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Separation of the Thorpe–Ingold and Reactive Rotamer Effect by Using the Formation of Bicyclic Aziridinium Ions

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The geminal dialkyl effect is widely used in organic synthesis to promote cyclization reactions, although the exact origin of its rate enhancement remains unclear. In the present study, we demonstrate the applicability of this effect for the intramolecular formation of bicyclic aziridinium ions and assign it to angle contractions provided by introduction of sterically demanding substituents. Due to the cyclic structure of the examined 3-chloropiperidines the acceleration of this ring closure cannot be explained by an increased population of reactive gauche rotamers and therefore agrees with the original Thorpe-Ingold theory. Furthermore, introduction of strained aliphatic rings resulted in internal angle expansions and were accompanied by a preliminary decrease of rate constants for the investigated aziridinium ion formation. These results lead to a linear correlation between internal angle and relative reaction rate, supported by computational and X-ray crystallographic structural data.

Introduction

Intramolecular reactions can be accelerated by the introduction of a *gem*-substituent group in the carbon chain connecting two reactive centres. This is commonly known as the *gem*-disubstituent or *gem*-dialkyl effect.[1,2] Thorpe, Ingold and Beesley offered the first explanation of this rate enhancement, which was later termed the "Thorpe-Ingold effect". According to their theory, the angle α between two alkyl substituents is enlarged by increased steric repulsion compared to the unsubstituted homologue. Consequently, the opposite angle β is decreased to relieve steric strain moving the two reactive centres closer together, thus promoting cyclization (Figure 1a).[3] In 1960, Allinger and Zalkow concluded that the increased number of *gauche* interactions in *gem*-disubstituted acyclic compounds, compared to the corresponding cyclic system, reduces the enthalpy of activation $\Delta H^{\neq}$.[4] Furthermore, substitution restrains the rotational entropy in the open chain precursor more than in the cyclic product, resulting in a favourable entropy of activation $\Delta S^{\neq}$ for the cyclization of *gem*-disubstituted compounds. Two years later, Schleyer calculated the contribution of the angle compression to the *gem*-dialkyl effect and mentioned that the small changes of the β angle cannot solely explain the experimentally observed enhancements of rate constants up to several orders of magnitude.[5] Therefore, Bruice and Pandit developed a different theory and associated the rate enhancements with an increased population of reactive *gauche* rotamers, which was later entitled the "reactive-rotamer effect".[6] In these conformations, the two reactive centres are arranged properly for cyclization (Figure 1b). This concept is similar to the later developed theory of near attack conformers (NACs) by Bruice and Lightstone,[7–10] for which experimental evidence was given lately.[11] NACs represent ground state conformers, which are similar to the transition state in terms of geometry and orientation of the reactive centres, while still being separated by roughly 3 Å to ensure that bond formation as well as bond breaking has not occurred yet. This separation also represents the critical distance known from the spatiotemporal hypothesis of Menger,[12–17,18] which correlates distance between reactive

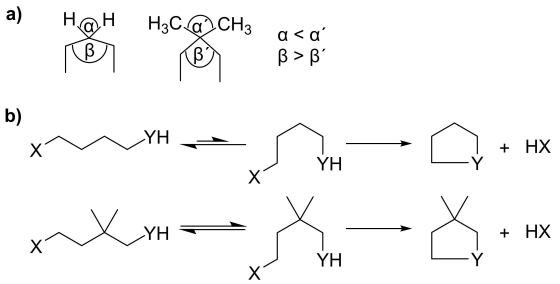

Figure 1. a) Compression of the β ′ angle by introduction of geminal methyl groups known as the "Thorpe-Ingold effect". b) Increase in the population of a reactive *gauche* rotamer, which readily undergoes cyclization, by *gem*-methylation known as the "reactive-rotamer effect".

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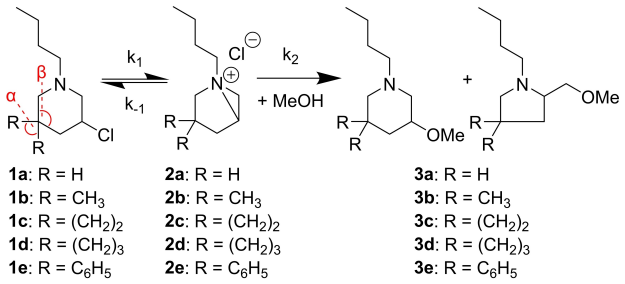
centres with the reaction rate. The concept postulates that a reaction is accelerated by several orders of magnitude, if the reactive moieties are kept in proximity, less than the critical distance, for a sufficient time. The aforementioned theories, along with many others, have also been extensively discussed to explain the severe rate accelerations achieved in enzyme catalysed reactions.[19]

Although several articles have been published to support or discourage either the Thorpe-Ingold or the reactive rotamer effect, this subject remains challenging since both effects contribute to rate enhancements provided by *gem*-disubstitution and are therefore difficult to distinguish. For instance, Parrill and Dolata showed that there is no linear correlation between the population of reactive rotamers and the relative reaction rates, suggesting a "facilitated transition" hypothesis instead.[20] Contrarily, Jung and Gervay gave evidence for the reactive rotamer effect by examination of intramolecular Diels-Alder experiments, demonstrating an increase in rate constants even if strained rings, like cyclobutane or cyclopropane, were used as *gem*-substituents.[21] The small angles of these cyclic systems should lead to larger internal angles and would therefore retard the reaction if valency deviation effects were the dominant factors in the examined reaction. Several other theories have been published, for instance "stereopopulation control"[22–24] and "relief of ground-state strain",[25,26] both discussed as the origin of the "trimethyl lock effect". This conformational restriction, which represents a combination of the "buttressing effect"[27] and the *gem*-disubstituent effect, provides extreme rate enhancements and was first observed for the cyclization of methylated hydrocoumarinic acid derivatives.[22–26,28] Moreover, a reduction of ring strain energy by *gem*-disubstitution of small ring systems has been discussed.[29] Although, the detailed origin of rate enhancements by *gem*-disubstitution is still up for discussion, there are numerous examples of successful applications of the geminal dialkyl effect leading to accelerated reactions, increased yields and selectivity in cyclization reactions[2,30] as well as in ligand design.[31]

Results and Discussion

In recent kinetic studies with substituted 3-chloropiperidines we noticed an enhanced reaction rate for the 5,5-dimethyl derivative **1 b** compared to the corresponding unsubstituted compound **1 a**.[32] The reaction of these compounds with nucleophiles proceeds *via* the highly electrophilic bicyclic aziridinium intermediate **2**, which is rapidly consumed by nucleophilic attack (Scheme 1). The observed increase in reaction rate is assumed to be the result of a *gem*-dialkyl effect, since a bicyclic system is obtained in the rate-determining formation of the aziridinium intermediate (k_1), for which the steady state approximation ($k_2 \gg k_{-1}$) can be applied. However, this rate acceleration cannot be explained by an increased population of reactive *gauche* conformers, since the cyclic structure of the 3-chloropiperidines already fixes the orientation of the reactive centres towards each other. Another explanation



Scheme 1. Reaction mechanism of the examined 3-chloropiperidines **1 a-e**, a mixture of the piperidine and pyrrolidine methyl ethers **3 a-e** are formed by methanolysis of the intermediate bicyclic aziridinium ions **2 a-e**.

would therefore be an angle contraction of the internal β angle, representing a classic Thorpe-Ingold effect, which could be studied separated from the reactive rotamer effect. If the hypothesis holds true for our 3-chloropiperidine system, it might be considered as a useful tool to modulate their reactivity as alkylating agents.[33] This would be of particular interest, since *gem*-dimethyl substitution has already been used to successfully improve the reactivity, stability or synthesis of various medical agents.[34]

In this study, we report for the first time a rate enhancement *via* distinct angle dependant Thorpe-Ingold effect for an intramolecular reaction in an already cyclic system. Furthermore, a preliminary deceleration of the examined solvolysis reaction, by introduction of strained cycloalkyl substituents, was observed. In the following, we will show a linear correlation between the internal β angle, provided by single crystal XRD and DFT[35] calculations, and the relative rate constant k_{rel} (with respect to the unsubstituted compound **1 a**) observed in ^{1}H-NMR kinetic experiments of the 3-chlorpiperidines **1 a-e**. Furthermore, we demonstrate an analogous tendency for the experimentally determined Gibbs free energies of activation $\Delta G^{\neq}$. These results demonstrate, to the best of our knowledge, the first kinetic study about the contribution of the Thorpe-Ingold effect towards cyclization reactions separated from the reactive rotamer effect. Therefore, the novel *spiro* compounds **1 c** and **1 d** as well as the diphenyl derivative **1 e** were synthesized from the corresponding unsaturated amines **4 c-e**, which can be obtained by allylation and reduction of the corresponding nitriles, as described in literature.[36] The amine precursors were then alkylated by imine formation and subsequent reduction, followed by simultaneous *N*-chlorination and cyclization using copper(II)chloride[37,38] (Scheme 2). The synthesis of the 3-chloropiperidines **1 a** and **1 b** has already been described in our previous work.[39,40]

The reactivity of the obtained 3-chloropiperidines **1 a-e** against methanol as an explorative nucleophile was examined by ^{1}H-NMR kinetic solvolysis experiments. The compounds were dissolved in methanol-d_4, containing dibenzylether as an internal standard. The NMR tubes were heated to 50 °C for 7.5 h (except **1 e**, which was incubated for only 2.5 h) in an oil bath and withdrawn for the measurements after an appropriate time. The consumption of the starting material, following the

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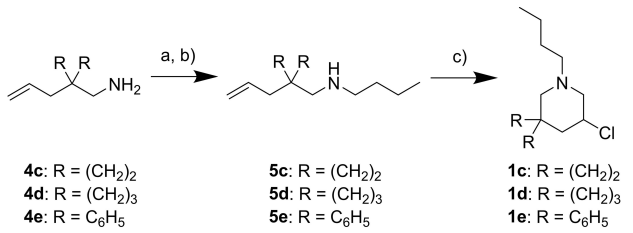

Scheme 2. Synthesis of 3-chloropiperidines **1 c-e**. a) *n*-butyraldehyde, $MgSO_4$, DCM, RT; b) $NaBH_4$, MeOH, 0 °C to RT; c) $CuCl_2 \cdot 2\ H_2O$, THF, RT (**1 c-d**) or $CuCl_2$, THF, RT to reflux (**1 e**).

mechanism depicted in Scheme 1, was monitored (Figures S1-S5) and the anticipated mixture of piperidine and pyrrolidine methyl ethers **3 a-e** was confirmed by GC/MS (see supplementary Experimental Section). The observed regioselectivity in favour of the six-membered piperidine compound is in accordance with several other experimental and theoretical studies on ring expansion of bicyclic aziridinium ions.[41] Sterically demanding substituents in C5 position therefore result in a higher fraction of the thermodynamic piperidine product, compared to the corresponding unsubstituted compound. The first order rate constants of the examined solvolysis reactions were calculated by plotting the natural logarithm of the integral of the corresponding starting material 3-H signal *In(3-H)* (except **1 e**, where an overlapping CH_2 signal was included in the integral) against the reaction time *t* (Table S1). As expected, we observed an increase in reactivity of the dimethyl derivative **1 b** ($k_{rel} = 1.56$) compared to the unsubstituted compound **1 a**. The acceleration for the diphenyl derivative **1 e** ($k_{rel} = 2.38$) was even stronger, resulting in complete consumption of the starting material after approximately five hours. We also recognized a decreased reaction rate for compounds **1 c** and **1 d** in comparison to compound **1 a**. This could be due to the strained cyclic substituents, as observed for the intramolecular catalytic activity of cycloalkyl-substituted malonic acid derivatives.[42] The decrease in reaction rate was more prominent for the cyclopropyl compound **1 c** ($k_{rel} = 0.53$) than for the cyclobutyl derivate **1 d** ($k_{rel} = 0.64$), suggesting a direct correlation of the internal β angle and the rate constant in our 3-chloropiperidine system, as originally proposed by the valency deviation theory of Thorpe and Ingold.[43] To show the robustness and reproducibility of our kinetic method, we repeated the kinetic measurements at 50 °C for all compounds, performing the reaction at this temperature in the NMR spectrometer while also taking ^{1}H-NMR spectra more frequently (representative ^{1}H-NMR spectra shown in Figure S8) and obtained nearly the same rate constants (Table 1).

To confirm the assumed angle distortion by introduction of different substituents in 5-position, we crystallized several 3-chloropiperidine derivatives as their corresponding hydrochloride salts and analysed their structure *via* single crystal XRD. The respective angles α and β (as depicted in Scheme 1), obtained from the crystal structures of the HCl salts of compounds **1 a**, **1 c** and **1 e** (see Tables S2–S7 and S21–32) are summarized in Table 1. Since a crystal structure of the dimethylated compound **1 b** could not be obtained, the angles of the crystal structures of compounds **6 a** and **6 b** (see Tables S8–S20), which represent the *N*-benzyl substituted derivatives of **1 a** and **1 b**, were added. A similar effect resulting from *gem*-dimethylation can be assumed for the *N*-benzyl and *N*-butyl substituted derivatives, considering that the reaction of **1 a** and **1 b** as well as **6 a** and **6 b** with 2'-desoxyguanosine in aqueous solution provided similar relative rate constants in our previous work (k_{rel}(**1 b**/**1 a**) = 4.67; k_{rel}(**6 b**/**6 a**) = 4.08).[32] In addition, we obtained a relative rate constant of $k_{rel} = 1.66$ in a separate kinetic study of **6 a** and **6 b** in methanol-d_4 at 50 °C (see Figure S6), which is comparable to the values of the respective *N*-butyl compounds reported in Table S1 and Table 1. Furthermore, we investigated the structure of the examined 3-chloropiperidine derivatives computationally using the orca program package (version 5.0.3.)[44] on the PCM(methanol)-PBEh-3c[45,46] level of theory, containing the corresponding modified def2-mSV(P) basis set[46,47] and confirmed the lowest energy conformers using the Crest program package.[48] The experimentally obtained as well as the calculated angles α and β shown in Table 1 are in good agreement among each other, considering that the crystal structures were obtained from the corresponding hydrochloride salts. Moreover, both values show a good linear correlation ($R^2_{XRD} = 0.98$ and $R^2_{DFT} = 0.87$) between the internal β angle and the relative rate constant k_{rel} (Figure 2). An analogous correlation cannot be observed for the exocyclic α angle (Figure S9), which is not surprising since α and β show no direct linear relationship either (Figure S10). Nonetheless, introduction of substituents containing small α angles lead to

Table 1. Rate constants k_1 and relative rate constants k_{rel} for the solvolysis reactions of 3-chloropiperidines **1 a**–**e** in methanol-d_4. Bond angles α and β in compounds **1 a**–**e** derived from single crystal XRDs (hydrochloride salts), with their corresponding ESD-values in brackets, and DFT calculations. Activation parameters for compounds **1 a**–**e** derived from the respective Arrhenius and Eyring plots. N/A = not available

	k_1 [10^{-3} min^{-1}][a]	k_{rel}	α (XRD) [°]	α (DFT) [°]	β (XRD) [°]	β (DFT) [°]	E_a [kcal/mol]	ΔH^{+}_{298} [kcal/mol]	ΔS^{+}_{298} [cal/(K*mol)]	ΔG^{+}_{298} [kcal/mol]
1 a	1.66 ± 0.05	1	107.9[b] 107.9[b,c]	107.07	111.8 (3) 112.07 (14)[c]	110.95	18.03 ± 1.00	17.41 ± 1.00	−17.30 ± 3.21	22.56 ± 1.96
1 b	2.97 ± 0.12	1.79	109.1 (2)[c]	109.12	109.35 (19)[c]	108.42	17.51 ± 0.91	16.88 ± 0.91	−17.62 ± 2.89	22.13 ± 1.77
1 c	0.99 ± 0.01	0.54	60.06 (11)	60.30	113.28 (13)	112.49	17.11 ± 0.62	16.49 ± 0.62	−21.17 ± 2.00	22.80 ± 1.22
1 d	1.44 ± 0.04	0.87	N/A	88.47	N/A	109.58	16.94 ± 1.01	16.31 ± 1.01	−21.36 ± 3.24	22.68 ± 2.35
1 e	4.19 ± 0.13	2.52	110.2 (2)	107.57	107.54 (12)	106.66	17.28 ± 1.01	16.66 ± 1.02	−17.94 ± 3.25	22.01 ± 1.98

[a] Samples were incubated at 50 °C directly in the NMR spectrometer. [b] $\measuredangle_{HC5H}$ values derived geometrically from the positions of non-hydrogen substituents of C5. [c] Values obtained from the corresponding hydrochloride salts of the *N*-benzyl derivates **6 a** and **6 b** (see Tables S8–S20).

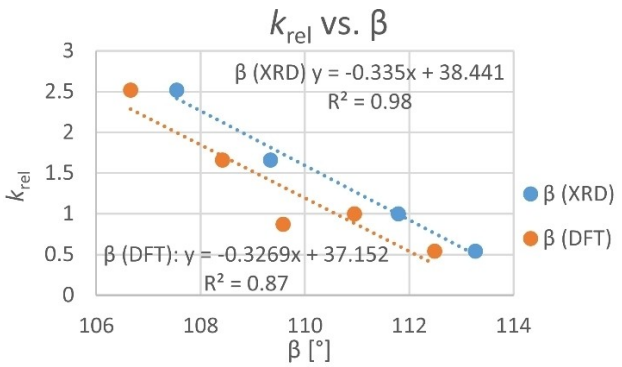

Figure 2. Linear correlation between the relative rate constants k_{rel} and the internal β angle, obtained by single crystal XRD and DFT calculations.

an increase of β and therefore retard the reaction, resulting in a lower relative rate constant, and *vice versa*, as originally proposed by Thorpe and Ingold. The obtained differences in rate constants are considerably smaller compared to reported systems in which the reactive rotamer effect is present,[2] but still show that angular distortion is capable of affecting the reaction rates. The change in the internal β angle is further accompanied by a slight change of the attack angle and distance of the nucleophilic nitrogen towards the electrophilic C3 centre, resulting from the geometrical distortion. Both are important factors to consider in a possible correlation following the spatiotemporal hypothesis.[12–17] The attack angle in the unsubstituted 3-chloropiperidine **1 a** was calculated to be 142.85° (depicted in Figure S11), while the cyclopropyl substituted derivative **1 c** performs the backside attack from an angle of 142.70° and the more reactive diphenyl compound **1 e** attacks the leaving group C3 carbon from an angle of 143.28° (for other attack angles see Table S1). On the other hand, the cyclobutyl compound **1 d** does not follow this trend, as its attack angle of 143° is closer to the angle of 180° typical for S_N2 nucleophilic substitutions, but its reactivity is lower compared to compound **1 a**. Moreover, the changes in NC3 distance (Table S1) compared to the unsubstituted compound **1 a** (2.428 Å) are very small ($\Delta r_{max.} = 0.02$ Å), while still following a tendency similar to the NC3Cl attack angles. The nitrogen atom of the more reactive diphenyl compound **1 e** is a little closer to the leaving-group C3 carbon (2.411 Å), while the distance for the cyclopropyl derivative **1 c** was calculated to be 2.432 Å. Again, the less reactive cyclobutyl derivate **1 d** represents an exception (2.422 Å). When also considering the mean absolute deviation of 0.009 Å for small first and second row molecules calculated by the PBEh-3c method,[46] we assumed that these small differences are no dominant factors in the examined solvolysis reaction of the substituted 3-chloropiperidines **1 a**–**e**.

To understand the observed effect in more detail we also determined the activation parameters for compounds **1 a**–**e**. Therefore, ^{1}H-NMR solvolysis experiments were performed between room temperature (22.5 °C) and 60 °C (oil bath temperature). The resulting rate constants (see Figures S12–S16) were then used to determine E_a (Arrhenius plots: Figures S17–S21) and $\Delta H^{\neq}$ as well as $\Delta S^{\neq}$ (Eyring plots: Figures S22–S26), while $\Delta G^{\neq}$ was calculated from these values (Table 1). The Gibbs free energies of activation $\Delta G^{\neq}$ obtained from the Eyring plots reflect the general tendency of reactivity we observed in the initial kinetic experiments. Even though the differences in Gibbs free energies of activation $\Delta\Delta G^{\neq}$ are smaller than expected from the relative rate constants, which can be attributed to the experimental error of roughly 2 kcal/mol. Interestingly all activation enthalpy $\Delta H^{\neq}$ and activation energy E_a values are decreased when introducing substituents in 5-position, including the strained cycloalkyl moieties present in compounds **1 c** and **1 d**. In addition, the substitution of compounds **1 b** and **1 e** with more bulky groups just slightly increases the activation entropy $\Delta S^{\neq}$ compared to the unsubstituted homologue **1 a**, accordingly their respective rate enhancements are almost entirely attributed to lower enthalpies of activation $\Delta H^{\neq}$. However, this is not the case for the cyclopropyl and cyclobutyl compounds **1 c** and **1 d**. Apparently the decrease in $\Delta H^{\neq}$ is overcompensated by a firmly negative entropy of activation $\Delta S^{\neq}$, resulting in higher Gibbs free energies of activation $\Delta G^{\neq}$ and therefore lower rate constants. The strained cycloalkyl moiety most likely further restricts the already constrained transition state by additional reduction of degrees of freedom. Similar effects on the activation parameters (lowering of $\Delta H^{\neq}$ and $\Delta S^{\neq}$) of cycloalkyl-substituted compounds have been reported by Jung and Gervay,[21] although in the examined system a strong decrease in $\Delta H^{\neq}$ resulted in small rate enhancements. The authors associated this with the presence of the reactive rotamer effect. However, this effect is not applicable in the reaction of our cyclic system, thus the related decrease in $\Delta H^{\neq}$ is lacking and cannot compensate the firmly negative $\Delta S^{\neq}$. As a result, the reaction is slowed down by the leftover angle distortion effect. Various studies discussed the entropic contribution in the accelerated intramolecular anhydride formation of substituted glutarates,[7–9,49] but most of them focus on conformational effects (*via* the NAC approach), which are not applicable in our rigid cyclic system. This is supported by the fact, that we observed only small changes in the entropy of activation $\Delta S^{\neq}$ for the *gem*-dimethyl and the *gem*-diphenyl derivatives (**1 b** and **1 e** respectively) in comparison to the unsubstituted compound **1 a**. In addition, the determined Gibbs free energies of activation $\Delta G^{\neq}$ show a linear correlation with the internal β angle (see Figure S27), just as the aforementioned relative rate constants k_{rel} (Figure 2). Generally, our investigations support the presence of a classic Thorpe-Ingold effect separated from conformational effects, such as the reactive rotamer effect, in the examined solvolysis reaction of *gem*-disubstituted 3-chloropiperidines.

Conclusion

In conclusion, we investigated the original, angle dependant Thorpe-Ingold effect, excluding the otherwise competing reactive rotamer effect, by ^{1}H-NMR kinetic and structural analysis of the substituted 3-chloropiperidine derivatives **1 a**–**e**. We could show a rate enhancement by introduction of bulky *gem*-

disubstituents in 5-position compared to the unsubstituted compound **1 a** as well as a first-time deceleration of the examined reaction for the novel *spiro* derivatives **1 c** and **1 d**, containing cyclopropyl and cyclobutyl rings respectively. The introduction of these strained cyclic substituents resulted in an enlargement of the internal β angle, confirmed by single crystal XRD and DFT calculations. In contrast, the internal angle decreases with increasing steric demand of 5-substituents, demonstrated by the *gem*-dimethyl compound **1 b** and the *gem*-diphenyl derivative **1 e**. As a bicyclic system is obtained in the rate determining aziridinium ion formation, a *gem*-disubstituent effect can be assumed for the investigated solvolysis reaction (MeOH) of our 3-chloropiperidines. Yet, the observed acceleration and deceleration of rate constants cannot be explained by the reactive rotamer effect, since the orientation of the reactive centres is already locked in the cyclic piperidine system. Furthermore, the obtained relative rate constants k_{rel} as well as the experimentally determined Gibbs free energies of activation $\Delta G^{\ddagger}$ show good linear correlations with the internal β angle. Taken all of these results together, there is strong evidence for the presence of a classic, angle dependent Thorpe-Ingold effect separated from the reactive rotamer effect in the formation of bicyclic aziridinium ions. Although these angular distortion effects might be overcompensated by conformational effects in open-chain substrates, cyclic compounds seem to be essentially affected by the internal angle between the reactive centres. Consequently, this effect can be used as another useful approach to tune the reactivity of 3-chloropiperidines as DNA alkylating agents.

Experimental Section

All solvents were purified by distillation prior to use, in case of anhydrous solvents AcroSeal™ bottles from ACROS Organics™ were used. Commercially available reagents were used as supplied if not stated different. Synthesis using anhydrous solvents were carried out under Schlenk conditions. For purification by flash column chromatography silica gel 60 (Merck) was used. ^{1}H and ^{13}C NMR spectra were recorded at the Bruker Avance II 400, the Avance III 400 and the Bruker Avance II 200 "Microbay" spectrometer (^{1}H at 400 MHz and 200 MHz; ^{13}C at 101 MHz) in deuterated solvents. ^{1}H-NMR kinetic experiments were carried out at the Bruker Avance II 200 "Microbay" spectrometer (^{1}H at 200 MHz) and the Bruker Avance III 600 spectrometer (^{1}H at 600 MHz). ^{1}H and ^{13}C chemical shifts were determined by reference to the residual solvent signals. High-resolution ESI mass spectra were recorded in methanol using a ESImicroTOF spectrometer (Bruker Daltonics) in positive ion mode. All GC/MS spectra were recorded at the Aligent 5977B GC/MSD instrument equipped with a 7820 A GC System. All elemental analysis (CHN) were performed on a Thermo FlashEA–1112 series instrument. NMR spectra of the synthesized compounds **1 c**–**e**, **4 c**–**e** and **5 c**–**e** as well as the synthetic procedures for the known primary amines **4 c**–**e**[37,38] and their corresponding nitrile precursors are included in the Supporting Information. The synthesis of compounds **1 a** and **1 b** has been described elsewhere.[39,40]

General procedure for synthesis of secondary amines (5 c–e)

To a solution of the corresponding primary amine **4 c**–**e** in DCM (0.5 mL/mmol) freshly distilled *n*-butyraldehyde (1.1–1.4 eq.) as well as $MgSO_4$ (approx. 5–10 g) were added. The mixture was stirred at room temperature for 2 h, filtered afterwards and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (0.5 mL/mmol) and $NaBH_4$ (1.5–2 eq.) was added at 0 °C. The mixture was stirred at room temperature for 16–18 h. The reaction was then quenched by the addition of 20% $NaOH_{(aq)}$ and DCM was added. The phases were separated and the aqueous phase was extracted with DCM (3x). The combined organic extracts were washed with brine, distilled water as well as brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was obtained, which was used in the next step without further purification.

N-[(propenyl)cyclopropyl]methylbutanamine (5 c)

Was prepared according to the general procedure from [(Propenyl)cyclopropyl]methanamine **4 c** (0.47 g, 4.25 mmol) yielding the title compound **5 c** as a colorless oil (0.45 g) which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.85–5.77 (m, 1H, CH_2=C*H*-CH_2), 5.09–5.00 (m, 2H, CH_2=CH-CH_2), 2.62–2.57 (m, 2H, NH-CH_2-CH_2-CH_2-CH_3), 2.48 (s, 2H, CH_2-NH), 2.13 (dt, J = 7.1, 1.3 Hz, 2H, CH_2=CH-CH_2), 1.51–1.44 (m, 2H, CH_3-CH_2-CH_2-CH_2-NH), 1.37–1.28 (m, 3H, N*H* and CH_2-CH_3), 0.92 (m, 3H, CH_3), 0.44–0.34 (m, 4H, (CH_2)$_2$) ppm; ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 136.50 (CH_2=CH-CH_2), 116.37 (CH_2=*C*H-CH_2), 56.14 (CH_2-CH_2-NH), 49.77 (*C*H_2-NH), 39.26 (CH_2=CH-*C*H_2), 32.09 (CH_3-CH_2-*C*H_2-CH_2-NH), 20.63 (CH_3-*C*H_2), 19.58 (C_q), 14.03 (*C*H_3), 10.10 ((*C*H_2)$_2$) ppm; HRMS (ESI): *m/z* calcd for $C_{11}H_{21}N^{+}$: 168.1747, found: 168.1750 $[M+H]^{+}$.

N-[(propenyl)cyclobutyl]methylbutanamine (5 d)

Was prepared according to the general procedure from crude [(Propenyl)cyclobutyl]methanamine **4 d** (1.02 g) yielding the title compound **5 d** as a colorless oil (1.60 g) which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.77–5.68 (m, 1H, CH_2=C*H*-CH_2), 5.03–4.96 (m, 2H, CH_2=CH-CH_2), 2.59–2.52 (m, 2H, NH-CH_2-CH_2-CH_2-CH_3), 2.51 (s, 2H, CH_2-NH), 2.18 (d, J = 7.3 Hz, 2H, CH_2=CH-CH_2), 1.78–1.69 (m, 6H, (CH_2)$_3$), 1.46–1.36 (m, 2H, CH_3-CH_2-CH_2-CH_2-NH), 1.33–1.19 (m, 3H, N*H* and CH_2-CH_3), 0.87–0.83 (m, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 135.47 (CH_2=CH-CH_2), 116.77 (CH_2=*C*H-CH_2), 57.53 (CH_2-CH_2-NH), 50.52 (*C*H_2-NH), 42.11 (CH_2=CH-*C*H_2), 41.77 (C_q), 32.15 (CH_3-CH_2-*C*H_2-CH_2-NH), 29.70 ((*C*H_2)$_3$), 20.61 (CH_3-*C*H_2), 15.43 ((*C*H_2)$_3$), 14.16 (*C*H_3) ppm; HRMS (ESI): *m/z* calcd for $C_{12}H_{24}N^{+}$: 182.1903, found: 182.1903 $[M+H]^{+}$.

N-butyl-2,2-diphenylpent-4-en-1-amine (5 e)

Was prepared according to the general procedure from 2,2-Diphenyl-4-penten-1-amine **4 e** (2.90 g, 9.95 mmol) yielding the title compound **5 e** as a colorless oil (2.79 g) which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.29–7.25 (m, 4H, Ar-*H*), 7.20–7.17 (m, 6H, Ar-*H*), 5.43–5.34 (m, 1H, CH_2=C*H*-CH_2), 5.04–4.93 (m, 2H, CH_2=CH-CH_2), 3.19 (s, 2H, CH_2-NH), 3.01 (d, J = 7.1 Hz, 2H, CH_2=CH-CH_2), 2.52 (m, 2H, NH-CH_2-CH_2-CH_2-CH_3), 1.37–1.31 (m, 2H, NH-CH_2-CH_2-CH_2-CH_3), 1.27–1.19 (m, 3H, N*H* and CH_2-CH_3), 0.84 (t, J = 7.3 Hz, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 147.10 (arom. C_q), 135.18 (CH_2=CH-CH_2), 128.23 (arom. *C*H), 128.06 (arom. *C*H), 126.04 (arom. *C*H), 117.65 (CH_2=*C*H-CH_2), 56.16 (*C*H_2-NH), 50.25 (CH_3-CH_2-CH_2-*C*H_2-NH), 50.24 (CH_2=CH-*C*H_2), 41.86 (C_q), 32.15 (CH_3-CH_2-*C*H_2-CH_2-NH), 20.50 (CH_3-*C*H_2), 14.11 (*C*H_3) ppm; HRMS (ESI): *m/z* calcd for $C_{21}H_{28}N^{+}$: 294.2216, found: 294.2216 $[M+H]^{+}$. These data are consistent with published data.[50]

General procedure for synthesis of 3-chloropiperidines (1 c–d)

To a solution of the corresponding secondary amine **5 c**–**d** in THF (2 mL/mmol) copper(II)chloride dihydrate (1.2–1.6 eq.) was added. The mixture was stirred at room temperature for 16–18 h and a second portion of copper(II)chloride dihydrate (1.2–1.6 eq.) was added and the mixture was stirred at room temperature for another 18–48 h. Afterwards, the reaction was quenched by the addition of conc. $NH_{3(aq)}$ and DCM was added. The phases were separated and the aqueous phase was extracted with DCM (3x). The combined organic extracts were washed with distilled water as well as brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was obtained, which was purified by flash column chromatography.

N-butyl-5-cyclopropyl-3-chloropiperidine (1 c)

Was prepared according to the general procedure from crude *N*-[(propenyl)cyclopropyl]methylbutanamine **5 c** (53 mg) and purified by flash column chromatography ($R_f = 0.12$ (pentane/TBME 20 : 1)) yielding the title compound **1 c** as a colorless oil (38 mg, 0.19 mmol; 50 % from **4 c**). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 4.13$ (ddd, $J = 14.6$, 10.7, 4.2 Hz, 1H, C*H*-Cl), 3.22 (dd, $J = 12.0$, 3.0 Hz, 1H, CH_2), 2.51–2.25 (m, 3H, CH_2), 2.17 (t, $J = 10.7$ Hz, 1H, CH_2), 2.07–1.84 (m, 2H, CH_2-CH_2-CH_2-CH_3), 1.53–1.23 (m, 5H, CH_2 and CH_2-CH_2-CH_2-CH_3), 0.90 (t, $J = 7.1$ Hz, 3H, CH_3), 0.56–0.31 (m, 4H, (CH_2)$_2$) ppm; ^{13}C NMR ($CDCl_3$, 101 MHz): $\delta = 61.67$ (*C*H_2), 61.13 (*C*H_2), 57.88 (*C*H_2), 54.87 (*C*H–Cl), 44.30 (*C*H_2), 34.27 (*C*H_2), 29.01 (*C*H_2), 22.48 (*C*H_2), 20.82 (*C*H_2), 18.10 (*C*H_2), 14.20 (*C*H_2), 14.12 (*C*H_3), 13.09 ((*C*H_2)$_2$), 9.64 ((*C*H_2)$_2$) ppm; HRMS (ESI): *m/z* calcd for $C_{11}H_{21}ClN^+$: 202.1357, found: 202.1357 [M + H]$^+$; elemental analysis calcd (%) for $C_{11}H_{21}Cl_2N$: C 55.47, H 8.89, N 7.44; found: C 55.78, H 8.83, N 7.64.

N-butyl-5-cyclobutyl-3-chloropiperidine (1 d)

Was prepared according to the general procedure from crude *N*-[(propenyl)cyclobutyl]methylbutanamine **5 d** (226 mg) and purified by flash column chromatography ($R_f = 0.29$ (DCM/acetone 50 : 1)) yielding the title compound **1 d** as a colorless oil (82 mg, 0.38 mmol; 33 % from **4 d**). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 3.90$ (td, $J = 10.9$, 5.7 Hz, 1H, C*H*-Cl), 3.08 (d, $J = 7.9$ Hz, 1H, CH_2), 2.79 (d, $J = 11.5$ Hz, 1H, CH_2), 2.42–2.25 (m, 3H, CH_2), 1.99 (t, $J = 10.9$ Hz, 1H, CH_2), 1.95–1.67 (m, 8H, (CH_2)$_3$ and CH_2-CH_2-CH_2-CH_3), 1.50–1.38 (m, 3H, CH_2 and CH_2-CH_2-CH_3), 1.32 (h, $J = 7.5$ Hz, 2H, CH_2-CH_3), 0.91 (t, $J = 7.3$ Hz, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 62.87$ (*C*H_2), 61.90 (*C*H_2), 57.91 (*C*H_2), 53.95 (*C*H–Cl), 47.20 (*C*H_2), 39.98 (*C*H_2), 31.54 ((*C*H_2)$_3$), 31.17 (*C*H_2), 29.11 (*C*H_2), 20.71 (*C*H_2), 15.94 (*C*$_q$), 14.14 (*C*H_3) ppm; HRMS (ESI): *m/z* calcd for $C_{12}H_{24}ClN^+$: 216.1514, found: 216.1514 [M + H]$^+$; elemental analysis calcd (%) for $C_{12}H_{24}Cl_2N$: C 57.14, H 9.19, N 5.55; found: C 57.17, H 9.11, N 5.78.

N-butyl-5,5-diphenyl-3-chloropiperidine (1 e)

To a solution of the secondary amine **5 e** (440 mg, 1.34 mmol) in THF (25 mL) copper(II)chloride (180 mg, 1.34 mmol, 1.0 eq.) was added. The mixture was stirred at room temperature for 3 h and was then heated to reflux for another 22 h. Afterwards, the reaction was quenched by the addition of conc. $NH_{3(aq)}$ and DCM was added. The phases were separated and the aqueous phase was extracted with DCM (3x). The combined organic extracts were washed with distilled water as well as brine and dried over $MgSO_4$ The solvent was removed under reduced pressure and the crude product was obtained, which was purified by flash column chromatography ($R_f =$ 0.37 (pentane/TBME 50 : 1)) yielding the title compound **1 e** as a colorless solid (198 mg, 0.60 mmol; 45 %). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.43$–7.39 (m, 2H, Ar-*H*), 7.31–7.24 (m, 4H, Ar-*H*), 7.20–7.14 (m, 4H, Ar-*H*), 3.90–3.78 (m, 1H, C*H*-Cl), 3.63 (d, $J = 12.1$ Hz, 1H, CH_2), 3.25 (dd, $J = 10.2$, 3.9 Hz, 1H, CH_2), 2.96 (d, $J = 12.3$ Hz, 1H, CH_2), 2.46 (t, $J = 7.4$ Hz, 2H, CH_2-CH_2-CH_2-CH_3), 2.34 (t, $J = 12.2$ Hz, 1H, CH_2), 2.23–2.14 (m, 2H, CH_2), 1.56 (ddt, $J = 20.6$, 13.1, 6.4 Hz, 2H, CH_2-CH_2-CH_2-CH_3), 1.37 (h, $J = 7.4$ Hz, 2H, CH_2-CH_3), 0.96 (t, $J = 7.3$ Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 147.72$ (arom. *C*H), 145.39 (arom. *C*H), 128.72 (arom. *C*H), 128.47 (arom. *C*H), 128.21 (arom. *C*H), 126.58 (arom. *C*H), 126.47 (arom. *C*$_q$), 126.05 (arom. *C*$_q$), 62.58 (*C*H_2), 61.80 (*C*H_2), 58.01 (*C*H_2), 53.96 (*C*H–Cl), 48.30 (*C*H_2), 46.24 (*C*H_2), 28.87 (*C*H_2), 20.82 (*C*H_2), 14.18 (*C*H_3) ppm; HRMS (ESI): *m/z* calcd for for $C_{21}H_{27}ClN^+$: 328.1827, found: 328.1826 [M + H]$^+$; elemental analysis calcd (%) for $C_{21}H_{27}Cl_2N$: C 69.23, H 7.47, N 3.84; found: C 68.88, H 7.58, N 3.82.

Crystallographic data: Deposition Numbers 2153718 (for **1 a**), 2153719 (for **6 b**), 2153720 (for **6 a**), 2153721 (for **1 c**), and 2154152 (for **1 e**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service < url

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Angle distortion · Geminal disubstituent effect · Kinetics · Structure-Activity relationship · Thorpe-Ingold-Effect

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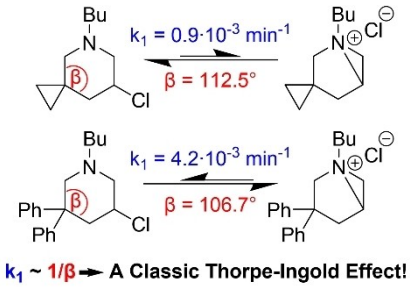
RESEARCH ARTICLE

A classic, angle dependent Thorpe-Ingold effect in the formation of bicyclic aziridinium ions is presented. Kinetic studies, backed up by SC-XRD and DFT calculations, reveal a linear correlation of the internal angle β with the rate constant k_1. Increased angles result in decreased rate constants and *vice versa*. The cyclic structure of the examined 3-chloropiperidines thereby excludes contribution of the reactive rotamer effect towards this cyclization.



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Separation of the Thorpe–Ingold and Reactive Rotamer Effect by Using the Formation of Bicyclic Aziridinium Ions