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Reaction of 1-(oxiran-2-ylmethyl)-1*H*-indole-3-carboxaldehyde with amines

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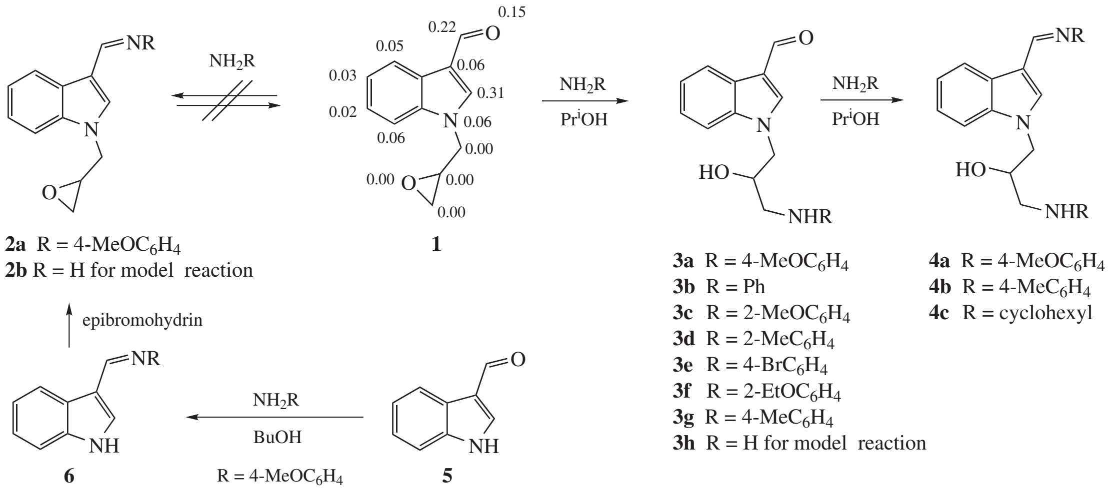
Interaction of 1-(oxiran-2-ylmethyl)-1*H*-indole-3-carboxaldehyde with primary amines occurs at oxirane moiety and leads to β-aminoalcohols. Quantum-chemical calculations show that these products are more stable than possible alternative Schiff bases arising from aldehyde group of the considered bielectrophiles.

1-(Oxiran-2-ylmethyl)-1*H*-indole-3-carboxaldehyde **1**[†] is of interest as a versatile reactant for organic synthesis having two unequivalent reaction sites, namely aldehyde and oxirane fragments. Herein, reaction of bifunctional compound **1** with primary amines was investigated. We supposed that the refluxing of compound **1** with amines in propan-2-ol can lead to formation of Schiff bases **2** similar to other indole-3-carboxaldehydes.[1,2] Moreover, our calculation of Fukui indices f^+ (Scheme 1) shows that the most electrophilic center in molecule **1** is the carbonyl group.[3,4]

However, we found out that oxirane ring opening did first occur affording β-aminoalcohols **3a–g** (Scheme 1, Table 1, entries 1–7).[‡] Increase in the reaction time in the case of anilines having p$K_a > 5$ led to the bis-adducts **4a**,**b** (entries 1, 7, in parentheses). In the case of anilines with electron-withdrawing groups reaction did not occur (entries 8–10). When aliphatic cyclohexylamine (entry 11) was used bis-adduct **4c** was at once formed.[§]

We could not exclude initial formation of Schiff bases **2** and further, as far as this reaction is reversible, more thermodynamically stable products **3a–g** accumulation in the reaction mixture.



Scheme 1 Fukui indices f^+ of compound **1** and its reactions with amines.

Table 1 Reactions of bifunctional compound **1** with amines RNH$_2$.[a]

Entry	R	pK_a of the amine	Reaction duration/h	Product	Yield (%)
1	4-MeOC$_6$H$_4$	5.29	1.5 (10)	**3a** (**4a**)	50 (30)
2	Ph	4.58	3	**3b**	26
3	2-MeOC$_6$H$_4$	4.49	2.5	**3c**	65
4	2-MeC$_6$H$_4$	4.39	6	**3d**	35
5	4-BrC$_6$H$_4$	3.91	4	**3e**	26
6	2-EtOC$_6$H$_4$	4.47	3	**3f**	43
7	4-MeC$_6$H$_4$	5.12	2 (8)	**3g** (**4b**)	34 (23)
8	4-O$_2$NC$_6$H$_4$	1.02	25	—	—
9	2-O$_2$NC$_6$H$_4$	–0.29	20	—	—
10	4-MeO$_2$CC$_6$H$_4$	3.78	11.5	—	—
11	Cyclohexyl	10.64	(3)	(**4c**)	(43)

[a] Parentheses are data related to bis-adduct **4**.

[†] *Synthesis of 1-(oxiran-2-ylmethyl)-1*H*-indole-3-carboxaldehyde* **1**. Sodium hydroxide (9.2 g, 0.22 mol) in water (10 ml) was added to 1*H*-indole-3-carboxaldehyde (30 g, 0.2 mol) in DMSO (40 ml). The reaction mixture was stirred for 1–1.5 h. To this solution epibromohydrin (51 ml, 0.6 mol) was added, and the mixture was stirred for 1 h, then poured into water (300 ml) and extracted with benzene. The extract was dried with sodium sulfate and concentrated. The solid residue was recrystallized from benzene. Yield 40%, mp 90–92 °C. ^{1}H NMR (CDCl$_3$) δ: 2.49 (dd, 1H, OCH$_2$, *J* 4.6 and 2.5 Hz), 2.86 (dd, 1H, OCH$_2$, *J* 4.6 and 4.0 Hz), 3.29–3.40 (m, 1H, OCH), 4.15 (dd, 1H, NCH$_2$, *J* 15.6 and 5.2 Hz), 4.56 (dd, 1H, NCH$_2$, *J* 15.6 and 3.3 Hz), 7.26–7.48 (m, 3H, H$_{\text{Ind}}$-5,6,7), 7.76 (s, 1H, H$_{\text{Ind}}$-2), 8.29–8.38 (m, 1H, H$_{\text{Ind}}$-4), 10.00 (s, 1H, CH=O). ^{13}C NMR (CDCl$_3$) δ: 45.5, 48.9, 50.6, 110.3, 119.1, 122.6, 123.5, 124.7, 125.6, 137.9, 139.3, 185.1. IR (ν/cm^{-1}): 1646 (C=O), 1611, 1574, 1528 (C–C$_{\text{Ar}}$). Found (%): C, 71.34; H, 5.49; N, 6.93. Calc. for C$_{12}$H$_{11}$NO$_2$ (%): C, 71.63; H, 5.51; N, 6.96.

Table 2 Total (E) and relative (ΔE) energies, total (E_{ZPE}) and relative (ΔE_{ZPE}) energies with zero-point energy correction, total (E_{solv}) and relative (ΔE_{solv}) energies in solutions calculated by the B3LYP/6-311++G(d,p).

Structure	E (a.u.)	ΔE/kJ mol^{-1}	E_{ZPE} (a.u.)	ΔE_{ZPE}/kJ mol^{-1}	E_{solv} (a.u.)	ΔE_{solv}/kJ mol^{-1}
1 + NH_3	–725.81259	0.0	–725.57326	0.0	–725.84395	0.0
2b	–649.34369	—	–649.12616	—	–649.36817	—
2b + H_2O	–725.80222	27.2	–725.56341	26.0	–725.83789	15.9
3h^a	–725.85510	–111.8	–725.60958	–95.5	–725.88130	–98.0
NH_3	–56.58272	—	–56.54845	—	–56.59005	—
H_2O	–76.45853	—	–76.43725	—	–76.46972	—

^{a}Characteristics of the energetically most stable conformer **3h** are given.

In order to verify this suggestion we independently synthesized compound **2a** from 1*H*-indole-3-carboxaldehyde **5** *via* Schiff base **6**.[¶] However, boiling of starting material **2a** in wet propan-2-ol did not lead to β-aminoalcohol **3a**, whereas only resinification took place. This experiment rules out thermodynamic control and shows that oxirane ring opening is a quicker process.

To explain experimental facts and compare the stability of reaction products **2b** or **3h** obtained by two alternative pathways, quantum chemical calculations for model reaction of compound **1** with ammonia (R = H) were carried out. Table 2 indicates that the total energy of system **2b** + H_2O is higher than the starting reaction point energy. The energy difference between them is 15.9 kJ mol^{-1} with taking into account solvation. This result demonstrates endothermic character of the attack of aldehyde group of compound **1** by ammonia molecule. At the same time the addition of ammonia to oxirane ring leading to compound **3h** looks more preferable than system **1** + ammonia by more than 90 kJ mol^{-1}.

Taking into consideration the ability of amines to form associates,[6] we calculated another potential supramolecular mechanism of reaction with ammonia dimer (Scheme 2). Two competitive processes start with the formation of pre-reaction complexes **1′**

[‡] *General procedure for the synthesis of 1-[3-(arylamino)-2-hydroxypropyl]-1*H*-indole-3-carboxaldehydes* **3a–f**. To compound **1** (0.2 g, 1 mmol) in propan-2-ol (3 ml), an aniline (2 mmol) was added and the mixture was refluxed for appropriate time (see Table 1). In case of **3a**,**c–f**, the formed precipitate was filtered off and recrystallised. In case of **3b**,**g**, the solvent was evaporated, benzene (2 ml) was added to the obtained oil (and heated in case of **3g**), the formed precipitate was filtered off and recrystallized with benzene.

For **3a**: yield 50%, mp 159–161 °C (propan-2-ol). ^{1}H NMR ($CDCl_3$) δ: 1.35–2.21 (bp, 2H, NH, OH), 3.03–3.16 (m, 1H, NCH_2), 3.24–3.35 (m, 1H, NCH_2), 3.73 (s, 3H, OMe), 4.17–4.50 (m, 3H, CH, CH_2), 6.57–6.66 (m, 2H, $\mathrm{H_{Ar}}$), 6.72–6.82 (m, 2H, $\mathrm{H_{Ar}}$), 7.27–7.41 (m, 3H, $\mathrm{H_{Ind}}$-5,6,7), 7.80 (s, 1H, $\mathrm{H_{Ind}}$-2), 8.22–8.32 (m, 1H, $\mathrm{H_{Ind}}$-4), 9.87 (s, 1H, CH=O). ^{13}C NMR ($CDCl_3$) δ: 49.1, 51.2, 56.2, 69.3, 110.4, 114.7, 115.4, 115.5, 118.7, 122.2, 122.7, 123.5, 124.6, 125.7, 137.9, 140.2, 142.1, 153.4, 185.1. IR (ν/cm^{-1}): 3337, 3369 (OH, NH), 1645 (C=O), 1614, 1576 ($\mathrm{C{-}C_{Ar}}$). Found (%): C, 70.07; H, 6.19; N, 8.61. Calc. for $C_{19}H_{20}N_2O_3$ (%): C, 70.35; H, 6.21; N, 8.64.

For **3b**: yield 26%, mp 138–140 °C (benzene). ^{1}H NMR ($CDCl_3$) δ: 2.74–2.97 (m, 1H, NH), 3.10–3.24 (m, 1H, NCH_2), 3.28–3.42 (m, 1H, NCH_2), 3.81–4.09 (bp, 1H, OH), 4.12–4.49 (m, 3H, CH, CH_2), 6.60–6.82 (m, 3H, $\mathrm{H_{Ar}}$), 7.08–7.45 (m, 5H, $\mathrm{H_{Ar}}$), 7.78 (s, 1H, $\mathrm{H_{Ind}}$-2), 8.20–8.31 (m, 1H, $\mathrm{H_{Ind}}$-4), 9.77 (s, 1H, CH=O). ^{13}C NMR ($CDCl_3$) δ: 48.1, 51.3, 69.1, 110.6, 114.0, 118.5, 118.9, 120.0, 122.5, 123.5, 124.5, 125.6, 129.8, 130.1, 137.9, 140.6, 148.1, 185.3. IR (ν/cm^{-1}): 3363 (OH, NH), 1651 (C=O), 1632, 1602 ($\mathrm{C{-}C_{Ar}}$). Found (%): C, 73.74; H, 6.18; N, 9.56. Calc. for $C_{18}H_{18}N_2O_2$ (%): C, 73.45; H, 6.16; N, 9.52.

For **3c**: yield 65%, mp 160–162 °C (propan-2-ol–acetonitrile, 4:1). ^{1}H NMR ($CDCl_3$) δ: 2.99–3.28 (m, 2H, NCH_2), 3.74 (s, 3H, OMe), 4.02–4.39 (m, 3H, CH, CH_2), 4.42–4.67 (bp, 1H, NH), 4.67–4.84 (bp, 1H, OH), 6.33-6.81 (m, 4H, $\mathrm{H_{Ar}}$), 7.10–7.37 (m, 3H, $\mathrm{H_{Ind}}$-5,6,7), 7.78 (s, 1H, $\mathrm{H_{Ind}}$-2), 8.09–8.25 (m, 1H, $\mathrm{H_{Ind}}$-4), 9.83 (s, 1H, CH=O). ^{13}C NMR ($CDCl_3$) δ: 47.8, 51.3, 55.8, 68.9, 110.1, 110.6, 110.7, 117.7, 118.5, 121.7, 122.5, 123.3, 124.4, 125.7, 138.0, 138.2, 140.7, 147.6, 185.2. IR (ν/cm^{-1}): 3330, 3408 (OH, NH), 1632 (C=O), 1614, 1600 ($\mathrm{C{-}C_{Ar}}$). Found (%): C, 70.63; H, 6.23; N, 8.67. Calc. for $C_{19}H_{20}N_2O_3$ (%): C, 70.35; H, 6.21; N, 8.64.

For characteristics of compounds **3d–g**, see Online Supplementary Materials.

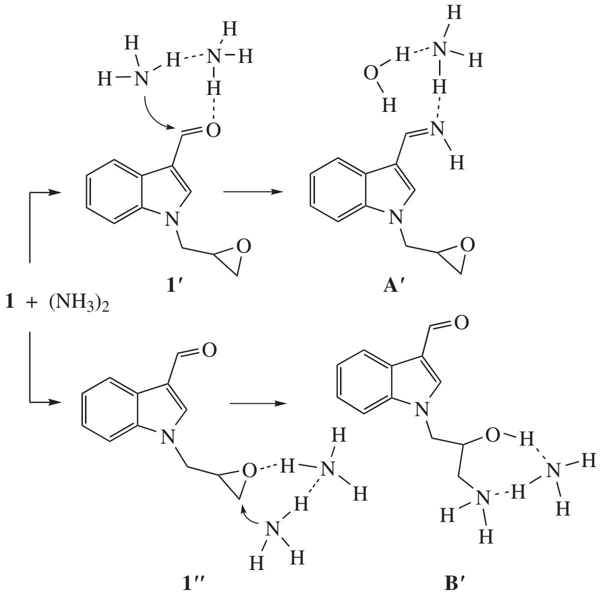
[§] *General procedure for the synthesis of bis-adducts* **4a–c**. To compound **1** (0.2 g, 1 mmol) in propan-2-ol (3 ml), an amine (2 mmol) was added and the mixture was refluxed for appropriate time (see Table 1).

For **4a**: the solvent was evaporated; diethyl ether (2–3 ml) was added to the obtained oil. The precipitate was filtered off and recrystallized from benzene. Yield 30%, mp 106–108 °C. ^{1}H NMR ($CDCl_3$) δ: 1.44–1.84 (bp, 1H, NH), 2.65–2.92 (bp, 1H, OH), 2.99–3.14 (m, 1H, NCH_2), 3.18–3.30 (m, 1H, NCH_2), 3.73 (s, 1H, OMe), 3.81 (s, 1H, OMe), 4.13–4.41 (m, 3H, CH_2, CH), 6.57 (d, 2H, $\mathrm{H_{Ar}}$, J 9.2 Hz), 6.75 (d, 2H, $\mathrm{H_{Ar}}$, J 8.9 Hz), 6.89 (d, 2H, $\mathrm{H_{Ar}}$, J 8.8 Hz), 7.16 (d, 2H, $\mathrm{H_{Ar}}$, J 8.9 Hz), 7.25–7.38 (m, 3H, $\mathrm{H_{Ind}}$-5,6,7), 7.63 (s, 1H, $\mathrm{H_{Ind}}$-2), 8.39–8.49 (m, 1H, $\mathrm{H_{Ind}}$-4), 8.59 (s, 1H, CH=). ^{13}C NMR ($CDCl_3$) δ: 49.0, 51.0, 55.9, 56.2, 69.4, 110.2, 114.8 (2C), 115.2, 115.3 (2C), 115.4 (2C), 116.9, 122.1, 122.2 (2C), 122.3, 123.8, 126.7, 134.1, 137.7, 142.3, 146.5, 153.2, 157.9. IR (ν/cm^{-1}): 3356, 3179 (OH, NH), 1609 (C=N), 1590, 1572 ($\mathrm{C{-}C_{Ar}}$). Found (%): C, 72.42; H, 6.31; N, 9.74. Calc. for $C_{26}H_{27}N_3O_3$ (%): C, 72.71; H, 6.34; N, 9.78.

For **4b**: the solvent was evaporated; diethyl ether (2 ml) and light petroleum (3 ml) were added to the obtained oil. The formed precipitate was filtered off and recrystallized from benzene. Yield 23%, mp 105–107 °C. ^{1}H NMR ($CDCl_3$) δ: 2.22 (s, 3H, Me), 2.35 (s, 3H, Me), 2.50–2.71 (m, 1H, NH), 3.02–3.15 (m, 1H, NCH_2), 3.22–3.33 (m, 1H, NCH_2), 3.64–3.90 (m, 1H, OH), 4.15–4.39 (m, 3H, CH, CH_2), 6.49–6.57 (m, 2H, $\mathrm{H_{Ar}}$), 6.93–7.02 (m, 2H, $\mathrm{H_{Ar}}$), 7.06–7.20 (m, 4H, $\mathrm{H_{Ar}}$), 7.25–7.38 (m, 3H, $\mathrm{H_{Ind}}$-5,6,7), 7.64 (s, 1H, $\mathrm{H_{Ind}}$-2), 8.41–8.49 (m, 1H, $\mathrm{H_{Ind}}$-4), 8.59 (s, 1H, CH=). ^{13}C NMR ($CDCl_3$) δ: 20.8, 21.4, 48.3, 51.0, 69.3, 110.3, 114.1 (2C), 115.2, 115.8, 121.1, 122.1, 123.7, 126.8, 128.0, 130.1 (2C), 130.3 (2C), 134.4, 135.1, 137.7, 145.9, 150.8, 154.2. IR (ν/cm^{-1}): 3367, 3178 (NH, OH), 1612 (C=N), 1587, 1571 ($\mathrm{C{-}C_{Ar}}$). Found (%): C, 78.87; H, 6.88; N, 10. 61. Calc. for $C_{26}H_{27}N_3O$ (%): C, 78.56; H, 6.85; N, 10. 57. MS, *m/z* (%): 397 (4.9 [M$^+$]).

For **4c**: the formed precipitate was filtered off and recrystallized from benzene. Yield 43%, mp 136–138 °C. ^{1}H NMR ($CDCl_3$) δ: 0.70–1.95 [m, 22H, NH, OH, $(CH_2)_{10}$], 2.14–2.34 [m, 1H, NH($C\mathit{H}$)$_{\mathrm{cyclohexyl}}$], 2.35–2.53 (m, 1H, NCH_2), 2.62–2.82 (m, 1H, NCH_2), 2.94–3.21 [m, 1H, =N(CH)$_{\mathrm{cyclohexyl}}$], 3.74–3.99 (m, 1H, CH), 4.00–4.27 (m, 2H, CH_2), 7.01–7.40 (m, 3H, $\mathrm{H_{Ind}}$-5,6,7), 7.47 (s, 1H, $\mathrm{H_{Ind}}$-2), 8.19–8.36 (m, 1H, $\mathrm{H_{Ind}}$-4), 8.48 (s, 1H, CH=). ^{13}C NMR ($CDCl_3$) δ: 25.3 (4C), 26.3, 33.9, 35.3 (4C), 49.8, 51.0, 57.1, 69.0, 70.6, 110.0, 115.0, 121.3, 122.2, 123.1, 126.7, 132.2, 137.7, 152.6. IR (ν/cm^{-1}): 3056 (NH, OH), 1637 (C=N), 1574, 1536 ($\mathrm{C{-}C_{Ar}}$). Found (%): C, 75.25; H, 9.21; N, 10.97. Calc. for $C_{24}H_{35}N_3O$ (%): C, 75.55; H, 9.25; N, 11.01. MS, *m/z* (%): 381 (14.8 [M$^+$]).

[¶] *Synthesis of 1-(oxiran-2-ylmethyl)-3-[(4-methoxyphenylimino)methyl]-1*H*-indole* **2a**: compound **6** (2.5 g, 10 mmol) in DMSO (7 ml) was added to sodium hydride (0.5 g of 60% suspension in mineral oil, 12.5 mmol) for 20 min. The reaction mixture was stirred for 1 h at room temperature. Then epibromohydrin (2.5 ml, 30 mmol) was added to a cooled solution. The reaction mixture was stirred for 30 min at room temperature and then quenched with water (5 ml). The formed precipitate was filtered off and recrystallized from benzene. Yield 59%, mp 94–96 °C. ^{1}H NMR ($CDCl_3$) δ: 2.42–2.48 (dd, 1H, OCH_2, J 4.6 and 2.5 Hz), 2.77–2.84 (dd, 1H, OCH_2, J 4.6 and 3.9 Hz), 3.24–3.34 (m, 1H, CH), 3.82 (s, 1H, OMe), 4.09–4.21 (dd, 1H, NCH_2, J 15.3 and 5.4 Hz), 4.41–4.52 (dd, 1H, NCH_2, J 15.3 and 2.8 Hz), 6.85–7.46 (m, 7H, $\mathrm{H_{Ind}}$-5,6,7, 4$\mathrm{H_{Ar}}$), 7.55 (s, 1H, $\mathrm{H_{Ind}}$-2), 8.42–8.57 (m, 1H, $\mathrm{H_{Ind}}$-4), 8.63 (s, 1H, CH=). IR (ν/cm^{-1}): 1619 (C=N), 1593, 1572, 1539 ($\mathrm{C{-}C_{Ar}}$). Found (%): C 74.19; H, 5.90; N, 9.10. Calc. for $C_{19}H_{18}N_2O_2$ (%): C, 74.49; H, 5.92; N, 9.14.



Scheme 2 The model reactions of compound **1** with ammonia dimer.

and **1″** between compound **1** and ammonia dimer, as shown in Scheme 2. Calculations indicate that the total energies of complexes **1′** and **1″** are lower than the starting reaction point energy (Table 3). The formation of intermediate **B′** requires minimum structural change of complex **1″**, whereas the formation of intermediate **A′** from complex **1′** is a multistep process. More detailed calculation demonstrates that the formation of intermediates **A′** and **B′** are both exothermic processes. However, the origination of intermediate **B′** is more energetically preferable than generation of adduct with the carbonyl group **A′** at 115.3 kJ mol^{-1}.

Table 3 Total (*E*) and relative (Δ*E*) energies calculated in the gas phase by the B3LYP/6-311++G(d,p) method.

Structure	*E* (a.u.)	Δ*E*/kJ mol^{-1}
1 + $(NH_3)_2$	–782.40059	0.0
1′	–782.41090	–27.2
1″	–782.41043	–26.0
A′	–782.40661	–15.8
B′	–782.45055	–131.1
$(NH_3)_2$	–113.17071	—

Thus, in the case of bifunctional compound **1** nucleophilic oxirane ring opening proceeds faster and gives most stable products in comparison with the addition of the nucleophile at the aldehyde group. Reactivity of compound **1** towards amines can be explained by the strain of oxirane ring rather than polarization effect of carbonyl group.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.07.021.

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