of the sum of $\sigma_{C4-Hax} \rightarrow \pi^*_{C=O}$ and $\sigma_{C6-Hax} \rightarrow \pi^*_{C=O}$ interactions, that supports axial selectivity, and the sum of $\sigma_{C1-C6} \rightarrow \pi^*_{C=O}$ and $\sigma_{C3-C4} \rightarrow \pi^*_{C=O}$ interactions, that supports equatorial selectivity, favors the highest axial selectivity for aza-**1**, middle level selectivity for oxa-**1** and the lowest selectivity for thia-**1**. The calculated 3D geometry of aza-**1**-H$_2$O is collected in **Figure 2**.

It is pertinent to compare the selectivity of the carbon-analog **1**, X = CH$_2$ with those of the title substrates. The sum of the $\sigma_{C1-C6} \rightarrow \pi^*_{C=O}$ and $\sigma_{C3-C4} \rightarrow \pi^*_{C=O}$ interactions in **1**, X = CH$_2$ is 6.16 kcal/mol

and 4.97 kcal/mol at the HF/6-31G* and B3LYP/6-31G* levels, respectively. Qualitatively, this interaction is larger than that in **1**, X = NBn, O and S. This suggests poorest axial selectivity from **1**, X = CH$_2$ among the four substrates. *Trans*-bicyclo[4.4.0]decan-5-one (**1**, X = CH$_2$) has been reported to exhibit 3:2 *ax*:*eq*-selectivity on reduction with NaBH$_4$ in methanol[14]. However, from the sum of $\sigma_{C4-Hax} \rightarrow \pi^*_{C=O}$ and $\sigma_{C6-Hax} \rightarrow \pi^*_{C=O}$ interactions, **1**, X = CH$_2$ is predicted to exhibit better axial selectivity than **1**, X = S. This constitutes a discrepancy. Also, how the $\sigma_{C1-C6} \rightarrow \pi^*_{C=O}$ and $\sigma_{C3-C4} \rightarrow \pi^*_{C=O}$ interactions in **1**, X = CH$_2$, are better than those in the hetro-species is not clear at present. The very similar data at entries 1 and 2 in **Table III** demonstrate that the vicinal interactions in **1**, X = NMe match closely with those in **1**, X = NBn. This justifies the choice of **1**, X = NMe as a suitable computational mimic for **1**, X = NBn with which the experiments were carried out.

The studies with 4-aza-cyclohexanone, 4-oxa-cyclohexanone, 4-thia-cyclohexanone and cyclo-hexanone (data not included here) demonstrated similar results. The axial TSs formed from the hetero-analogs and LiH did not show n→σ*# interactions. For the long σ_{C-H} incipient bond lengths (1.96-2.0 Å at the HF/6-31G* level), these TSs belonged to the *early* category. The axial TSs with LiCN were also investigated. These TSs, that belonged to the *late* category as the σ# length is ~1.88 Å at the HF/6-31G* level, are also devoid of the n→σ*# interaction.

Experimental Section

Typical procedure for the reduction with NaBH$_4$. NaBH$_4$ (0.2 mmole) was added to a solution of the substrate (0.2 mmole) in MeOH (2 mL) at 0 °C.

After the reaction was complete by TLC, MeOH was removed. Saturated aqueous NH_4Cl (2 mL) was added to the residue and the product(s) extracted into EtOAc (2 × 5 mL). The combined EtOAc solution was dried and the solvent removed. The residue was filtered through a column of silica gel to furnish a mixture of the alcohols.

Typical procedure for the reduction with $Na(CN)BH_3$. A small crystal of methyl orange was added to a solution of the substrate (0.2 mmol) in MeOH (2 mL) at 25°C. The solution turned yellow. A few drops of 2N HCl/MeOH were added so that the solution turned red. At this stage $Na(CN)BH_3$ (0.2 mmole) was added slowly. Whenever the color of the reaction mixture started to turn to yellow during the addition of $Na(CN)BH_3$, a few drops of 2*N* HCl/MeOH were added immediately to restore the red color. When the reaction was complete by TLC, it was concentrated, mixed with saturated aqueous NH_4Cl (2 mL), and the product(s) extracted into EtOAc (2 × 5 mL). The combined extract was dried and the solvent removed. The residue was filtered through a column of silica gel to furnish a mixture of alcohols.

Spectral data of 1, X = NBn[15,16a]. ^{1}H NMR: δ 7.36-7.24 (5H, m), 4.16 (1H, d, *J* = 13.4 Hz), 3.28 (1H, d, *J* = 13.4 Hz), 3.13-3.08 (1H, ddd, *J* = 12.0, 6.5, 2.2 Hz), 2.63-2.55 (1H, dt, *J* = 12.9, 6.5 Hz), 2.38-2.34 (1H, dd, *J* = 12.0, 3.0 Hz), 2.32-2.20 (4H, m), 2.04-2.00 (1H, m), 1.84-1.77 (2H, m), 1.48-1.18 (4H, m); ^{13}C NMR: δ 210.4, 139.1, 128.8, 128.3, 127.0, 67.0, 55.4, 54.0, 52.5, 41.0, 31.8, 24.9, 24.8, 24.0. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.78; H, 8.59; N, 5.67.

Spectral data of 1, X = O[17]. ^{1}H NMR: δ 4.32-4.27 (1H, m), 3.78-3.70 (1H, m), 3.25-3.18 (1H, m), 2.76-2.67 (1H, m), 2.35-2.31 (1H, m), 2.24-2.20 (1H, m), 2.11-2.07 (1H, m), 2.02-1.98 (1H, m), 1.83-1.74 (2H, m), 1.52-1.44 (1H, m), 1.32-1.18 (3H, m); ^{13}C NMR: δ 207.9, 82.2, 67.5, 56.1, 42.7, 33.1, 24.6, 24.2, 23.0. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.96; H, 9.06.

Spectral data of 1, X = S[16b]. ^{1}H NMR: δ 3.08-3.00 (1H, m), 2.91-2.85 (1H, m), 2.85-2.78 (1H, dt, *J* = 11.5, 3.5 Hz), 2.74-2.66 (2H, m), 2.45-2.39 (1H, dt, *J* = 11.0, 3.5 Hz), 2.03-1.94 (2H, m), 1.85-1.76 (2H, m), 1.52-1.42 (1H, m), 1.36-1.25 (3H, m); ^{13}C NMR: δ 209.9, 57.6, 49.0, 44.0, 32.9, 29.6, 25.8, 25.3, 25.0. Anal. Calcd for $C_9H_{14}OS$: C, 63.48; H, 8.29. Found: C, 63.30; H, 8.16.

Spectral data of 1a, X = NBn[15,16a]. ^{1}H NMR: δ 7.33-7.23 (5H, m), 4.08 (1H, d, *J* = 13.5 Hz), 3.21-3.15 (1H, m), 3.19 (1H, d, *J* = 13.5 Hz), 2.85-2.81 (1H, td, *J* = 12.0, 3.5 Hz), 2.29-2.23 (1H, m), 2.20-2.15 (1H, m), 2.06-2.00 (1H, dt, *J* = 12.4, 2.4 Hz), 1.90-1.65 (5H, m), 1.60-1.50 (1H, m), 1.32-1.17 (4H, m), 0.99-0.89 (1H, m); ^{13}C NMR: δ 139.0, 129.1, 128.2, 126.8, 73.4, 64.4, 56.5, 50.9, 49.3, 34.4, 30.6, 28.1, 25.4, 25.3. Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.15; H, 9.29; N, 5.64.

Spectral data of 1a, X = O. ^{1}H NMR: δ 4.02-3.97 (1H, ddd, *J* = 11.7, 4.9, 1.7 Hz), 3.53-3.46 (1H, dt, *J* = 13.3, 2.2 Hz), 3.43-3.36 (1H, dt, *J* = 14.6, 4.6 Hz), 2.96-2.90 (1H, dt, *J* = 10.5, 4.2 Hz), 2.17-2.12 (1H, m), 1.95-1.88 (2H, m), 1.80-1.55 (4H, m), 1.35-1.12 (4H, m), 0.98-0.97 (1H, m). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.10; H, 10.25.

Spectral data of 1a, X = S. ^{1}H NMR: δ 3.20-3.14 (1H, ddd, *J* = 11.0, 9.9, 4.0 Hz), 2.83-2.75 (1H, dt, *J* = 13.3, 2.5 Hz), 2.61-2.56 (1H, td, *J* = 13.7, 3.7 Hz), 2.55-2.49 (1H, m), 2.29-2.24 (2H, m), 1.88-1.65 (4H, m), 1.37-1.29 (4H, m), 0.97-0.87 (1H, m); ^{13}C NMR: δ 74.5, 51.6, 45.5, 37.2, 32.0, 28.7, 27.4, 26.3, 25.7. Anal. Calcd for $C_9H_{16}OS$: C, 62.74; H, 9.36. Found: C, 62.57; H, 9.20.

Spectral data of 1b, X = S. ^{1}H NMR: δ 3.82 (1H, br s), 3.22-3.14 (1H, dt, *J* = 13.4, 2.7 Hz), 3.00-2.93 (1H, dt, *J* = 10.4, 3.5 Hz), 2.31-2.26 (1H, td, *J* = 13.4, 3.5 Hz), 2.16-2.10 (1H, qd, *J* = 13.9, 3.5 Hz), 1.94-1.86 (1H, ddt, *J* = 13.4, 3.9, 2.2 Hz), 1.84-1.73 (4H, m), 1.56-1.22 (5H, m); ^{13}C NMR: δ 69.5, 48.0, 38.6, 35.0, 32.5, 30.3, 26.32, 26.27, 22.7. Anal. Calcd for $C_9H_{16}OS$: C, 62.74; H, 9.36. Found: C, 62.60; H, 9.26.

Spectral data of the *p*-bromobenzoate of 1a, X = NBn. ^{1}H NMR: δ 7.90-7.88 (2H, d, *J* = 8.5 Hz), 7.58-7.56 (2H, d, *J* = 8.5 Hz), 7.32-7.30 (5H, m), 4.74-4.67 (1H, m), 4.14-4.10 (1H, d, *J* = 13.5 Hz), 3.22-3.18 (1H, d, *J* = 13.5 Hz), 2.90-2.86 (1H, m), 2.32-2.27 (1H, m), 1.19-2.13 (1H, t, *J* = 12.4 Hz), 2.07-1.97 (2H, m), 1.92-1.82 (2H, m), 1.77-1.60 (2H, m), 1.33-1.20 (4H, m), 1.03-0.95 (1H, m). Anal. Calcd for $C_{23}H_{26}BrNO_2$: C, 64.49; H, 6.12. Found: C, 64.40; H, 6.05.

Spectral data of the *p*-bromobenzoate of 1a, X = O. ^{1}H NMR: δ 7.90 (2H, d, *J* = 8.3 Hz), 7.58 (2H, *J* = 8.3 Hz), 4.91-4.85 (1H, dt, *J* = 10.7, 4.6 Hz), 4.07-4.02 (1H, ddd, *J* = 11.8, 5.0, 1.6 Hz), 3.64-3.58 (1H, dt, *J* = 12.2, 2.0 Hz), 3.12-3.06 (1H, dt, *J* = 10.1, 4.1 Hz), 2.12-1.67 (6H, m), 1.59-1.50 (1H, m), 1.43-1.17 (3H, m), 1.02-0.92 (1H, dq, *J* = 12.7, 3.6 Hz); ^{13}C

NMR: δ 165.5, 131.7, 131.1, 129.2, 128.0, 79.7, 75.2, 65.2, 47.3, 32.6, 32.3, 27.2, 25.1, 24.6. Anal. Calcd. for $C_{16}H_{19}BrO_3$: C, 56.65; H, 5.65. Found: C, 56.56; H, 5.52.

Spectral data of the *p*-bromobenzoate of 1b, X = O. ^{1}H NMR: δ 7.93 (2H, d, *J* = 8.2 Hz), 7.61 (2H, d, *J* = 8.2 Hz), 5.28-5.26 (1H, q, *J* = 2.7 Hz), 3.90-3.80 (2H, m), 3.57-3.50 (1H, m), 2.09-1.98 (2H, m), 1.91-1.87 (1H, md, *J* = 15.9 Hz), 1.80-1.76 (1H, m), 1.70-1.65 (1H, m), 1.62-155 (1H, m), 1.35-1.19 (5H, m). Anal. Calcd for $C_{16}H_{19}BrO_3$: C, 56.65; H, 5.65. Found: C, 56.54; H, 5.60.

Spectral data of the *p*-bromobenzoate of 1a, X = S. ^{1}H NMR: δ 7.91-7.89 (2H, d, *J* = 8.6 Hz), 7.60-7.58 (2H, d, *J* = 8.6 Hz), 4.76-4.69 (1H, dt, *J* = 11.0, 4.1 Hz), 2.95-2.88 (1H, dt, *J* = 13.5, 2.& Hz), 2.69-2.61 (2H, m), 2.41-2.36 (1H, m), 1.97-1.71 (6H, m), 1.34-1.29 (3H, m), 1.02-0.94 (1H, m); ^{13}C NMR: δ 165.3, 131.7, 131.1, 129.2, 128.1, 77.2, 49.0, 45.6, 33.8, 32.0, 28.8, 27.2, 26.2, 25.6.

Conclusion

In conclusion, aza-**1** exhibits the highest axial selectivity[15] and thia-**1** the lowest among **1**, X = NBn, O, S. This contradicts the n→σ*# hypothesis proposed previously. Ab initio MO calculations of the TSs formed from 2-heterobicyclo[4.4.0]decan-5-ones and LiH do not show such n→σ*# interactions. Similar results were obtained from the study of simpler analogs, *e.g.*, 4-aza-cyclohexanone, 4-oxa-cyclohexanone and 4-thia-cyclohexanone. Both the *early* TSs formed from LiH and the *late* TSs formed from LiCN were devoid of n→σ*# interactions. The observed relative axial selectivity of aza-**1**, oxa-**1**, thia-**1**, and carba-**1** is explained reasonably well by the differential σ_{vicinal}→π*_{C=O} interactions. The possible hydrogen bonding of the nitrogen in aza-**1** with the reaction medium is expected to contribute to its higher axial selectivity than oxa-**1**.

Acknowledgements

References

1 Geneste P, Durand R, Hugon I & Reminac C, *J Org Chem*, 44, **1979**, 1971.

2 (a) Cieplak A S, *J Am Chem Soc*, 103, **1981**, 4540; (b) Cieplak A S, Tait B D & Johnson C R, *J Am Chem Soc*, 111, **1989**, 8447.

3 Deslongchamps P, in *Stereoelectronic Effects in Organic Chemistry*, edited by Baldwin J E, (Pergamon, New York) **1983**, Vol. 1, Chapters 2 and 3.

4 Aue D H, Webb H M & Bowers M T, *J Am Chem Soc*, 98, **1976**, 311.

5 NBO 5.0: Glendening E D, Badenhoop J K, Reed A, Carpenter J E, Bohmann J A, Morales C M & Weinhold F (Theoretical Chemistry Institute, University of Wisconsin, Madison, WI, **2001**; http://www.chem.wisc.edu/~nbo5).

6 Gaussian 98 (revision A.11.1). Frisch M J, Trucks G W, Schlegel H B, Scuseria G E, Robb M A, Cheeseman J R, Zakrzewski V G, Montgomery J A, Stratmann, Jr, R E, Burant J C, Dapprich S, Millam J M, Daniels A D, Kudin K N, Strain M C, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Jochterski J, Petersson G A, Ayala P Y, Cui Q, Morokuma K, Salvador P, Dannenberg J J, Malick D K, Rabuck A D, Raghavachari K, Foresman J B, Cioslowski J, Ortiz J V, Baboul A G, Stefanov B B, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin R L, Fox D J, Keith T, Al-Laham M A, Peng C Y, Nanayakkara A, Challacombe M, Gill P M W, Johnson B, Chen W, Wong M W, Andres J L, Gonzalez C, Head-Gordon M, Replogle E S & Pople J A *Gaussian Inc*, (Pittsburgh, PA) **2001**.

7 (a) Mehta G, Ravikrishna C, Ganguly B & Chandrasekhar J, *Chem Commun*, **1997**, 75; (b) Gung B W, *Tetrahedron*, 52, **1996**, 5263; (c) Shi Z & Boyd R, *J Am Chem Soc*, 115, **1993**, 9614; (d) Wong S S & Paddon-Row M N, *Chem Commun*, **1991**, 327; (e) Kaufman E, Schleyer P v R, Houk K N & Wu Y-D, *J Am Chem Soc*, 107, **1985**, 5560.

8 Parvez M, Yadav V K & Balamurugan R, *Acta Cryst*, C57, **2001**, 1084.

9 Yadav V K, Ganesh Babu K & Parvez M, *J Org Chem*, 69, **2004**, 3866.

10 (a) The electron-donating ability of σ-bonds increases in the order: σ_{C-O} < σ_{C-C} < σ_{C-H} < σ_{C-S}; (b) Epiotis N D, Cherry W R, Shaik S, Yates R L, Bernardi F, *Top Curr Chem*, 70, **1977**, 250; (c) Yadav V K, *J Org Chem*, 66, **2001**, 2501; (d) Yadav V K, Sriramurthy V, *Tetrahedron*, 57, **2001**, 3987; (e) Yadav V K, Jeyaraj D A & Parvez M, *J Chem Soc Perkin Trans 1*, **2000**, 1423; (f) Yadav V K, Jeyaraj D A & Balamurugan R, *Tetrahedron*, 56, **2000**, 7581; (g) Yadav V K, Senthil G & Jeyaraj D A, *Tetrahedron*, 55, **1999**, 14211; (h) Yadav V K, Jeyaraj D A, Parvez M & Yamdagni R, *J Org Chem*, 64, **1999**, 2928; (i) Jeyaraj D A, Yadav V K, Parvez M & Gauniyal H M, *J Org Chem*, 63, **1998**, 3831; (j) Jeyaraj D A & Yadav V K, *Tetrahedron Lett*, 38, **1997**, 6095; (k) Jeyaraj D A, Yadav A & Yadav V K, *Tetrahedron Lett*, 38, **1997**, 4483.

11 (a) Hahn J M & le Noble W J, *J Am Chem Soc*, 114, **1992**, 1916; (b) For the electrophilic activation of aldehydes by hydrogen bonding, see: Ameer F, Drews S E, Freese S & Kaye P T, *Synth Commun*, 18, **1988**, 495; (c) Marku I E, Giles P R & Hindley N T, *Tetrahedron*, 53, **1997**, 1015; (d) Yamada Y M A & Ikegami S, *Tetrahedron Lett*, 41, **2000**, 2165.

12 (a) Yadav V K & Singh L, *J Org Chem*, 70, **2005**, 692; (b) Yadav V K, Ganesh Babu K & Balamurugan R, *Tetrahedron Lett*, 44, **2003**, 6617; (c) Yadav V K & Balamurugan R, *J Org*

Chem, 67, **2002**, 587; (d) Yadav V K & Balamurugan R, *J Chem Soc Perkin Trans 2*, **2001**, 1.

13 These calculations were performed first by keeping the N…H distance fixed at 2.10 Å which was relaxed during the final geometry optimization. This distance changed to 2.076 Å, 2.079 Å, and 1.941 Å at HF/6-31G*, HF/6-31+G*, and B3LYP/6-31G* levels, respectively.

14 Wu Y D,Tucker J A & Houk K N, *J Am Chem Soc*, 113, **1991**, 5018.

15 For the exclusive axial reduction of **1**, X = NCH₂Ph with (*i*-PrO)₃Al, see: Marshall J A & Babler J H, *J Org Chem*, 34, **1969**, 4186.

16 (a) Prost M, Urbain M, Schumer A, Houben C & Meerbeeck C V, *Helv Chim Acta*, 58, **1975**, 40; (b) Ding Z & Tufariello J J, *Synth Commun*, 20, **1990**, 227.

17 (a) Kozikowski A P & Li C-S, *J Org Chem*, 50, **1985**, 778; (b) Dolmazon R & Gelin S, *J Org Chem*, 49, **1984**, 4003; (c) Hirsch J A & Schwartzkopf G, *J Org Chem*, 39, **1974**, 2040.