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Debromination of *endo-(+)-3-Bromocamphor with Primary Amines*

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A desbromação redutiva da *endo*-(+)-3-bromocânfora com diferentes aminas primárias seguida da formação de imina foi investigada. Esta reação requer procedimento experimental simples sem qualquer solvente orgânico, metal ou agente de redução convencional. Observou-se uma forte influência da polaridade da amina na eficiência do processo de desbromação, e que etanolamina e etilenodiamina tendo pontos de ebulições elevados o suficiente podem desbromação da 3-bromocânfora com etanolamina e *n*-hexilamina foram investigados no nível B3LYP/6-311+G(d,p). Revelou-se o mecanismo radical, e que a reação com etanolamina mais polar é energeticamente mais favorável.

Reductive debromination of *endo*-(+)-3-bromocamphor with different primary amines followed by imine formation was investigated. This reaction requires simple experimental procedure without any organic solvent, metal or conventional reducing agent. A strong influence of amine polarity on the efficacy of debromination process was observed, and ethanolamine and ethylene diamine having sufficiently high boiling points can debrominate 3-bromocamphor giving corresponding camphanimines in good isolated yields. The mechanisms of debromination of 3-bromocamphor with ethanolamine and *n*-hexylamine were investigated at the B3LYP/6-311+G(d,p) level of theory. The radical mechanism was revealed, and it was shown that the reaction with more polar ethanolamine is energetically more favorable.

Keywords: 3-bromocamphor, primary amines, reductive debromination, reaction mechanism, DFT

Introduction

The debromination of α -bromoketones plays an important role in the synthetic organic chemistry as one of the most useful reaction for the construction of more complex organic molecules. A number of reagents have been reported for the debromination of α -bromocarbonyl compounds such as triphenylphosphine,¹ pyridinium salts,² molybdenum hexacarbonyl,³ sodium iodide-chlorotrimethylsilane,⁴ triphenylphosphonium iodide,⁵ sodium borohydride-antimony tribromide,⁶ sodium

amalgam,⁷ tributyltin hydride,⁸ zinc in acetic acid,⁹ aqueous titanium trichloride,¹⁰ tellurium reagents,¹¹ nickel boride,¹² selenium,¹³ sodium dithionite,¹⁴ inorganic phosphorus compounds¹⁵ and ionic liquids.¹⁶

On the other hand, a central need of different synthetic transformations in the last years, especially in pharmaceutical industry, is the preparation of compounds that are derived from the chiral sources. Among these compounds, *vic*-amino alcohols obtained from D-camphor¹⁷ and ketimines prepared from camphor-imine¹⁸ serve as template for many applications in asymmetric synthesis. Camphor-based imino alcohols are precursors for preparation of chiral aryl phosphates in the role of

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P, *N*-bidentate ligands for asymmetric catalysis by metal complexes.¹⁹

In conjunction with these facts, herein we report the synthesis of a series of imino compounds containing camphane scaffold derived from *endo*-(+)-3-bromocamphor, accompanied with its simultaneous reductive debromination. In addition, a mechanism for the model reaction, i.e., that of 3-bromocamphor with ethanolamine, is proposed.

Experimental

Materials and methods

All amines were obtained from commercial sources and distilled before use while *endo*-(+)-3-bromocamphor was purchased from Fluka and used without further purification. Melting points were determined on a Mel-Temp capillary melting point apparatus, model 1001 and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum One FTIR spectrometer. All ¹H and ¹³C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III 500 MHz spectrometer. The full assignments of all reported NMR signals were made by use of 1D and 2D NMR experiments.

X-ray crystal structure determination

Single colorless crystal was selected and glued on glass fiber. Diffraction data were collected on an Oxford Diffraction KM4 four-circle goniometer equipped with Sapphire CCD detector. The crystal to detector distance was 45.0 mm and a graphite monochromated Mo K_{α} ($\lambda = 0.71073$ Å) radiation was employed in the measurement. The frame width of 1° in ω , with experimental time of 2.5 s was used to acquire each frame. More than one hemisphere of three-dimensional data was collected in the measurement. The data were reduced using the Oxford Diffraction program CrysAlis^{Pro.20} A semiempirical absorption-correction based upon the intensities of equivalent reflections was applied,²¹ and the data were corrected for Lorentz, polarization and background effects. Scattering curves for neutral atoms, together with anomalous-dispersion corrections, were taken from International Tables for X-ray Crystallography.²² The structure was solved by direct methods,²³ and the figures were drawn using Mercury.²⁴ Refinements were based on F^2 values and done by full-matrix least-squares²⁵ with all non-H anisotropic atoms. The positions of all non-H atoms were located by direct methods. The positions of hydrogen atoms were found from the inspection of the difference Fourier maps. The final refinement included atomic positional and displacement parameters for all non-H

atoms. At the final stage of the refinement, H atoms were positioned geometrically (O–H = 0.82, N–H = 0.86 and C–H = 0.96-0.98 Å) and refined using a riding model with fixed isotropic displacement parameters. Crystallographic data for the structural analysis were deposited with the Cambridge Crystallographic Data Centre, CCDC No. 824664 for compound 2_A .

General procedure for synthesis of debrominated imines 2_{A-F}

A mixture of *endo*-(+)-3-bromocamphor (1.156 g, 5 mmol) and corresponding amine (50 mmol) in a 25 mL round-bottomed flask was heated at 130-135 °C in an oil bath for 12 or 24 h. After removal of the excess of the amine under reduced pressure, 30 mL of water were added and the mixture was extracted with ether (40 mL). The organic layer was washed with water (2 × 30 mL). After drying with anhydrous sodium sulfate, the solvent was evaporated and pure compounds were isolated by column chromatography on silica gel using different eluent mixtures.

Computational details

All calculations were conducted using the Gaussian 09 program package, Revision A.02²⁶ at the B3LYP/6-311+G(d,p) level of theory.^{27,28} This triple split valence basis set adds p functions to hydrogen atoms in addition to the d and diffuse functions on heavy atoms. The geometries of all participants in the reactions with ethanolamine (dielectric constant = 30.83)²⁹ and *n*-hexylamine (dielectric constant = 4.08)³⁰ were fully optimized by applying the conductor-like polarizable continuum (CPCM) solvation model.^{31,32} All radical species were evaluated by using an unrestricted scheme in order to take spin polarization into account. Vibrational analysis was performed for all structures. All calculated structures were confirmed to be energy minima (all real vibrational frequencies) for equilibrium structures, or first-order saddle points (one imaginary vibrational frequency) for transition state structures. To verify that each transition state is linked with two putative minima, the intrinsic reaction coordinates (IRCs), from the transition states down to the two lower energy structures, were traced using the IRC routine in Gaussian. The natural bond orbital (NBO) analysis was performed for all structures using the GenNBO 5.0 program.³³ Relative energies for the reactions with ethanolamine and n-hexylamine were calculated at 385 and 405 K (112 and 122 °C), respectively (experimental temperatures).

To estimate homolytic dissociation enthalpies of the C–Br and C–H bonds in some participants the gas-phase



Figure 1. Isodesmic reactions used to estimate the C–Br and C–H bond dissociation enthalpies. The predicted values for all homolytic bond dissociation enthalpies are given.

isodesmic reactions at 298 K (25 $^{\circ}$ C) were constructed (Figure 1).

The homolytic dissociation enthalpies were calculated as follows:

$\Delta H_{C-Br} = \Delta H_r + 293 \text{ kJ mol}^{-1}$	(11)
$\Delta H_{C-H} = \Delta H_r + 435 \text{ kJ mol}^{-1}$	(12)

In equations 11 and 12, ΔH_{C-Br} and ΔH_{C-H} stand for the homolytic dissociation enthalpies of the C–Br and C–H bonds, respectively, ΔH_r represents the calculated enthalpy of a given isodesmic reaction, 293 kJ mol⁻¹ is the experimental value for the enthalpy of homolytic cleavage of the C–Br bond in methyl bromide, and 435 kJ mol⁻¹ is the experimental value for the enthalpy of homolytic cleavage of the C–H bond in methane.³⁴ Both experimental enthalpies refer to the gas phase at 25 °C.

Results and Discussion

The secondary and tertiary amines are known as dehalogenating agents. The reduction of α -bromocamphor

has been reported to yield camphor in the presence of *N*,*N*-dimethylaniline at 200 $^{\circ}$ C.³⁵ The reduction can be affected at much lower temperatures in the presence of di-tert-butylperoxide in acetonitrile.36 In the reaction of α -bromocamphor with N-methylaniline as a debrominating agent, hydrocarbon camphane, tricyclene and bornylaniline were formed.37 However, an attempt to use primary amines as debrominating agents had never previously been reported in the literature. To the best of our knowledge, only ethanolamine gave N-(2-hydroxyethyl)camphanimine in the reaction with 3-bromocamphor, but in presence of copper as dehalogenating agent.³⁸ In addition, it is noteworthy to point out that condensation of camphor with primary amines requires long reaction time and high temperatures in order to achieve reasonable yields of the desired imines.^{39,40} On the basis of our investigation of this synthetic methodology, here it is reported several representative examples of the synthesis of N-substituted camphanimines using α -bromocamphor as chiral bicyclic ketone precursor (Scheme 1).



Scheme 1. Reductive debromination of *endo-*(+)-3-bromocamphor with some primary amines accompanied with imine formation.

Our initial research was focused on the study of solvents, temperature and 3-bromocamphor/ethanolamine molar ratio in order to establish the optimal reaction conditions for one-pot reductive debromination followed by Schiff base formation. After a number of attempts to perform the reaction in solvents of different polarity and boiling points, it was found that ethanolamine reacts only in refluxing xylene after 24 h giving the desired product in very low isolated yield (7%). However, in the absence of solvent, the reaction became facile, and after 12 h of heating at 130-135 °C (temp. of oil bath) imine 2_A was isolated in 73% yield (Table 1). Due to poor solubility of 3-bromocamphor

in ethanolamine and its partial sublimation, it was necessary to return it in the reaction flask mechanically from time to time. To overcome this problem, a Schlenk bomb was used to provide a closed reaction system. It is important to note that there was no significant difference in the vields, but the time required for the complete conversion of 3-bromocamphor was prolonged by additional 12 h. The molar ratio 3-bromocamphor/ethanolamine 1:10 was found to be optimal for this reaction. The decreasing of this ratio leads to extended reaction time while the increasing affords lower yields. With optimized reaction conditions, the debromination and imine formation were explored using primary amines with different polarities and boiling points. To successfully carry out this reaction, the superior results were obtained by selection of polar amine with sufficiently high boiling point in the role of reactant and solvent. For example, in comparison with *n*-hexylamine, as a consequence of the similar polarity but a lower boiling point, n-butylamine did not react with 3-bromocamphor even after extended time of heating.

The reaction of ethylene diamine also proceeded smoothly to afford products 2_B and 2_C in 47 and 29% yields, respectively. A better yield of 2_B is possible to achieve by increasing of the amine/3-bromocamphor molar ratio. The absence of the desired debrominated product in reaction of 2-amino-2-methyl-1-propanol clearly suggests a crucial role of the substituent size for successful debromination of *endo*-(+)-3-bromocamphor. Aniline reacted with 3-bromocamphor only at elevated temperature leading to low yield of debrominated product (16%) together with camphor (11%), significant amount of diphenylamine and resinous material of undefined composition.

The compound 2_A is selected as an illustrative example for the structure elucidation and ¹H and ¹³C NMR assignments of all signals of the bicyclic skeleton. The downfield signal in the ¹H NMR spectrum (δ 2.35 ppm) must be 3H_a or 3H_a as a consequence of the proximity to the imino group. That it is 3H_a can be established by the connectivities in the correlation spectroscopy (COSY) spectrum in which this low field signal has three cross peaks which correspond to coupling to $3H_a$ (δ 1.84 ppm), 4H (δ 1.95 ppm) and 5H_e (δ 1.89 ppm). These assignments are confirmed by ¹H NMR signals for 3H₂ and 4H. 3H₂ is a doublet (J 17.00 Hz, geminal coupling), though coupling to the vicinal 4H might be expected. However, 3H, and 4H showed absolutely no coupling, indicating a dihedral angle of approximately 90° between them. Similarly, the dihedral angle between 4H and 5H_a is approximately 90°, thus, this coupling constant is also 0 Hz.

Consequently, on the basis of two cross peaks in the COSY spectrum, 4H is only coupled to two $(3H_e \text{ and } 5H_e)$

Amine	3-BrC ^a /Amine molar ratio	time / h	Temperature / °C	Conversion of 3-BrC ^b / %	Products	Isolated yield / %
Ethanolamine	1:25	12	130-135°	> 99	2 _A	70 ^d
Ethanolamine	1:10	12	130-135°	> 99	2 _A	73 ^d
Ethylene diamine	1:25	12	reflux ^e	> 99	$2_{_{\mathrm{B}}}$ and $2_{_{\mathrm{C}}}$	79 ^f
Ethylene diamine	1:10	12	reflux ^e	> 99	2_{B} and 2_{C}	76 ^g
Aniline	1:10	12	130-135 ^h	0	-	_
Aniline	1:10	24	170-175 ^h	> 99	2 _D ⁱ	16
n-Butylamine	1:10	36	reflux ^j	0	-	-
<i>n</i> -Hexylamine	1:10	24	reflux ^k	35	$2_{\rm E}$	26
Cyclohexylamine	1:10	24	reflux ¹	21	$2_{\rm F}$	14
AMP^m	1:10	24	130-135 ⁿ	0	_	_

Table 1. Optimization of reaction conditions for the synthesis of camphanimine derivatives

^a3-Bromocamphor; ^bdetermined by NMR; ^ctemperature of oil bath, b.p. (amine) = 170 °C; ^dSchlenk bomb is used to provide a closed reaction system; ^eb.p. (amine) = 118 °C; ⁶61% ($\mathbf{2}_{B}$) and 18% ($\mathbf{2}_{C}$); ^g47% ($\mathbf{2}_{B}$) and 29% ($\mathbf{2}_{C}$); ^btemperature of oil bath, b.p. (amine) = 184 °C; ⁱ11% of camphor was isolated. Large amount of diphenylamine was detected; ^jb.p. (amine) = 78 °C; ^kb.p. (amine) = 131-132 °C; ⁱb.p. (amine) = 134 °C; ^m2-amino-2-methyl-1-propanol; ^mtemperature of oil bath, b.p. (amine) = 165 °C.

of four neighbors and the signal is observed to be a triplet. In addition, a strong NOESY (nuclear Overhauser effect spectroscopy) cross peak was observed between $3H_e$ and C9 methyl protons at 0.75 ppm, whereas none of methyl groups gave NOESY cross peak with doublet at 1.84 ppm assigned to $3H_a$, confirming that dt at 2.35 ppm is on the *exo* face away from the *gem*-dimethyl bridge.

The quaternary carbon atoms C1 and C7 are assigned using DEPT (distortionless enhancement by polarization transfer), one-bond (HSQC) and long-range (HMBC) ¹H-¹³C NMR correlation experiments. Both carbons at 47.05 and 53.75 ppm display HMBC correlations with all methyl protons but only signal at 47.05 ppm shows a strong correlation with 3H_a and weaker one with 6H_a. In the ¹H, ¹⁵N HMBC spectrum nitrogen shows strong couplings to C12 protons and 3H_a (–97.8 ppm in F₁ and 1.84 ppm in F₂) as well as one weak correlation with 3H_e (–97.8 ppm in F₁ and 2.35 ppm in F₂). Finally, the HMBC spectrum showed a strong three-bond correlation between C10 methyl protons and imino group.

An additional confirmation of the structure of 2_A is provided by an X-ray analysis. Suitable crystals for X-ray measurements are obtained by fast cooling of the solution of 2_A in hexane at -20 °C. An ORTEP presentation of 2_A is given in Figure 2. The crystallographic data, the data collection parameters and the refinement parameters for compound 2_A are summarized in Table 2. Selected molecular structural parameters and hydrogen bond geometrical parameters for 2_A are given in Tables 3 and 4, respectively.

Our assumption for the most probable mechanism of the debromination of 3-bromocamphor is outlined in



Figure 2. ORTEP type view of the asymmetric unit of 2_A together with the atoms labeling scheme and displacement ellipsoids at the 50% probability level.

Scheme 2. Initially, 3-bromocamphor 1 adds one mole of primary amine to generate the intermediate Schiff base adduct $\mathbf{3}_{\mathbf{R}}$. The ionic mechanism of debromination of 3-bromocamphor Schiff base 3_{R} is not considered because the conventional literature mechanisms for typical $S_N 1$, $S_N 2$ or elimination reactions are not in accordance with the obtained experimental products. As a thermal decomposition of 3-bromocamphor itself at 200 °C yields only a small amount of camphor,³⁵ it is not reasonable to expect a homolytic cleavage of the C-Br bond and formation of free radicals at operating temperatures. In agreement with this reasoning is our numerous unsuccessful attempts to reveal a transition state for either homolytic cleavage of the C–Br bond in $\mathbf{3}_{A}$, or C–H bond in ethanolamine. However, a relevant number of initiating radicals (I' in Scheme 2) can be formed at these temperatures (but not at

Empirical formula	C ₁₂ H ₂₁ NO
$M / (\text{g mol}^{-1})$	195.3
Temperature / K	295
Wavelength / Å	0.71073
Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
Unit cell dimensions / Å	a = 8.5206(6) b = 9.6686(5) c = 14.0849(9)
Volume / Å ³	1160.40 (13)
Mosaicity / degree	0.796(2)
Z	4
$D_{calc} / (g m L^{-1})$	1.115
Absorption coefficient / mm ⁻¹	0.07
F(000)	432
Crystal size / mm	$0.19\times0.12\times0.09$
Color/Shape	colorless/prism
θ range / degree 3.55-24.99	
Index ranges –h +h; –k +k; –l +l	-4 +10; -6 +11; -16 +16
Reflections collected	2804 ($R_{int} = 0.0143$)
Unique reflections	1919
Refinement methods	Full matrix L.S. on F^2
Data/restraints/parameters	1919/0/132
Goodness-of-fit on F^2	0.981
Final R indices $[F_o > 4\sigma F_o]$	R1 = 0.0406 (1789)
R indices (all unique data)	R1 = 0.0445, wR2 = 0.1133
Extinction coefficient	0.088(12)
Larg.diff. peak and hole / (e $Å^{-3}$)	0.156 and -0.126

Table 2. Selected crystallographic data for 2_A

Table 3. Geometric parameters for 2_A

78 °C as it was found for *n*-butylamine) in the reactions of 3-bromocamphor or amine and reactive oxygen species generated by electron-transfer or energy-transfer processes. Hydroperoxides, like RCH(NH₂)OOH formed in early stages of amine compound oxidation, decompose readily at ca. 120-130 °C giving reactive radical species.⁴¹ Relevant to question of mechanism is the observation that reaction performed in a closed Schlenk apparatus requires a significantly longer time due to insufficient amount of oxygen gas in the system. It is reasonable to expect that these initiating radicals can trigger chain reactions leading to the products of the reactions of 3-bromocamphor with primary amines. According to the predicted bond dissociation enthalpies in Figure 1, C-H bonds in both amines are much stronger than C-Br bonds in the Schiff bases $\mathbf{3}_{A}$ and $\mathbf{3}_{E}$. If it is assumed that reactivity of I' towards present reactants (3_{R} or amine) is inversely proportional to the bond strengths, it turns out that the initiation reaction will be abstraction of Br. from $\mathbf{3}_{\mathbf{R}}$ by **I**, leading to the formation of radical $\mathbf{4}_{\mathbf{R}}$. This radical abstracts H[•] from the amine yielding the product 2_{R} and radical 'RNH₂, which further takes Br[•] from $\mathbf{3}_{\mathbf{R}}$, forming again radical $\mathbf{4}_{\mathbf{R}}$. (Scheme 2). To confirm this assumption, the transformation of $\mathbf{3}_{A}$ and $\mathbf{3}_{E}$ was examined by means of density functional theory (DFT). Ethanolamine and n-hexylamine are selected as reactants with sufficiently high boiling points but of different polarity to possibly explain much lower yield of the reaction with *n*-hexylamine.

Bond le	ength / Å	Bond angle / degree		Torsion angle / degree	
C1-C6	1.5135 (27)	C1-C6-O	109.80 (15)	C1-N-C3-C4	-178.97 (16)
C1–N	1.4710 (25)	C1-N-C3	118.41 (16)	C2-C3-C4-C5	-35.01 (17)
C2–C3	1.5190 (25)	C2-C3-N	129.83 (17)	C2-C3-C4-C7	-162.12 (16)
C2-C10	1.5289 (30)	C2-C10-C5	102.72 (14)	C2-C3-C4-C12	70.00 (18)
C3–C4	1.5188 (26)	C2-C10-C11	106.14 (16)	C2-C10-C11-C12	70.65 (20)
C3–N	1.2693 (24)	C3-C2-C10	102.35 (15)	C3-C2-C10-C5	35.09 (16)
C4–C5	1.5688 (25)	C3-C4-C5	100.39 (15)	C3-C2-C10-C11	-72.36 (18)
C4–C7	1.5211 (29)	C3-C4-C7	115.76 (17)	C4-C5-C10-C2	-54.82 (15)
C4-C12	1.5495 (28)	C3-C4-C12	104.21 (16)	C5-C10-C11-C12	-36.82 (20)
C5-C10	1.5454 (29)	C4-C5-C10	93.48 (14)	C5-C4-C3-N	144.99 (16)
C6–O	1.4090 (25)	C4-C12-C11	104.65 (16)	C8-C5-C10-C2	-173.30 (17)
C10-C11	1.5452 (29)	C5-C4-C12	101.70 (15)	C9-C5-C10-C2	62.32 (18)
C11-C12	1.5334 (36)	C5-C10-C11	102.70 (17)	C10-C2-C3-N	-179.49 (18)
		C6-C1-N	111.88 (15)	C12-C4-C3-N	-109.99 (20)
		C7-C4-C12	115.43 (17)	N-C1-C6-O	-70.31 (20)
		C10-C11-C12	102.80 (17)	C1-N-C3-C4	-178.97 (16)

Table 4. Hydrogen-bond geometry for 2_A

D—H…A	<i>D</i> —H / Å	H…A / Å	<i>D</i> … <i>A</i> / Å	D—H…A /degree
O—H0…N ⁱ	0.82	2.02	2.837	170.83

Symmetry codes: (i) -x + 1, y + 1/2, -z + 3/2.



Scheme 2. A suggested mechanism for reductive debromination followed by imine formation.

In the step 13 with ethanolamine, hydrogen atom can be abstracted from C11 or C12 (Scheme 1), implying that two radicals can be produced: 'A1NH₂ or 'A2NH₂ (Figure 1). Similarly, six radicals ('E1NH₂ - 'E6NH₂) can be formed upon abstraction of hydrogen atom from different carbons of *n*-hexylamine. In this work, abstraction of hydrogen from both C11 and C12 of ethanolamine as well as from C11 and C13 of *n*-hexylamine were examined. Note that C11–H is the weakest C–H bond in both amines (Figure 1). In addition, all corresponding pathways 14 were investigated. The revealed transition states are presented in Figure 3, whereas the optimized geometries of corresponding reactants and products are depicted in the Supplementary Information (SI) section. In Table 5, the relevant relative free energies, as well as activation enthalpies and entropy terms, are listed.

The NBO analysis of 4_{R} , shows that the unpaired electron is delocalized between C3 and imine nitrogen. In $TS1_R$ (Figure 3), a C–H bond in amine is being cleaved, whereas the C3–H bond is being formed. Step 13 yields the product of the overall reaction 2_R and an amine radical. Due to the vicinity of electron donating amino group which stabilizes electron deficient C11, 'A1NH₂ is by 21.1 kJ mol⁻¹ more stable than 'A2NH₂, and 'E1NH₂ is by 24.0 kJ mol⁻¹ more stable than 'E3NH₂. As a consequence, abstraction of hydrogen from C11 of both amines is less endothermic (Table 5). A radical formed in step 13 abstracts bromine atom from 3_R via transition state $TS2_R$. In $TS2_R$, a simultaneous cleavage of the C3–Br bond in 3_R and formation of the

bond between bromine and corresponding carbon in **'RNH**₂ occur. Elementary step 14 is exothermic, and yields a bromide and radical $\mathbf{4}_{R}$ which is again involved in step 13, thus propagating the chain reaction.

In all transition states, spin density is distributed among C3, imine nitrogen and corresponding carbon of the amine. In transition states with ethanolamine, delocalization of the unpaired electron also involves the amine oxygen. In addition, in transition states involving C11, significant spin density values on the nitrogen of the amino group were observed. Due to better delocalization of the unpaired electron, transition states with ethanolamine require lower activation barriers in comparison with those with *n*-hexylamine. Similarly, transition states involving C11 require lower activation barriers in comparison with those involving C12 and C13 (Table 2).

Table 5 shows that activation energies are in general proportional to the predicted bond strengths (Figure 1), i.e., activation barriers for abstraction of hydrogen are much higher than those for abstraction of bromine. These findings confirm our assumption of initial formation of $\mathbf{4}_{R}$ radical. Furthermore, since all C–H bonds in *n*-hexylamine are stronger than C11–H, it is reasonable to expect that only abstraction of hydrogen from C11 will be energetically favored. In addition, step 14 is entropy-controlled ($\Delta H^{*}_{a} < -T\Delta S^{*}_{a}$). This finding implies that the rate of step 14 is predominantly governed by the issues of orientation, trajectory, accessibility, etc. All these



Figure 3. Transition states in elementary reactions 13 and 14 with crucial bond distances (Å) indicated.

facts indicate that only small fraction of intermolecular collisions in the reaction with *n*-hexylamine is successful at the experimental temperature, which leads to the low reaction yield.

The solvents can often have an important role on the rate of many radical reactions.⁴² The rate constant for hydrogen abstraction from amine substrate by alkoxyl radicals was strongly affected by the solvent polarity.⁴³ It was found that abstraction rate constant dramatically depends on the solvent dielectric constant. Indeed, the conversion of 3-bromocamphor to the corresponding debrominated imine in the reaction with *n*-hexylamine (amine appears as a solvent and reactant) was much lower (only 35% after 24 h and 26% of isolated product). Polar ethanolamine and ethylenediamine stabilize polar transition states better than less polar *n*-hexylamine and provide the delocalization of the nitrogen lone pair in the α -hydrogen abstraction from the amine more successfully. As a consequence of

Table 5. Activation parameters: enthalpies (ΔH_a^{\dagger}) , entropy terms $(-T\Delta S_a^{\dagger})$, and free energies (ΔG_a^{\dagger}) ; and reaction free energies (ΔG_r) in elementary steps 13 and 14

Reaction step	$\Delta H_a^{\ddagger} / (kJ \text{ mol}^{-1})$	$-T\Delta S^{\ddagger}_{a} / (kJ \text{ mol}^{-1})$	$\Delta G_{a}^{\ddagger} / (kJ \text{ mol}^{-1})$	$\Delta G_{r}^{\ddagger}/(kJ mol^{-1})$
$\overline{4_{\mathbf{A}\cdot} + \mathrm{HO}(\mathrm{CH}_{2})_{2}\mathrm{NH}_{2} \rightarrow 2_{\mathbf{A}} + \mathbf{A}1\mathbf{NH}_{2}}$	68.3	65.9	134.2	5.4
$\mathbf{A1NH}_2 + 3_A \rightarrow 4_A + \mathrm{HOCH}_2\mathrm{CHBr}_{\mathrm{N}}\mathrm{H2}$	12.8	60.1	72.9	-59.4
Overall reaction			134.2	-54.0
$\overline{4_{A^{\bullet}} + \mathrm{HO}(\mathrm{CH}_2)_2 \mathrm{NH}_2 \rightarrow 2_A + \mathbf{A2NH}_2}$	81.4	61.6	143.1	26.5
$\mathbf{A2NH}_2 + 3_A \rightarrow 4_{A} + \mathrm{HOCHBrCH}_2\mathrm{NH}_2$	23.7	58.5	82.2	-56.5
Overall reaction			143.1	-30.0
$4_{\mathbf{E}} + \mathrm{CH}_{3}(\mathrm{CH}_{2})_{5}\mathrm{NH}_{2} \rightarrow 2_{\mathbf{E}} + \mathbf{E}1_{\mathbf{N}}\mathbf{H}2$	76.6	66.8	143.4	6.0
$\mathbf{E1NH}_{2} + 3_{E} \rightarrow 4_{E} + \mathrm{CH}_{3}(\mathrm{CH}_{2})_{4}\mathrm{CHBrNH}_{2}$	11.6	57.9	69.5	-69.0
Overall reaction			143.4	-63.0
$\overline{4_{\mathbf{E}} + \mathrm{CH}_{3}(\mathrm{CH}_{2})_{5}\mathrm{NH}_{2}} \rightarrow 2_{\mathbf{E}} + \mathbf{E3NH}_{2}$	101.0	65.4	166.4	30.0
$\mathbf{^{*}E3NH}_{2} + 3_{E} \rightarrow 4_{E} + \mathrm{CH}_{3}(\mathrm{CH}_{2})_{2}\mathrm{CHBr}(\mathrm{CH}_{2})_{2}\mathrm{NH}_{2}$	35.6	62.2	97.8	-53.3
Overall reaction			166.4	-23.3

increasing steric bulk of cyclohexylamine reactant, the yield of isolated imine was even lower (21% of 3-bromocamphor conversion and 14% of isolated imine product). The fact that *n*-butylamine does not react with 3-bromocamphor even after 36 h can be attributed to the insufficiently high reaction temperature (b.p. of *n*-butylamine = 78 °C) for generation of reactive radical species.

Conclusion

Our group found that ethanolamine and ethylene diamine can serve as efficient reagents for the one-step imine formation and effective reductive debromination of 3-bromocamphor. Although this reaction is also limited by steric factors, solvent polarity and boiling point of applied amine strongly influence the yields of the debrominated products. These findings are in accord with our DFT based investigation of the radical reaction mechanism with ethanolamine and *n*-hexylamine. It was found that the reaction with more polar ethanolamine is energetically more favorable. The entropy-controlled abstraction of the bromine atom from the Schiff base also contributes to the lower yield of the reaction with *n*-hexylamine.

Supplementary Information

Supplementary data (IR and NMR spectra, spectral data, experimental and calculated geometrical parameters of 2_A , optimized geometries of the reactants and products in the reactions with ethanolamine and *n*-hexylamine, and results of the IRC calculations for the corresponding transition states) are available free of charge at http://jbcs.sbq.org.br as a PDF file.

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