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Reduction of 2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione with $NaBH_4$: Investigation of *exo*-selectivity and reaction mechanism *via* theoretical computations

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ABSTRACT

The reaction of the bicyclic imide with $NaBH_4$ afforded acylaminocarbinol and carboxamide derivatives. The exact configuration of acylaminocarbinol **7** was determined by X-ray crystal analysis. Theoretical studies were carried out to explain the mechanism of the *exo*-selectivity observed in the first step of the reduction reaction and the formation of the secondary product in the second step. According to the obtained findings, i) in the first step of the reaction, the *exo*-path is kinetically more favorable, and ii) an alternative mechanism has been proposed instead of the mechanism proposed in the literature. The canonical forms of the amide group in the lactam ring were found to make an important contribution to the mechanism. iii) The amount of products formed in the reduction reaction depends on the reaction conditions.

1. Introduction

The reduction of amides to the corresponding amines has been studied with various metal hydrides. Most of them are extremely strong reducing agents that can reduce almost all functional groups in an organic molecule [1]. The reduction of phthalimides has been studied with a limited number of metal hydrides, indicating that the compounds obtained depend on the nature of the reducing agent used in the reaction. For example, *N*-benzyl phthalimide has been reduced with lithium aluminum hydride to yield substantially *N*-benzyl isoindoline with only trace amounts of the corresponding isoindole [2]. In this context, Horii et al. [3] obtained benzamide derivatives in the reduction reaction of *N*-substituted phthalimides with sodium borohydride in methanol. Reduction of phthalimide derivatives with sodium borohydride in methanol results in the formation of 3-hydroxyphthalimidines, or a mixture of the 3-hydroxyphthalimidines and *o*-hydroxymethylbenzamides depending on the amount of reducing agent present. Strassert and Awruch [4] have also studied the reduction of substituted phthalimides to the corresponding isoindolines by means of diborane. Speckamp et al. [5] investigated the selective reduction of one of the carbonyl functions of succinimides and glutarimides by sodium borohydride in presence of hydrochloric acid. In their study, depending on the conditions, pyrrolidinones, cyclic enamides, or dimeric lactams were formed upon treatment of ω-carbinol-lactams with acid. In the same manner, Ilkei et al. [6] also used the reduction of succinimide with sodium borohydride for the synthesis of sessiline. Acylaminocarbinols obtained from the reduction reactions of succinimide are electrophilic compounds such as iminium ions that can be used as key compounds in the synthesis of sessiline derivatives. In the literature, reduction of imides has been explored with a limited number of metal hydrides, showing that the compounds obtained depend on the type of reducing agent employed in the reaction.

Recently, we examined the reduction reactions of a cyclic imide for the synthesis of new isoindole derivatives. We obtained a very interesting product, which is a pyrrolidine derivative **2**, from the reduction reaction of imide **1** with $LiAlH_4$ (Scheme 1) [7]. On the other hand, isoindole derivatives are protean building blocks in organic synthesis. In recent years, the biological significance of different *N*-substituted isoindole-1,3-dione analogues has been explored by various research groups [8-12].

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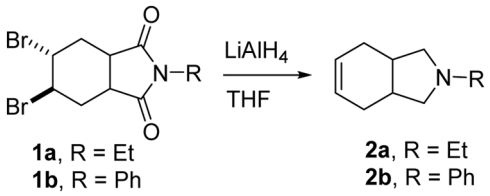


Scheme 1. The reduction reaction of isoindole-1,3-dione **1** with lithium aluminum hydride.

In this context, as part of our current studies on the development of methods for the synthesis of isoindole derivatives from readily available building blocks, herein we report our results involving the reduction of 2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (**6**) to the corresponding acylaminocarbinol **7** and carboxamide **8** by employing sodium borohydride. We performed spectroscopic studies for structure determination and absolute configuration. The mechanism for the formation of products is explained by theoretical computations.

2. Experimental section

2.1. Material and instrumentation

All reagents and substrates were purchased from commercial sources and used without further purification. The solvents were purified and dried by standard procedures before use. ^{1}H NMR and ^{13}C NMR spectra were recorded by Bruker UltraShield spectrometer (Rheinstetten, Germany) at 400 MHz (^{1}H: 400 and ^{13}C: 100 MHz) in deuterated chloroform ($CDCl_3$), and Me4Si was used the internal standard for the NMR analyses. Chemical shifts (δ) are given in ppm, relative to an internal standard, *J* in Hz. Spectra were recorded at room temperature using the program TOPSPIN 2.1. M.p. was measured with Gallenkamp melting point devices. X-ray: Rigaku R-AXIS RAPID IP diffractometer. HRMS: electron spray technique (*M*+/M-) from the soln. in MeOH (Waters LCT PremierTM XE UPLC/MS TOF (Manchester, UK)).

2.2. Synthesis of the molecules

2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (6): Compound **6** was synthesized according to the procedure reported in our previous study [7].

The reduction reaction of 2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (6) with sodium borohydride

To a magnetically stirred solution of 2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (**6**) (500 mg, 2.2 mmol) in THF/H_2O (20 mL) was added $NaBH_4$ (83.25 mg, 2.2 mmol) at 0 °C and the reaction mixture was stirred for an additional 0.5 h at this temperature. Then the reaction was stirred for 10 h at room temperature. During this time, the reaction was monitored by TLC. The solvent was evaporated. EtOAc (5 mL) was added and the mixture was washed with saturated NH_4Cl (10 mL). The solid was filtered off and extracted with EtOAc (3 × 15 mL). The combined organic phase was washed with saturated NH_4Cl (20 mL), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane) to give 3-hydroxy-2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-1-one (**7**) and 6-(hydroxymethyl)-*N*-phenylcyclohex-3-ene-1-carboxamide (**8**).

3-hydroxy-2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-1-one (7).

Yield = 290 mg, 57.5 %, white solid, M.p. 108–109 °C. ^{1}H NMR (400 MHz $CDCl_3$): δ 7.52 (t, *J* = 7.8 Hz, 2H, (H—C2'/H—C6')), 7.36 (t, *J* = 7.8 Hz, 2H (H—C3'/H—C5')), 7.23 – 7.16 (m, 1H, (H—C4')), 5.84 – 5.60 (m, 2H, 2xH—C=), 5.15 (d, *J* = 6.7 Hz, 1H, H—C-O), 3.60 (dd, *J* = 6.8, 1.7 Hz, 1H, H—C), 3.16 – 3.00 (m, 1H, H—C), 2.45 (m, 2H, 2xH—C), 2.34 – 2.13 (m, 2H, 2xH—C), 1.80–1.87 (m, 1H, H—C). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.43, 138.12, 129.28, 126.46, 126.06, 124.69, 122.80, 89.87, 38.32, 37.88, 24.44, 22.05. HRMS: (ESI), *m/z*: [*M* + *H*]+ C14H15NO2 Calcd 230.1103; Found 230.1138.

Table 1
Crystal data, data collection and structure refinement details of compound **7**.

Empirical formula	$C_{14}H_{15}NO_2$
Formula weight	483.38
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	triclinic
Space group	*P*-1
Unit cell dimensions	$a = 6.5380(2)$ Å $\alpha = 95.944(2)^\circ$ $b = 7.2161(2)$Å $\beta = 99.446(3)^\circ$ $c = 12.8184(4)$ Å $\gamma = 101.4860^\circ$
Volume (Å^3)	578.78(3)
Z	2
Density (calculated) (g/cm^3)	1.31
Absorption coefficient (mm^{-1})	0.088
F(000)	224
Theta range for data collection	1.6 to 33.4°
Index ranges	$-9 \le h \le 9$, $-10 \le k \le 11$, $-19 \le l \le 19$
Reflections collected	16,813
Independent reflections	4439 [*R*(int) = 0.0176]
Data Completeness (%)	99.7
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3552/0/155
Goodness-of-fit on F^2	1.008
Final R indices [I > 2sigma(I)]	*R*1 = 0.050, w*R*2 = 0.143
R indices (all data)	*R*1 = 0.0627, w*R*2 = 0.156
Largest diff. peak and hole	0.280 and 0.220

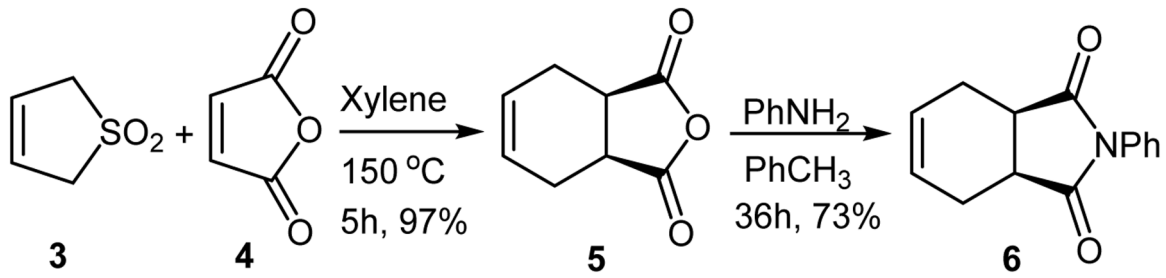
6-(hydroxymethyl)-*N*-phenyl cyclohex-3-ene-1-carboxamide (8)

Yield = 213 mg, 41.86 %, white solid, M.p. 155–157 °C. ^{1}H NMR (400 MHz $CDCl_3$): δ 7.96 (brs, 1H, N—H), 7.52–7.47 (m, 2H, (H—C2'/H—C6')), 7.36–7.30 (m, 2H, (H—C3'/H—C5')), 7.16–7.10 (m, 1H (H—C4')), 5.85 (brs, 2H, (H—C3/H—C4), 3.75–3.62 (m, 2H, (H2-C7)), 3.07–3.02 (m, 1H, (H—C1)), 2.61–2.26 (m, 3H, (H—C2/H2-C5), 2.24–2.12 (m, 1H, (H—C6)), 1.98–1.88 (m, 1H, (H—C2)). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.41 (C8(C = O)), 137.61 (C1'), 129.02 (C3'/C5'), 127.35 (C4'), 124.98 (C4), 124.51(C3), 120.13 (C2'/C6'), 64.24 (C7), 41.96 (C1), 37.23 (C6), 26.36(C2/C5). HRMS: (ESI), *m/z*: [*M* + *H*]+ C14H17NO2 Calcd. 232.1259; Found 232.1313.

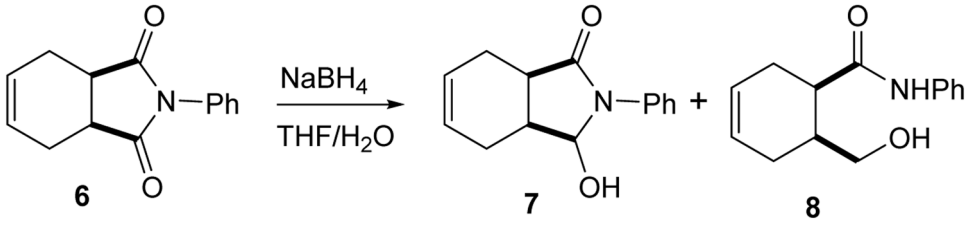
2.3. X-ray crystallography

For the determination of the crystal structure, a single crystal of the molecule **7** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). Graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) and oscillation scans with $\Delta w = 5^\circ$ for one image were used for data collection. The lattice parameters were determined by the least-squares method based on all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects, and cell refinement were performed using the software CrystalClear (Rigaku/MSC Inc., 2005). The structure was determined by direct methods using the program SHELXS-97 and non-hydrogen atoms were refined using anisotropic displacement parameters by full-matrix least-squares procedure also using SHELXL-97 [13]. *H* atoms were positioned geometrically and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. The crystallographic details are summarized in Table 1.

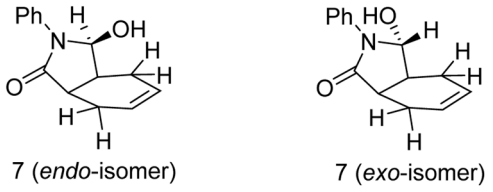
The supporting crystallographic data for molecule **7** is available under the accession number CCDC-1,917,917. These data can be accessed free of charge through the joint deposition service provided by the Cambridge Crystallographic Data Centre (CCDC) and FIZ Karlsruhe. For more detailed information or to download the data, please visit



Scheme 2. Synthesis of imide derivative **6**.



Scheme 3. The reduction reaction of isoindole-1,3-dione **6** with $NaBH_4$.



Scheme 4. Structures of isomers expected to be formed in the reduction reaction.

www.ccdc.cam.ac.uk/structures. This resource provides comprehensive structural data sets that are valuable for further research and analysis.

3. Results and discussion

Very recently, we developed a versatile approach for the synthesis of novel isoindole-1,3-dione derivatives from the reaction of 3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (**5**) [7,14,15]. The latter, used as the starting material, was prepared from 3-sulfolene **3** and maleic anhydride **4** (Scheme 2). Condensation of aniline with 1,3-dione **5** in presence of toluene: triethylamine mixture (3:1) gave the imide **6**.

Parallel to previous studies [7] we investigated the reduction reaction of the imide **6** with sodium borohydride for the synthesis of new isoindole derivatives. The reduction was carried out by adding molar equivalent sodium borohydride to a solution of the bicyclic imide **6** in THF at 0 °C, followed by stirring at room temperature for 10 h. After six hours, the recorded ^{1}H NMR spectrum of the reaction mixture showed that besides the unreacted bicyclic imide **6** and the expected acylaminocarbinol **7**, a second product was formed (Scheme 3). The products were purified using column chromatography and their structures were determined by spectroscopic methods.

In particular, considering the structure of the bicyclic imide **6**, the two faces of the carbonyl group(s) of the imide ring are not symmetrical. Therefore, the hydride (B-H) can approach the carbonyl group from either side, resulting in the formation of two isomers containing *exo*- and *endo*-hydroxyl groups (Scheme 4). However, in the present reaction a single isomer was obtained.

Although the ^{1}H and ^{13}C NMR spectra were consistent with the structure of the reduction product acylaminocarbinol **7**, the exact configuration of the product could not be determined from these spectroscopic data. Ultimately, X-ray crystal analysis of acylaminocarbinol **7** showed that the *exo*-isomer was formed.

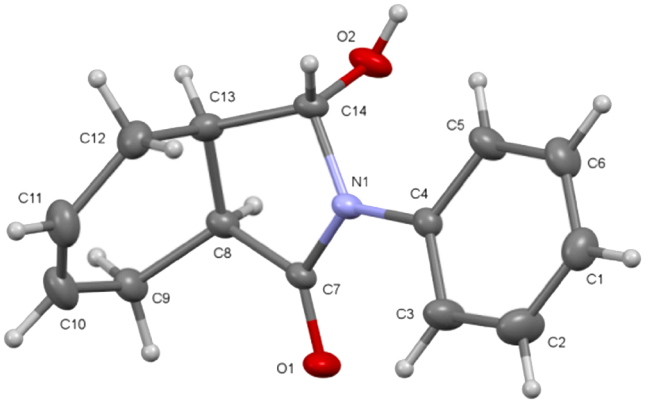


Fig. 1. Molecular structure of the acylaminocarbinol **7**. Thermal ellipsoids are drawn at 40 % probability level.

The structure of carboxamide **8**, the secondary product of acylaminocarbinol **7** was determined based on the analysis of Correlation Spectroscopy (COSY), Heteronuclear Multiple Quantum Correlation (HMQC) experiments (Fig. SI-p: 4–5). We assigned the proton-proton coupling and proton-carbon correlations using the COSY and HMQC spectrum of carboxamide **8**. The spectral data are agreement with the structure of compound **8**.

We performed X-ray structure analysis on the molecule 3-hydroxy-2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-1-one (**7**) to identify the conformation and possible interactions (Fig. 1). The structure has a racemic form. The structure crystallizes in the triclinic centrosymmetric space group *P*-1 with two enantiomers in the unit cell. The C–C (cyclohexene) distances are in the typical single bond range [1.487(3)–1.539 (3) Å]. The C11 = C10 double bond is 1.323(3) Å and the C–N bonds are between 1.365 and 1.471(3) Å. The conformation is defined by steric effects, which force a fold in the cyclohexene ring relative to the mean plane through the pyrrolidine group. For both enantiomers, the cyclohexene ring has a half-chair conformation and the maximum deviation from the mean plane for atom O8 is 0.250 Å. The conformation of the pyrrolidine ring was as follows: a nonplanar five-membered saturated ring; four of its ring atoms lie in one plane and the remaining atom C13

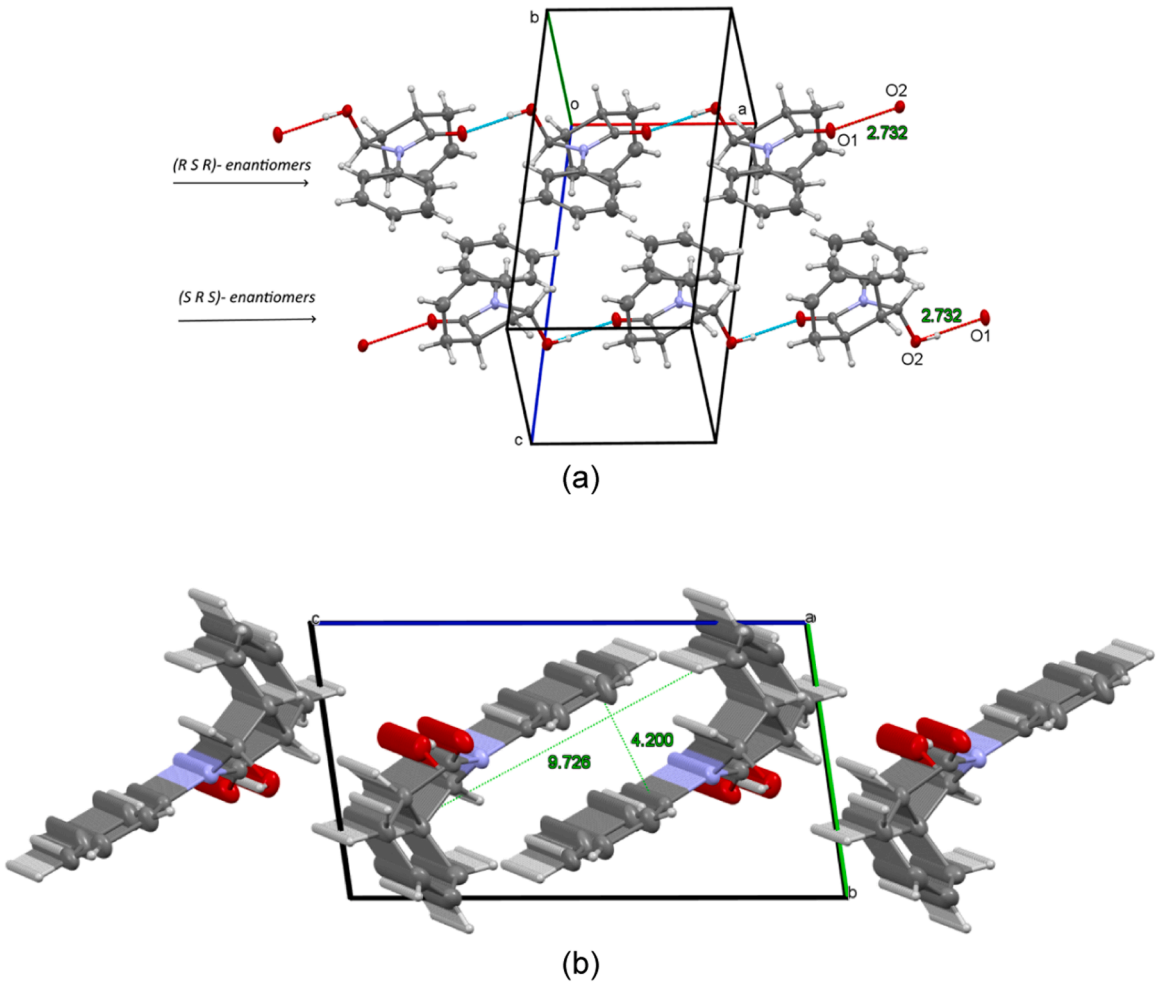


Fig. 2. a) 1D-polymeric chains of each enantiomer with the crystal packing b) Porous structure of the acylaminocarbinol **7** viewed along the a-axis.

lies outside that plane in an envelope conformation (deviation from the mean plane for atom C13 is 0.245 Å). The structure contains three asymmetric carbon atoms and the stereogenic centers are as follows: C8 (*S,R*), C13(*R,S*), C14(*S,R*), where the -OH unit attached to the pyrrolidine changes the stereochemistry.

The crystal packing (Fig. 2a) shows that each enantiomer forms a one-dimensional polymeric chain connected by effective O2-H2•••O1 [D•••A = 2.732(3)Å] [symmetry code: x-1,+y,+z] hydrogen bonds. These 1D-polymeric units form hollow tubes viewed along the a-axis (Fig. 2b). The π-π stacking interactions between the delocalized π-electrons of the phenyl rings are relatively weak. Distances between the rings' centroids are in the range of 4.37–5.21 Å.

After determining the exact structures of the products formed in the reduction reaction of bicyclic imide **6** with $NaBH_4$, we decided to carry out theoretical studies to explain the *exo*-selectivity in the first step and to investigate the mechanism for the formation of the secondary product. For this purpose, we employed the density functional theory (DFT) with the M06–2X functional [16]for geometry optimizations of all transition states and minima. We computed vibrational frequencies to characterize each stationary structure. In all computations, we utilized Pople's polarized double-ζ split valence basis set with diffuse functions, 6–31+*G*(d) [17]. All computations were performed using the Gaussian 09 program package [18]. The energies of all structures are at the M06–2X/6–31G+(d) level, including zero-point vibrational energy (ZPVE) corrections. Throughout this study, all relative energies refer to the ZPVE-corrected energies. For the transition state (TS) between species A and B, we use the notation A/B throughout the article.

In the reduction reaction of aldehydes or ketones with $NaBH_4$, counter cation and solvent effect play an important role in decreasing the activation energy of the reaction. In this context, in the previous studies the activation energy of nucleophilic addition of only BH_4^- to the carbonyl is so high. However, it has been observed that this energy decreases to reasonable levels when both counter cation (Na^+) and solvent molecules (H_2O) are taken into account [19,20]. In the light of this information, the reaction mechanism in our study is investigated. In the first step of the reaction, the nucleophilic attack of the $BH_4^-$to carbonyl in the bicyclic imide **6** can occur at the *endo* or *exo*- positions. The computed reaction barriers in the *endo* and *exo*- cases, taking into account the Na^+ and three H_2O molecules, are 11.8 kcal/mol for **6/7a** (*exo*-) and 12.9 kcal/mol for **6/7a** (*endo*-) (Fig. 3) at the M06–2X/6–31G+(d) level, respectively. This shows that the *exo*-pathway is kinetically more favorable in the first step of the reaction. In the second step, the hydrolysis process occurs to form the final product acylaminocarbinol **7a**. For this step, the computed reaction energy is 28.9 kcal/mol at the M06–2X/6–31G+(d) level (Fig. 3). These computational results are good agreement with the experimental results.

After determining that the *exo* isomer is kinetically preferred in the first step, we focused on the mechanism for formation of the secondary product. When the reduction reactions of cyclic imides with $NaBH_4$ are examined in the literature [5], 3-hydroxy lactam **10** is formed as a result of the reduction of the carbonyl group of the imide in the first step and it is assumed that lactam **10** is in equilibrium with aldehyde compound **11**. In this case, aldehyde compound **11** reacts with $NaBH_4$ to convert to primary alcohol and the corresponding carboxamide **12** is formed

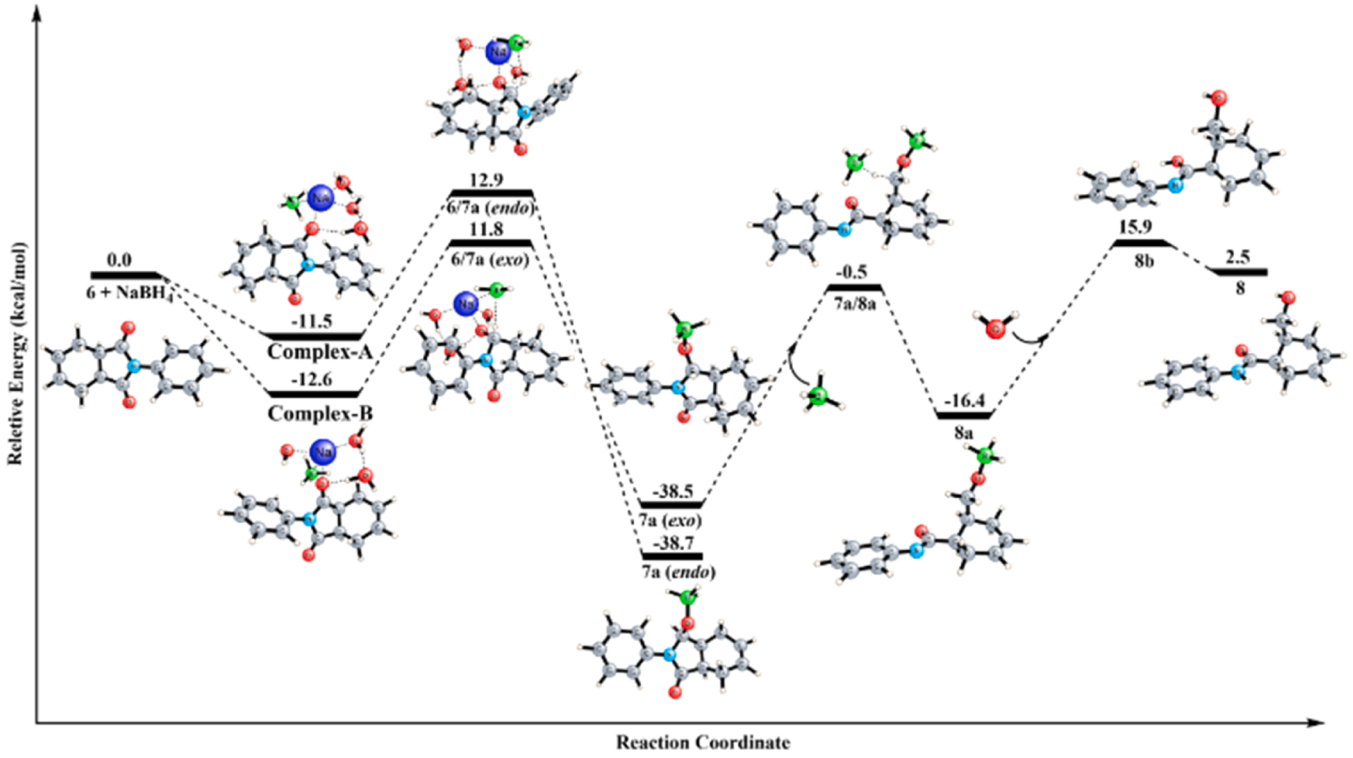
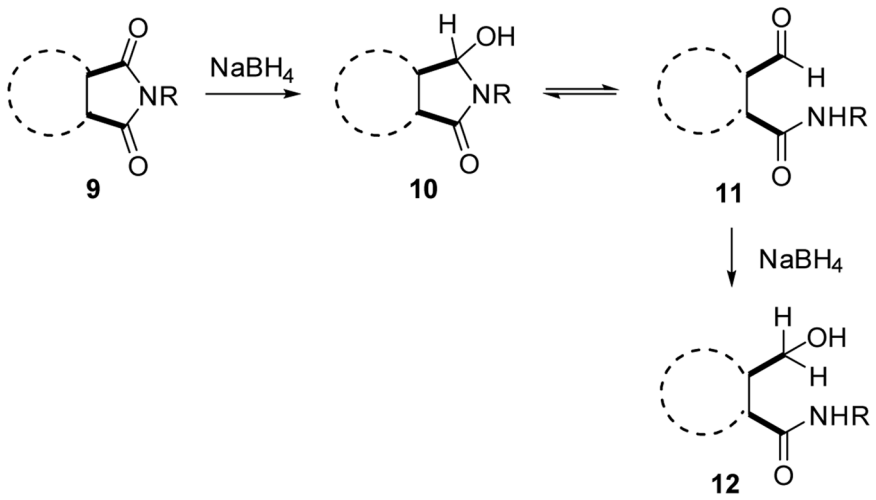


Fig. 3. The potential energy profile for the reduction reaction of bicyclic imide **6** by $NaBH_4$. Complexes A and B are *endo* and *exo* isomers of **6**····$NaBH_4$ complexes with three water molecules, respectively.



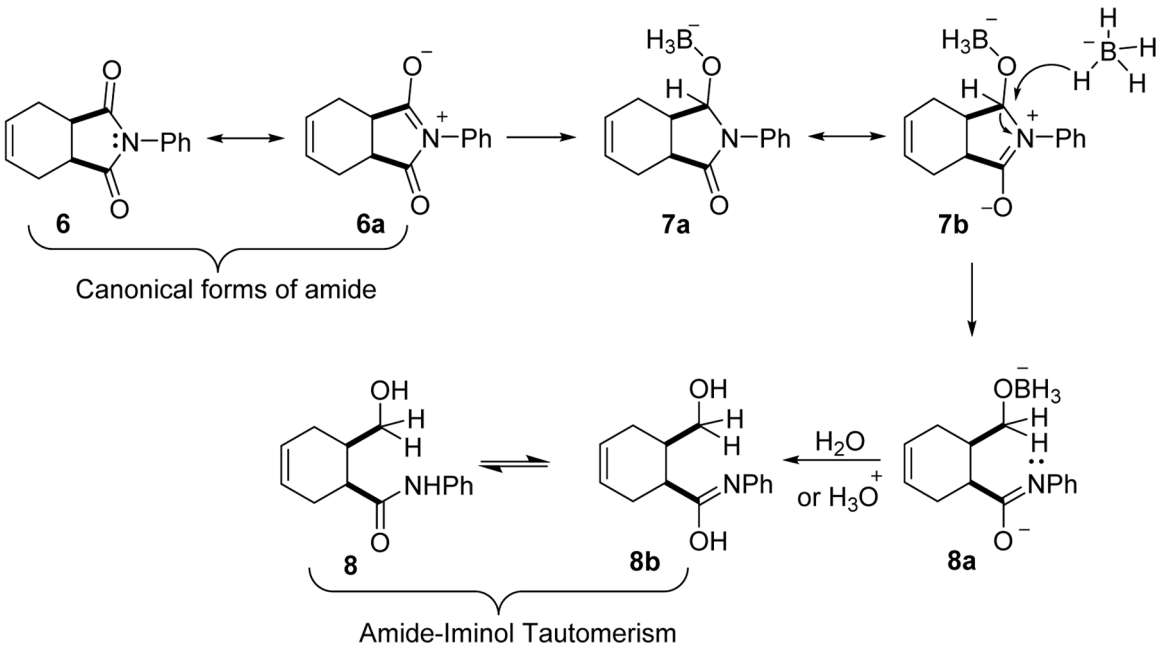
Scheme 5. The proposed reaction mechanism for the reduction reaction of imides with $NaBH_4$ in the literature [5].

(Scheme 5). Initially, we performed theoretical studies considering this mechanism proposed in the literature.

However, our theoretical studies showed that an equilibrium does not occur as indicated by the proposed mechanism. In other words, we were not able to optimize any compound in which the ring opens to a carbonyl compound. In this case, we focused on alternative mechanisms. The most important aspect of the proposed mechanism was to provide an alternative for how the reduction would occur without opening the lactam ring. Starting from the idea that this could be explained by the mechanism given in Scheme 6, we decided to investigate the mechanism theoretically. We believe that the most important reason for the reaction to proceed through the proposed mechanism is the canonical forms of the amide group. In this context, it has been found in our previous studies that canonical structures affect the mechanism of product or product formation [21,22].

There are two canonical forms for the lactam ring (such as the amide-iminol tautomer) and the reduction in the second step takes place *via* canonical form **7b**. This is because in the latter, the nitrogen (N) atom has a positive (+) charge and hence becomes a more easily leaving group. The carbon-nitrogen bond will cleavage more easily as a result of the hydride attacking the carbon neighboring the nitrogen. In line with this approach, we have carried out theoretical studies.

As seen mechanism in Scheme 6, as a result of hydride attack from BH_4^- to **7a** or **7b**, intermediate **8a** is formed *via* TS **7a/8a**. According to computational results, the computed reaction barrier for this reaction is 38.0 kcal/mol at the M06–2X/6–31G+(d) level. After that, the intermediate **8b** is formed by protonating the 8a molecule with H_2O. For this reaction, the computed reaction energy is 32.3 kcal/mol at the M06–2X/



Scheme 6. The formation mechanism of carboxamide **8**.

6–31G+(d) level. Finally, intermediate **8b** forms the secondary product **8** *via* amide-iminol tautomerization and the computed reaction energy for this step is −13.4 kcal/mol at the M06–2X/6–31G+(d) level. These calculation results are in harmony with the proposed mechanism depending on the structure of the secondary product formed.

After explaining the formation mechanism of compound **8**, studies were conducted to enhance its yield. These studies are summarized in Table 1 (Table 1 SI-p: 5). As shown in Table 1, the amount of reagent and solvent significantly affects product formation.

4. Conclusions

Acylaminocarbinol **7** and carboxamide **8** derivatives were obtained from the reduction reaction of bicyclic imide with $NaBH_4$. The exact configuration of acylaminocarbinol **7**, the precursor compound of carboxamide **8**, was determined by X-ray crystal analysis. The structure **7** crystallizes in the triclinic centrosymmetric space group P-1 with two enantiomers in the unit cell. Theoretical studies were carried out to explain the formation mechanism of carboxamide **8** formed in the reduction reaction. In this context, the *exo*-selectivity observed in the formation of acylaminocarbinol **7** was explained. On the other hand, a different mechanism for the formation of carboxamide **8** was proposed instead of the mechanism proposed in the literature for similar systems. In particular, canonical forms of the amide group in the lactam ring were found to contribute significantly to the mechanism. It was also found that the amount of products formed in the reduction reaction depends on the reaction conditions.

CRediT authorship contribution statement

Özlem Gündoğdu: Writing – original draft, Methodology, Investigation. **Abdurrahman Atalay:** Investigation, Formal analysis. **Pınar Turhan:** Investigation. **Barış Anıl:** Software, Formal analysis. **Ertan Şahin:** Software, Formal analysis. **Uğur Bozkaya:** Writing – review & editing, Software, Formal analysis. **Nurhan H. Kishalı:** Writing – original draft, Visualization. **Yunus Kara:** Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2024.139520.

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