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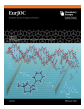

Understanding the Alkylation Mechanism of 3-Chloropiperidines – NMR Kinetic Studies and Isolation of Bicyclic Aziridinium Ions

Tim Helbing,[a] Mats Georg,[a] Fabian Stöhr,[a, b] Caterina Carraro,[c] Jonathan Becker,[b] Barbara Gatto,[c] and Richard Göttlich*[a]

The present study describes the kinetic analysis of the 3-chloropiperidine alkylation mechanism. These nitrogen mustard-based compounds are expected to react via a highly electrophilic bicyclic aziridinium ion, which is readily attacked by nucleophiles. Halide abstraction using silver salts with weakly coordinating anions lead to the isolation of these proposed intermediates, whereas their structure was confirmed by single crystal XRD. Kinetic studies of the aziridinium ions also revealed notable reactivity differences of the C5 gem-methylated compounds and their unmethylated counterparts. The observed reactivity trends were also reflected by NMR studies in aqueous solution and DNA alkylation experiments of the related 3-chloropiperidines. Therefore, the underlying Thorpe-Ingold effect might be considered as another option to adjust the alkylation activity of these compounds.

Introduction

Since many years alkylating agents serve as therapeutic agents for the treatment of cancer.[1] Amongst these therapeutic alkylating agents, nitrogen mustards like mechlorethamine and chlorambucil (Figure 1a) represent one of the first clinically applied chemotherapeutics which are used in cancer treatment.[2] Their simple but effective molecular mode of action involves the formation of an electrophilic aziridinium ion by intramolecular displacement of a chloride, which is then readily attacked by nucleophiles such as the guanine base in DNA.[3] The resulting covalent adducts eventually lead to depurination and strand cleavage, potentially followed by apoptosis of the cancer cell.[4] Despite the fact that there are numerous other promising candidates for the treatment of cancer and that alkylating agents suffer from severe side effects, these compounds continue to be an important class of therapeutics in today's clinical use. Consequently, our working group developed 3-chloropiperidines as cyclic analogues of nitrogen mustards, whose simple and easily modifiable synthesis led to a broad set of compounds.[5] These novel compounds also demonstrated to be effective DNA alkylating agents with different *in vitro* potencies, confirmed to be preferentially attacked by the N^7-position of the guanine nucleobase.[6]

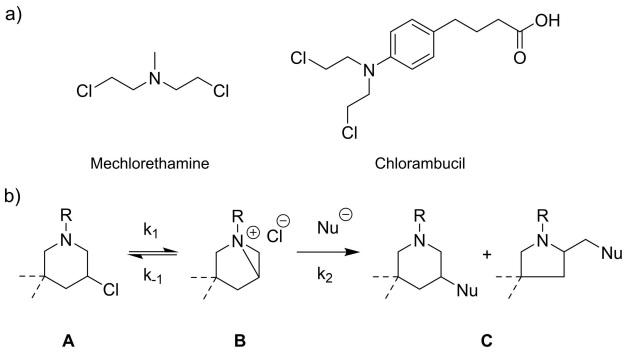

Figure 1. a) Structures of the nitrogen mustards mechlorethamine and chlorambucil. b) General structure of a 3-chloropiperidine **A** in equilibrium with the corresponding aziridinium ion **B**, which is attacked by a nucleophile forming the alkylation products **C**.

In our previous studies on monofunctional 3-chloropiperidines (Figure 1b, **A**) we noticed that the two methyl groups attached in the 5-position of the piperidine ring highly effect the reactivity of the 3-chloropiperidines in comparison to their respective unmethylated analogues.[7] This observation seemed to be worth a detailed examination, since the gem-methylation resulted from our original synthesis and should accelerate the cyclisation *via* Thorpe-Ingold effect.[8] Hence, in the present work we focused on analysing the kinetics of the underlying alkylation reaction while also taking a closer look at the

[a] *T. Helbing, M. Georg, F. Stöhr, Prof. Dr. R. Göttlich*
Institute of Organic Chemistry,
Justus Liebig University Giessen
Heinrich-Buff-Ring 17, 35392 Giessen, Germany
E-mail: richard.göttlich@org.chemie.uni-giessen.de
https://www.uni-giessen.de/fbz/fb08/Inst/organische-chemie/AGGoettlich
[b] *F. Stöhr, J. Becker*
Institute of Inorganic and Analytical Chemistry,
Justus Liebig University Giessen
Heinrich-Buff-Ring 17, 35392 Giessen, Germany
[c] *C. Carraro, Prof. Dr. B. Gatto*
Department of Pharmaceutical and Pharmacological Sciences,
University of Padova
Via Francesco Marzolo 5, 35131 Padova, Italy

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intermediate bicyclic aziridinium ion **B**. The regioselective ring opening reactions of these intermediates proved to be useful for various synthetic applications and have been studied intensively.[9] We therefore investigated the reaction of the four 3-chloropiperdines **1–4** as well as the reference compound 2-chloroethyl diethylamine **5** (Figure 2) in aqueous solution and the presence of 2'-desoxyguanosine as a nucleophile by NMR spectroscopy. The selected series of compounds cover electronic effects induced by different substituents on the piperidine nitrogen as well as the impact of ring methylation in 5-position. Beside these aqueous solution studies, we also isolated the corresponding aziridinium ions of these compounds, which are expected to be the intermediates of the alkylation reaction and studied their respective reactivity with different nucleophiles. These experiments also led to the crystallization of some of the aziridinium ions, confirming the bicyclic structure of the proposed reaction intermediate by single crystal XRD.

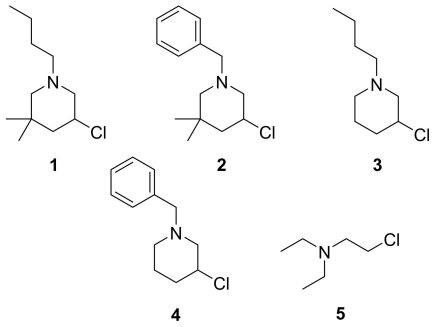
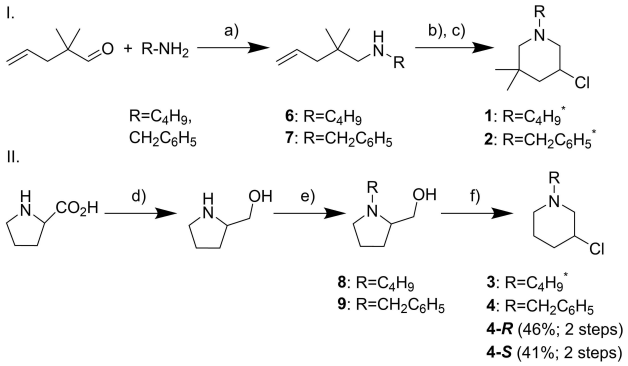


Figure 2. Structures of the analysed 3-chloropiperidines **1–4** and the half-mustard 2-chloroethyl diethylamine **5** used as a reference compound.

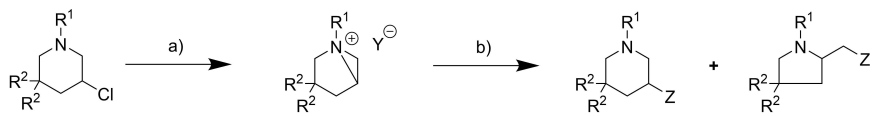


Scheme 1. Synthesis of 3-chloropiperidines **1–4**. a) $NaBH(OAc)_3$, AcOH, dry CH_2Cl_2, 0 °C to RT; b) NCS, dry CH_2Cl_2, 0 °C to RT; c) TBAI (cat.), dry $CHCl_3$, 60 °C (inseparable diastereomeric mixture); d) $LiAlH_4$, dry THF, 0 °C to reflux; e) butyl iodide, K_2CO_3, dry THF, reflux (**8**) or NEt_3, dry THF, RT (**9**); f) $SOCl_2$, pyridine, dry CH_2Cl_2, 0 °C to RT (**3**) or MsCl, DIPEA, dry CH_2Cl_2, 0 °C to RT (**4**). *The synthesis of compounds **1**, **2** and **3** has been described elsewhere.[7,8,10]

Results and Discussion

The synthesis of the 3-chloropiperidines **1**, **2** and **3** has already been described in our previous work.[7,8,10] The applied synthetic strategy for the methylated compounds **1** and **2** involves a reductive amination of 2,2-dimethyl-4-pentenal[11] with butylamine or benzylamine respectively, followed by *N*-chlorination with NCS and iodine catalysed cyclization[8] to obtain the final cyclic products in high yield (Scheme 1, I). For the unmethylated analogues **3** and **4** the synthesis starts from proline, which enables the preparation of enantiopure compounds by selecting either D- or L-proline as the starting material, as described recently.[7] The amino acid was reduced to prolinol using lithium aluminium hydride, afterwards substituted with butyl iodide or benzylic bromide to obtain the alcohols **8** and **9** respectively, which were finally reacted with thionyl chloride or methanesulfonyl chloride to afford the desired 3-chloropiperidine *via* stereoconvergent ring expansion (Scheme 1, II).

The obtained 3-chloropiperidines **1–4** were used as starting materials for the formation of their corresponding aziridinium ions **10–13**. Therefore, a halide abstraction reaction of the corresponding 3-chloropiperidines with one equivalent of silver perchlorate or silver tetrafluoroborate in anhydrous acetone was performed inside a glove box under exclusion of light and the reaction was monitored by TLC (Scheme 2). After filtration of the precipitated inorganic salts and removal of the solvent, the aziridinium ions were obtained and analysed by NMR spectroscopy. Notably the formation of the gem-methylated aziridinium ions seemed to occur faster than for their respective non-methylated analogues, since TLC control showed completion of the reaction after several hours rather than days for the



Scheme 2. Synthesis of aziridinium ions from 3-chloropiperidines **1–4** and subsequent reaction with nucleophiles. a) $AgClO_4$ or $AgBF_4$, dry Acetone; b) Imidazole or MeOH, dry CD_3CN, RT or 50 °C.

unmethylated piperidines. Therefore, the reactions of **1** and **3** with silver tetrafluoroborate in deuterated acetone were studied by NMR spectroscopy. Small aliquots of the solution were taken after appropriate points in time, mixed with dibenzyl ether as an internal standard and filtered to remove the precipitated silver chloride. This analysis confirmed that the conversion of both reactions is almost quantitative (>95%). According to these measurements the aziridinium ion formation of the methylated piperidine **1** was completed in less than one hour while the reaction of the unmethylated compound **3** with $AgBF_4$ took roughly 24 h until the starting material was not detectable anymore. This last sample still showed small amounts of silver chloride precipitating even after 24 h, indicating that the reaction was not finished. A possible explanation for the accelerated aziridinium ion formation might be an amplification of the neighbouring group effect, induced by the angle contraction arising from the gem-methylation in 5-position, just as the previously mentioned faster cyclization of gem-methylated *N*-chloroamines.

Similarly, we noticed a fast aziridinium ion formation for 3-chloropiperidine **2**, although prolonged stirring resulted in the formation of a complex and inseparable mixture of compounds including an oxazolidinium salt by solvolysis reaction (confirmed by HRMS), as previously reported for other reactive aziridinium salts.[12] Therefore, the reaction was stopped after one hour and remaining starting material was removed by precipitation of the product with diethyl ether. Although the aziridinium ion **11** could be isolated under these conditions, a similar side reaction took place after a couple of hours with the NMR solvent (CD_3CN).[13] If the counter ion was changed to BF_4^-, the crude product showed additional decomposition visible by colourization, and was therefore excluded in further studies.

Since the aziridinium ions **10** and **11** could be isolated as colourless solids we also tried to crystallize these compounds. Vapour diffusion crystallization with diethyl ether finally led to crystals of **10a** and **11** suitable for structure determination by single crystal XRD (Figure 3). Primarily the obtained crystal structures confirm the bicyclic structure of the aziridinium ion proposed as the intermediate of the reaction of our 3-chloropiperidines with nucleophiles, while the structure of **11** is congruent with an already described aziridinium ion obtained by a different method.[14] Furthermore, the boat-like structures of these intermediates match the computational calculations

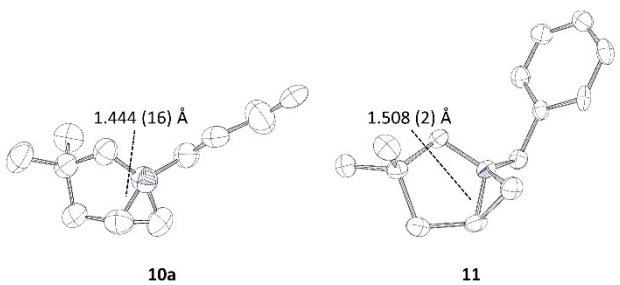
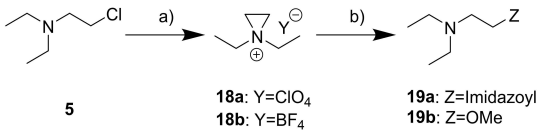


Figure 3. Molecular structures of the bicyclic aziridinium ions **10a** and **11** derived from single crystal structures. Hydrogens and ClO_4^- anions are omitted for clarity, ellipsoids are drawn at 50% probability.

for C4 fluorinated bicyclic aziridinium ions obtained from the corresponding prolinol derivatives.[15] Comparison of the two structures also allows assumptions about the reactivity of the benzyl substituted aziridinium ion **11** compared to the butyl analogue **10a**. Although **10a** in crystalline state exhibits whole molecule disorder (see Table S4-S7 for details), the length of the newly formed bond between the piperidine nitrogen and C3 is shorter compared to the benzyl aziridinium ion **11** (Figure 3). This difference in bond length, and therefore in bond strength, might be a first explanation for the fast decomposition of compound **11**, while also indicating a higher reactivity compared to the butyl analogue **10a**. Although we tested multiple anions and conditions, we were not able to crystallize the unmethylated aziridinium ions **12** and **13** to strengthen our estimation of a correlation between reactivity and bond length observed in accessible aziridinium ion crystal structures.

Next, to further explore the previously mentioned reactivity hypothesis we started to study the reaction of the aziridinium ions **10–13** with nucleophiles, choosing imidazole and methanol as model compounds for biologically relevant nucleophiles. The aziridinium ions obtained above were dissolved in deuterated acetonitrile and reacted with two equivalents of the corresponding nucleophile to obtain a mixture of the piperidine and pyrrolidine adducts **14–17** (Scheme 2). This mixture was directly analysed in the NMR and after aqueous workup also by GC-MS to determine the ratio of five-membered to six-membered ring product. The corresponding anion (ClO_4^- and BF_4^-) did not influence the reactivity of the aziridinium ions with nucleophiles in our experiments. Moreover, comparative samples of these compounds were obtained from the corresponding 3-chloropiperidines by reaction with an excess of the according nucleophile (see Supporting Information for details). In both, the reaction of the aziridinium ions with the nucleophiles and the direct alkylation reactions of the 3-chloropiperidines, we observed a strong preference of the gem-methylated compounds **14** and **15** (or **1** and **2** respectively) for the piperidine adduct, while the unmethylated compounds **16** and **17** (or **3** and **4** respectively) generally preferred the pyrrolidine adduct. Overall, the regiochemistry of ring opening reactions of bicyclic aziridinium ions is dependent on several factors such as the attacking nucleophile[16] as well as substituents[17] and has also been studied intensively under theoretical aspects.[18,19] In line with our results, the ring opening of gem-methylated bicyclic aziridinium ions favours the thermodynamic six-membered piperidine product,[20] while the unmethylated compounds typically prefer the kinetic five-membered pyrrolidine product with the exact ratio depending on the aforementioned aspects.

In addition to the bicyclic aziridinium ions derived from our 3-chloropiperidines, we synthesised the aziridinium ions **18a** and **18b** of the half-mustard 2-chloroethyl diethylamine **5** and reacted them with two equivalents of imidazole and methanol respectively (Scheme 3). This enabled a direct comparison with a reference compound known to undergo alkylation reactions *via* the aziridinium ion **18**.[21] Again, comparative samples of the alkylation products were synthesised from 2-chloroethyl diethyl-



Scheme 3. Synthesis of the aziridinium ion of 2-chloroethyl diethylamine **5** and subsequent reaction with nucleophiles. a) $AgClO_4$ or $AgBF_4$, dry Acetone; b) Imidazole or MeOH, dry CD_3CN, RT or 50 °C.

amine **5** and the corresponding nucleophiles (see Supporting Information for details).

While the reaction of all aziridinium ions with imidazole occurred immediately at room temperature and according to NMR quantitatively (> 95 %), the compounds proved to be less reactive against methanol. After incubation of a sample of **10 b** with two equivalents of methanol overnight at room temperature, only half of the aziridinium ion reacted with the alcohol. We therefore analysed that reaction at 50 °C for 16 h, recording an NMR spectrum every 30 mins. In this case only a small amount of the starting material remained, leading to a product mixture primarily containing the 3-methoxypiperidine product of **14 b**. This approach was also applied to the different aziridinium ions **12 b**, **13 b** and **18 b**, which enabled a direct comparison of their reactivity by plotting the natural logarithm of the integral from a distinct aziridinium ion signal *Ln(Az⁺)* against the reaction time *t* (Figure 4). Due to the already observed instability, the aziridinium ion **11** had to be excluded in this analysis.

All methanolysis reactions seem to follow pseudo first order kinetics, as a reasonable linear regression was only possible in case of a first order reaction. Even though, the different reaction behaviour with respect to methanol and imidazole as nucleophiles supports previous studies of 3-chloro-1-ethylpiperidine with various nucleophiles.[22] Nevertheless, this method allowed a comparison of the bicyclic aziridinium ions **10 b**, **12 b** and **13 b** as well as the half-mustard based reference aziridinium ion **18 b** by determining their respective rate constants from the slope of the linear regression. The most remarkable difference is again noticed between the C-5 gem-methylated aziridinium ion **10 b** ($t_{1/2}$ = 507 min) and the corresponding unmethylated analogue **12 b** ($t_{1/2}$ = 12583 min) since their respective half-lives vary by two orders of magnitude. As already observed for the formation of the aziridinium ions, the methylated compounds react much faster than the unmethylated analogues. Once again, the gem-methylation could be the reason. Due to the boat-like structure of the aziridinium ions the methyl groups in 5-position induce additional strain into the bicyclic system, thus favouring a ring opening reaction resulting in a more reactive aziridinium ion. On one hand, this explains the higher reactivity of the bicyclic compound **10 b** compared with the monocyclic half-mustard reference **18 b**, although the difference in rate constants is not as outstanding as compared to the unmethylated aziridinium ions **12 b** and **13 b**. On the other hand, the aziridinium ions **12 b** and **13 b** were expected to be more reactive than the reference compound **18 b** due to their bicyclic character, which is apparently not the case in our kinetic studies. These findings suggest that the unmethylated aziridinium ions are also quite stable towards hydrolysis, while their fast reaction with imidazole shows that they are still able to alkylate nitrogen nucleophiles efficiently. Looking to support these results we dissolved a sample of the most reactive aziridinium ion **10 b**

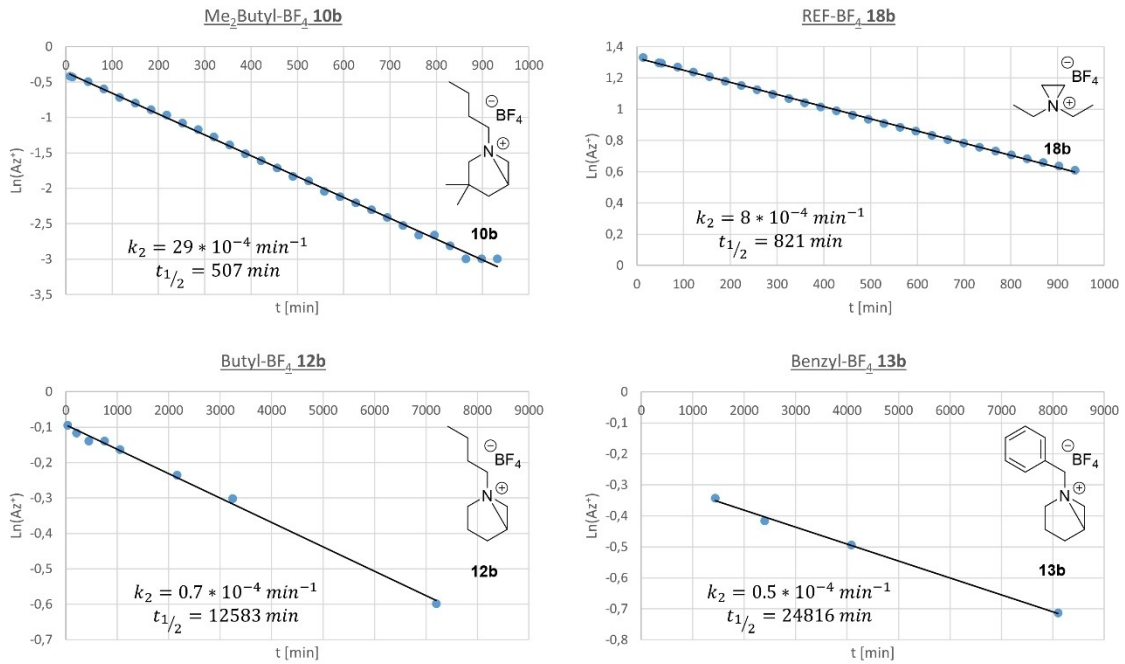
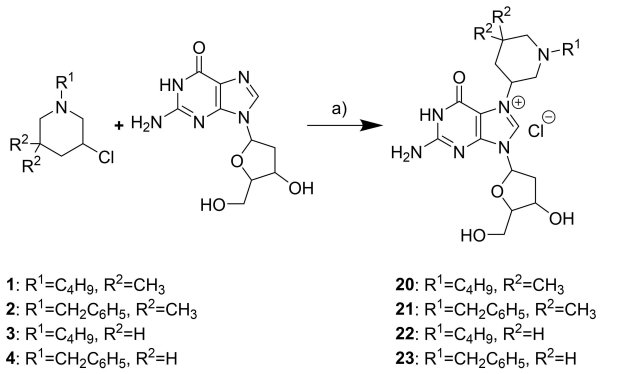


Figure 4. Reaction of aziridinium ions **10 b**, **12 b**, **13 b** and **18 b** with methanol at 50 °C observed in the NMR. The natural logarithm of the integral from a distinct aziridinium ion signal *Ln(Az⁺)* is plotted against the reaction time *t* and from the slope of the linear regressions the reaction rate constants k_2 are determined.

and the least reactive compound **13b** in methanol (0.1 M) and added two equivalents of imidazole. GC/MS analysis of the product mixture showed a 3:1 preference for the imidazole product of **10b**, while the reaction of **13b** with imidazole was favoured by a factor of 13:1.

To further explore this striking reactivity difference, we chose to directly measure the reaction rate of an alkylation reaction for the 3-chloropiperidines **1–4** in aqueous solution. We therefore studied the reaction of these compounds in the NMR using one equivalent of 2′-desoxyguanosine (Scheme 4) in a 1:1 mixture of DMSO-d^6 and phosphate buffered D_2O (pH = 7.4). The reaction mixture was heated to 50 °C and analysed for 16 h, recording an NMR spectrum every 30 mins. Figure 5 shows sections of four different recorded ^{1}H-NMR spectra over the course of the reaction. In the initial spectrum, recorded after four minutes, distinct signals of the 3-chloropiperidine **2** (red) and 2′-desoxyguanosine (green) are visible. After roughly three hours (t = 174 min) these signals significantly decrease in intensity and an additional signal of the alkylation product **21** (grey) is visible. Over the course of reaction (t = 548 and 888 min) the signals of the starting material and the 2′-desoxygunaosine constantly decrease in intensity, while the signal of the alkylation product stays rather constant, a consequence of the increased acidity of the C-8 proton as a result of the alkylation, which undergoes exchange with the deuterated solvent.[23] In addition, small signals of the corresponding hydrolysis side product **2OH** start to appear, increasing in intensity very slowly and staying low even after 16 h, again showing that the *N*-alkylation reaction is much faster compared to the hydrolysis of the 3-chloropiperidines.



1: R^1=C_4H_9, R^2=CH_3
2: R^1=$CH_2C_6H_5$, R^2=CH_3
3: R^1=C_4H_9, R^2=H
4: R^1=$CH_2C_6H_5$, R^2=H

20: R^1=C_4H_9, R^2=CH_3
21: R^1=$CH_2C_6H_5$, R^2=CH_3
22: R^1=C_4H_9, R^2=H
23: R^1=$CH_2C_6H_5$, R^2=H

Scheme 4. Alkylation reaction of 3-chloropiperidines 1–4 with 2′-desoxyguanosine to the alkylation products **20–23**. a) 50 °C, 1:1 DMSO-d^6/phosphate buffered D_2O (pH = 7.4).

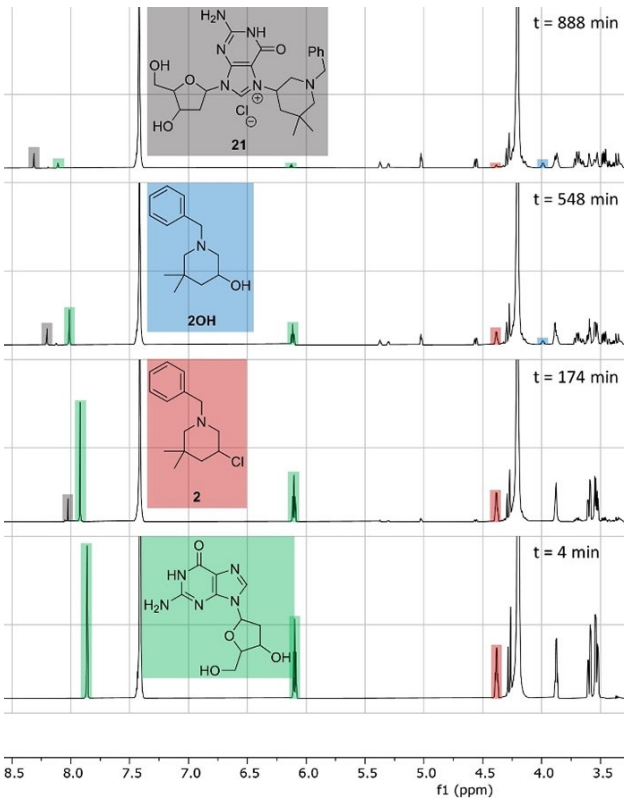


Figure 5. NMR spectra recorded at different times during the reaction of 3-chloropiperidine **2** with 2′-desoxyguanosine at 50 °C in a 1:1 mixture of DMSO-d^6 and phosphate buffered D_2O (pH = 7.4).

This experiment was repeated with the 3-chloropiperidines **1**, **3** and **4**, while the consumption of the starting material was monitored by referencing the integration to the residual DMSO signal. The natural logarithm of one distinct 3-chloropiperidine signal *Ln(Cl)* was plotted against the reaction time *t*. From the slope of the linear regression the rate constant k_1 was determined (Figure 6). All reactions follow first order kinetics regarding the 3-chloropiperidine, as the first step of their alkylation reaction is the formation of the corresponding aziridinium ion, which is rapidly consumed afterwards, implementing the steady state approximation ($k_2 \gg k_{-1}$). For the unmethylated compounds **3** ($t_{1/2}$ = 3306 min) and **4** ($t_{1/2}$ = 1728 min) the reaction was again much slower compared to their methylated analogues **1** ($t_{1/2}$ = 708 min) and **2** ($t_{1/2}$ = 423 min), as apparent from their respective half-lives and the reduced consumption of the starting materials after 16 h of reaction time (Table S2). The rate constants of the methylated 3-chloropiperidines **1** and **2** were only determined in the first half of the reaction time. After this point the rapid consumption of the aziridinium ion seems to become inconsistent due to the lower concentration of available nitrogen nucleophile, which might also explain the appearance of the hydrolysis side product **2OH** solely after eight to nine hours of incubation. Nonetheless, the reactivity trend we previously observed in the consumption kinetics of the aziridinium ions **10b**, **12b** and **13b**, as well as our estimations from their crystal structures and formation rate of aziridinium ions appear to match the alkylation reactions of the 3-chloropiperidines **1–4** in aqueous solution. The *N*-benzyl substitution seems to accelerate the reaction compared to the corresponding *N*-butyl compounds while the gem-methylation in 5-position again results in a much faster consumption of the starting material. Accordingly, the double ring methylation increased the reactivity of **1** and **2** also with plasmid DNA after 8 h of incubation at 37 °C (Figure S3), in line with previous observations at different incubation times.[7] When analysing a complex model nucleophile as in the case of plasmid DNA, the *N*-benzyl substitution slightly accelerated the reactivity of the unmethylated analogue **4** while this effect was not seen in the case of **2**.

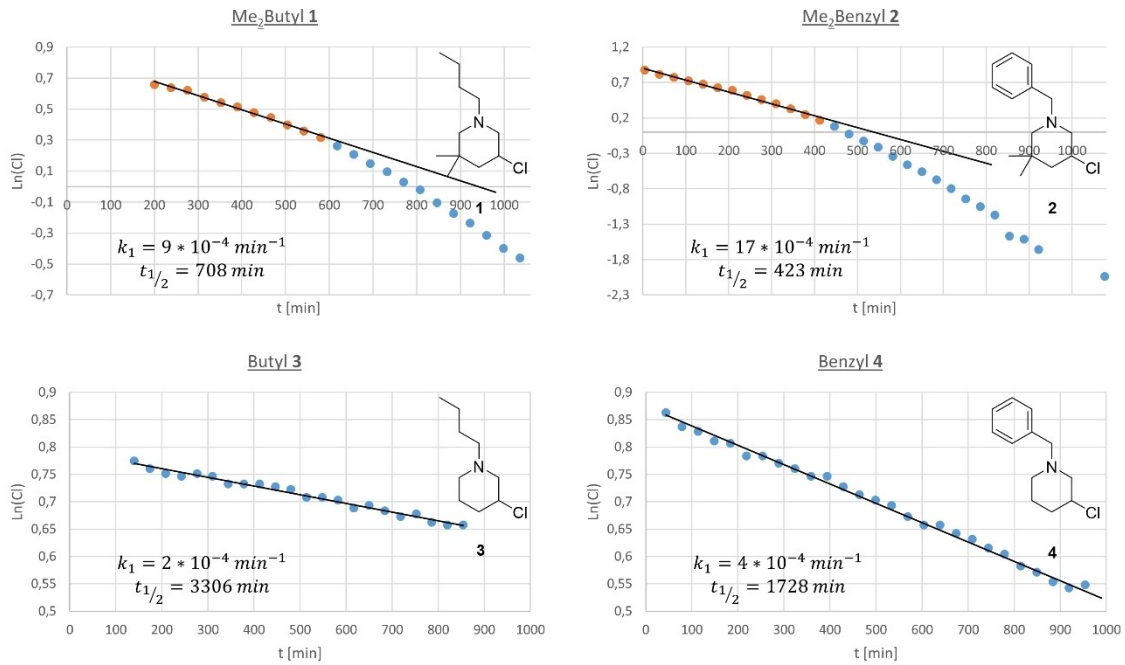


Figure 6. Reaction of 3-chloropiperidines **1–4** with 2′-desoxyguanosin at 50 °C observed in the NMR. The natural logarithm of the integral from a distinct aziridinium ion signal *Ln(Cl)* is plotted against the reaction time *t* and from the slope of the linear regressions the reaction rate constants k_1 are determined.

To get a final validation for our established NMR-method we repeated the aqueous reaction kinetic using the reference compound **5** and 2′-desoxyguanosine as a nucleophile. Since the reaction of its corresponding nitrogen mustard analogue mechlorethamine with nucleophiles in aqueous solution is known to proceed rapidly[24] and studies of the half-mustard derivative **5** with different nucleophiles in DMF show fast first-order rate constants,[25] therefore the reaction is expected to be a suitable comparison in our case. Indeed, the observed half-life ($t_{1/2}$ = 286 min) was lower compared to our 3-chloropiperidines **1–4** and after already 15 h reaction time no starting material could be detected (Figure 7). Furthermore, we observed a behaviour similar to the reactions of the gem-methylated 3-chloropiperidines **1** and **2**. After a considerable amount of alkylation product **24** has built up, the reaction seemed to not follow first order kinetics anymore. This might be a consequence of the increasing chloride concentration, which can compete with the 2′-desoxyguanosine as a nucleophile. This results in a fast equilibrium between the starting material and the aziridinium ion, changing the kinetic behaviour.[18] Since we also observed this change in kinetics for the more reactive gem-methylated 3-chloropiperidines **1** and **2**, these findings support the applicability of this method for mustard based alkylating agents.

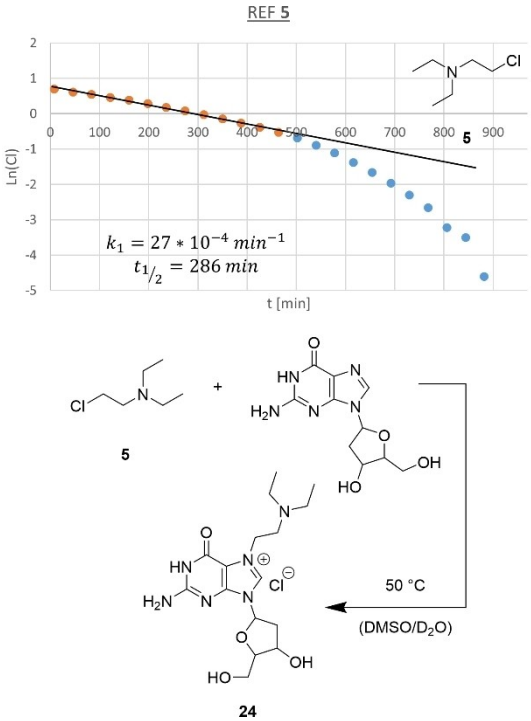


Figure 7. Reaction of 2-chloroethyl diethylamine **5** with 2′-desoxyguanosin to the alkylation product **24** observed in the NMR at 50 °C in a 1:1 mixture of DMSO-d^6/phosphate buffered D_2O (pH = 7.4). Plotted is the natural logarithm of the integral from a distinct signal *Ln(Cl)* against the reaction time *t*, from the slope of the linear regression the reaction rate constant k_1 was determined.

Conclusion

In conclusion, we developed a fast and easy method for the initial estimation of the reactivity of our 3-chloropiperidines by NMR spectroscopy, demonstrated by the reactions of com-

pounds **1–4** in aqueous solution with 2′-desoxyguanosine as a nucleophile. Accordingly, the alkylation activity of these compounds is significantly increased by C-5 gem-methylation, as also suggested by results with model DNA.[7] The *N*-substitution has a lower influence on the reactivity and is affected by the complexity of the structure and the context of the examined nucleophile. We could also demonstrate that these reactions follow first order kinetics and behave similar to the known half-mustard 2-chloroethyl diethylamine **5** in aqueous solution. Furthermore, we were able to isolate the corresponding aziridinium ions of the 3-chloropiperidines **1–4** and yet obtained crystal structures of the two aziridinium salts **10a** and **11**, confirming their boat-like bicyclic structure and enabling a direct structure-activity comparison. Kinetic studies of these aziridinium ions again confirmed the higher reactivity of the C-5 gem-methylated compounds, while also demonstrating their ability to alkylate nitrogen nucleophiles efficiently. These results indicate that the Thorpe-Ingold effect induced by the gem-methylation seems to be more relevant for the reactivity of our 3-chloropiperidines than initially expected. Therefore, ongoing kinetic and computer chemical studies intent to reveal a possible correlation between the C-5 angle contraction and the alkylation activity of monofunctional 3-chloropiperidines.

Experimental Section

All solvents were purified by distillation prior to use, in case of anhydrous solvents 100 mL AcroSeal™ bottles from ACROS Organics™ were used. Commercially available reagents were used as supplied if not stated different, reagents used in the glovebox were dried in advance using standard procedures. Synthesis using anhydrous solvents were carried out under Schlenk conditions or in a nitrogen-filled glovebox if specifically stated. 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 and Avance III 400 spectrometer (^{1}H at 400 MHz; ^{13}C at 100 MHz) in deuterated solvents. NMR kinetic experiments were carried out at the Bruker Avance III 600 spectrometer (^{1}H at 600 MHz). ^{1}H 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 **4-*S*, 4-*R*, 10a, 10b, 11, 12a, 12b, 13a** and **13b** as well as the synthetic procedures for the compounds **14–17** (obtained from the corresponding aziridinium ions and 3-chloropiperidines) are included in the supplementary information. The synthesis of compounds **1–3** as well as their corresponding precursors has been described elsewhere.[7,8,10]

(3R)-1-benzyl-3-chloropiperidine (4-R)

Under a nitrogen atmosphere (*S*)-2-(hydroxymethyl)pyrrolidine (505 mg, 4.99 mmol) was dissolved in anhydrous THF (25 mL) and anhydrous triethylamine (0.78 mL, 5.63 mmol) was added. Afterwards benzyl bromide (0.48 mL, 4.04 mmol) was added dropwise at 0 °C and the mixture was stirred at room temperature for 21 h. The solvent was removed under reduced pressure, the crude product was redissolved in anhydrous DCM (25 mL) and anhydrous DIPEA (2.1 mL, 12.06 mmol) was added. Afterwards freshly distilled methanesulfonyl chloride (0.63 mL, 8.14 mmol) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 2 and for 18 h at room temperature. The mixture was then partitioned between brine and ethyl acetate (50 mL each) and the phases were separated. The aqueous phase was then extracted twice with ethyl acetate and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (DCM/acetone 100:1) yielding the title compound as a colourless oil (390 mg, 1.86 mmol, 46%). $[\alpha]_{589}^{25} = -18.6 \pm 1.4$ (c = 25 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.26 (m, 5H, aromatic C*H*), 4.05–3.96 (m, 1H, C*H*), 3.55 (s, 2H, ArCH_2), 3.05 (d, J = 11.1 Hz, 1H, CH_2), 2.72 (d, J = 11.6 Hz, 1H, CH_2), 2.25–2.07 (m, 3H, overlap CH_2), 1.81–1.75 (m, 1H, CH_2), 1.68–1.52 (m, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.89, 129.17, 128.41, 127.32, 62.81, 61.37, 56.17, 52.92, 34.99, 24.90 ppm. HRMS (ESI): *m/z* calcd for $C_{12}H_{17}ClN^+$: 210.1044; found: 210.1047 $[M+H]^+$; elementary analysis calcd (%) for $C_{12}H_{16}ClN$: C 68.73, H 7.69, N 6.68; found: C 68.82, H 7.63, N 6.59.

(3S)-1-benzyl-3-chloropiperidine (4-S)

Under a nitrogen atmosphere (*R*)-2-(hydroxymethyl)pyrrolidine (494 mg, 4.88 mmol) was dissolved in anhydrous THF (25 mL) and anhydrous triethylamine (0.79 mL, 5.70 mmol) was added. Afterwards benzyl bromide (0.49 mL, 4.12 mmol) was added dropwise at 0 °C and the mixture was stirred at room temperature for 64 h. The solvent was removed under reduced pressure, the crude product was redissolved in anhydrous DCM (25 mL) and anhydrous DIPEA (2.1 mL, 12.35 mmol) was added. Afterwards freshly distilled methanesulfonyl chloride (0.64 mL, 8.27 mmol) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 2 and for 18 h at room temperature. The mixture was then partitioned between brine and ethyl acetate (50 mL each) and the phases were separated. The aqueous phase was then extracted twice with ethyl acetate and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (DCM/acetone 100:1) yielding the title compound as a colourless oil (353 mg, 1.68 mmol, 41%). $[\alpha]_{589}^{25} = +16.6 \pm 2.6$ (c = 25 mg/mL, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.26 (m, 5H, aromatic C*H*), 4.05–3.96 (m, 1H C*H*), 3.55 (s, 2H, Ar CH_2), 3.05 (d, J = 9.0 Hz, 1H, CH_2), 2.72 (d, J = 11.4 Hz, 1H, CH_2), 2.25–2.07 (m, 3H, overlap CH_2), 1.82–1.75 (m, 1H, CH_2), 1.68–1.50 (m, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.89, 129.17, 128.41, 127.32, 62.81, 61.37, 56.17, 52.92, 34.99, 24.90 ppm. HRMS (ESI): *m/z* calcd for $C_{12}H_{17}ClN^+$: 210.1044; found: 210.1051 $[M+H]^+$; elementary analysis calcd (%) for $C_{12}H_{17}Cl_2N$: C 58.55, H 6.96, N 5.69; found: C 58.87, H 6.77, N 5.71.

2-chloroethyl diethylamine (5)

To a solution of NaOH (20.0 g, 0.5 mol) in distilled water (80 mL) was added 2-chloroethyl diethylamine hydrochloride (17.21 g, 0.1 mol) dissolved in distilled water (20 mL) at 0 °C. The solution was stirred at room temperature for 15 min and then extracted three times with Et_2O. The combined organic extracts were dried by stirring with $MgSO_4$ for 30 min and the solvent was removed under reduced pressure. The crude product was purified by vacuum distillation (47 °C at 30 mbar) over CaH_2 yielding the title compound as a colourless liquid (10.6 g, 78 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.54–3.46 (m, 2H, CH_2), 2.80–2.74 (m, 2H, CH_2), 2.57 (q, J = 7.2 Hz, 4H, CH_2), 1.03 (t, J = 7.2 Hz, 6H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 54.99, 47.74, 42.15, 11.96 ppm. HRMS (ESI): *m/z* calcd for

$C_6H_{15}ClN^+$: 136.0888; found: 136.0886 $[M+H]^+$; These data are consistent with published data.[26]

General procedure for synthesis of aziridinium ions (10–13, 18)

Under a nitrogen atmosphere the corresponding 3-chloropiperidine/β-chloroethylamine (0.25–0.5 mmol) was weighted into a 10 mL schlenk tube, the tube was then evacuated and backfilled with nitrogen five times. After a final evacuation, the valve was closed and the schlenk tube transferred into a nitrogen-filled glovebox. Anhydrous acetone (0.25 mL/0.1 mmol of starting material) was added and a solution of the appropriate silver salt (1 eq., dried over P_2O_5) in anhydrous acetone (0.25 mL/0.1 mmol of silver salt) was added. The mixture was stirred at room temperature under exclusion of light for the times indicated (monitored by TLC), afterwards filtered through a syringe filter (0.2 μm PTFE) and the solvent was removed under high vacuum. The residue was dissolved in anhydrous DCM (0.5 mL/0.1 mmol starting material) and again filtered through a syringe filter (0.2 μm PTFE). The solvent was removed under high vacuum and the crude product analysed by NMR spectroscopy.

1-Butyl-5,5-dimethyl-1-azoniabicyclo[3.1.0]hexane perchlorate (10 a)

Was prepared according to the general procedure (reaction time: 4 h) from 1-butyl-3-chloro-5,5-dimethylpiperidine (**1**; 102 mg, 0.5 mmol) and silver perchlorate (104 mg, 0.5 mmol) yielding the title compound as a colourless solid. Crystals for XRD analysis were obtained by vapour diffusion crystallization with DCM/Et_2O. ^{1}H NMR (400 MHz, CD_3CN) δ = 3.80–3.71 (m, 1H, C*H*), 3.52–3.44 (m, 1H, CH_2), 3.38 (d, J = 12.3 Hz, 1H, CH_2), 3.28 (d, J = 12.3 Hz, 1H, CH_2), 3.16 (dd, J = 8.0, 4.1 Hz, 1H, N$^+$CH_2CH), 3.06–3.02 (m, 1H, N$^+$CH_2CH), 2.92–2.84 (m, 1H, CH_2), 2.37 (dd, J = 13.7, 6.5 Hz, 1H, CH_2), 1.94 (dd, J = 13.6, 2.7 Hz, 1H, CH_2), 1.75–1.67 (m, 2H, CH_2), 1.41–1.32 (m, 2H, CH_2), 1.25 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 0.94 (t, J = 7.4 Hz, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, CD_3CN) δ = 68.87, 61.04, 56.65, 48.98, 45.06, 40.79, 29.75, 28.62, 28.07, 20.05, 13.88 ppm.

1-Butyl-5,5-dimethyl-1-azoniabicyclo[3.1.0]hexane tetrafluoroborate (10 b)

Was prepared according to the general procedure (reaction time: 4 h) from 1-butyl-3-chloro-5,5-dimethylpiperidine (**1**; 102 mg, 0.5 mmol) and silver tetrafluoroborate (97 mg, 0.5 mmol) yielding the title compound as a colourless solid. ^{1}H NMR (400 MHz, CD_3CN) δ = 3.80–3.71 (m, 1H, C*H*), 3.51–3.44 (m, 1H, CH_2), 3.37 (d, J = 12.3 Hz, 1H, CH_2), 3.27 (d, J = 12.3 Hz, 1H, CH_2), 3.15 (dd, J = 8.0, 4.1 Hz, 1H, N$^+$CH_2CH), 3.05–3.01 (m, 1H, N$^+$CH_2CH), 2.92–2.83 (m, 1H, CH_2), 2.37 (dd, J = 13.7, 6.5 Hz, 1H, CH_2), 1.93 (dd, J = 13.5, 2.7 Hz, 1H, CH_2), 1.74–1.67 (m, 2H, CH_2), 1.41–1.32 (m, 2H, CH_2), 1.24 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 0.94 (t, J = 7.4 Hz, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, CD_3CN) δ = 68.86, 61.04, 56.64, 48.99, 45.08, 40.80, 29.75, 28.62, 28.06, 20.06, 13.89 ppm.

1-Benzyl-5,5-dimethyl-1-azoniabicyclo[3.1.0]hexane perchlorate (11)

Was prepared by a slight variation of the general procedure (reaction time: 1 h) from 1-benzyl-3-chloro-5,5-dimethylpiperidine (**2**; 71 mg, 0.3 mmol) and silver perchlorate (62 mg, 0.3 mmol). After filtration and removal of the solvent the crude product was dissolved in anhydrous DCM (1.5 mL) and added dropwise to vigorously stirred anhydrous Et_2O (6 mL). The solvent was decanted and the solid dired under high vacuum yielding the title compound as a colourless solid. Crystals for XRD analysis were obtained by vapour diffusion crystallization with DCM/Et_2O. ^{1}H NMR (400 MHz, CD_3CN) δ = 7.53–7.50 (m, 5H, aromatic C*H*), 4.55 (d, J = 13.7 Hz, 1H, ArCH_2), 4.28 (d, J = 13.7 Hz, 1H, ArCH_2), 3.96–3.90 (m, 1H, C*H*), 3.46 (d, J = 12.5 Hz, 1H, CH_2), 3.34 (dd, J = 8.1, 4.3 Hz, 1H, N$^+$CH_2CH), 3.18 (d, J = 12.3 Hz, 1H, CH_2), 3.08 (dd, J = 6.4, 4.2 Hz, 1H, N$^+$CH_2CH), 2.39 (dd, J = 13.8, 6.5 Hz, 1H, CH_2), 1.99 (dd, J = 13.8, 2.3 Hz, 1H, CH_2), 1.09 (s, 6H, CH_3) ppm; ^{13}C NMR (101 MHz, CD_3CN) δ = 133.30, 131.50, 131.22, 130.42, 68.91, 63.49, 56.04, 48.30, 44.50, 40.96, 29.64, 28.35 ppm.

1-Butyl-1-azoniabicyclo[3.1.0]hexane perchlorate (12 a)

Was prepared according to the general procedure (reaction time: 72 h) from (3*R*)-1-butyl-3-chloropiperidine (**3-*R***; 87 mg, 0.5 mmol) and silver perchlorate (104 mg, 0.5 mmol) yielding the title compound as a yellow oil. ^{1}H NMR (400 MHz, CD_3CN) δ = 3.63–3.54 (m, 2H, overlap C*H* and CH_2), 3.42–3.34 (m, 2H, CH_2), 3.31–3.23 (m, 1H, CH_2), 3.08–3.00 (m, 1H, CH_2), 2.97–2.88 (m, 2H, N$^+$CH_2CH), 2.41–2.30 (m, 1H, CH_2), 2.19–2.05 (m, 2H, CH_2), 1.83–1.68 (m, 3H, overlap CH_2), 1.37 (dq, J = 14.9, 7.4 Hz, 2H, CH_2), 0.94 (t, J = 7.4 Hz, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, CD_3CN) δ = 58.94, 54.91, 53.54, 38.62, 28.31, 24.85, 20.96, 20.13, 13.86 ppm.

1-Butyl-1-azoniabicyclo[3.1.0]hexane tetrafluoroborate (12 b)

Was prepared according to the general procedure (reaction time: 120 h) from (3*R*)-1-butyl-3-chloropiperidine (**3-*R***; 87 mg, 0.5 mmol) and silver tetrafluoroborate (97 mg, 0.5 mmol) yielding the title compound as an orange oil. ^{1}H NMR (400 MHz, CD_3CN) δ = 3.63–3.54 (m, 2H, overlap C*H* and CH_2), 3.41–3.34 (m, 1H, CH_2), 3.31–3.23 (m, 1H, CH_2), 3.08–3.00 (m, 1H, CH_2), 2.95–2.88 (m, 2H, N$^+$CH_2CH), 2.40–2.30 (m, 1H, CH_2), 2.19–2.05 (m, 2H, CH_2), 1.83–1.67 (m, 3H, overlap CH_2), 1.37 (dq, J = 15.2, 7.5 Hz, 2H, CH_2), 0.94 (t, J = 7.3 Hz, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, CD_3CN) δ = 58.94, 54.89, 53.54, 38.60, 28.32, 24.84, 20.96, 20.14, 13.88 ppm.

1-Benzyl-1-azoniabicyclo[3.1.0]hexane perchlorate (13 a)

Was prepared according to the general procedure (reaction time: 120 h) from (3*R*)-1-benzyl-3-chloropiperidine (**4-*R***; 52 mg, 0.25 mmol) and silver perchlorate (52 mg, 0.25 mmol) yielding the title compound as a yellow oil. ^{1}H NMR (400 MHz, CD_3CN) δ = 7.53–7.46 (m, 5H, aromatic CH_2), 4.54 (d, J = 13.7 Hz, 1H, ArCH_2), 4.33 (d, J = 13.6 Hz, 1H, ArCH_2), 3.82–3.75 (m, 1H, C*H*), 3.43–3.29 (m, 2H, CH_2), 3.12–3.07 (m, 1H, N$^+$CH_2CH), 2.98–2.94 (m, 1H, N$^+$CH_2CH), 2.40–2.29 (m, 1H, CH_2), 2.22–2.16 (m, 1H, CH_2), 2.07–1.99 (m, 1H, CH_2), 1.80–1.70 (m, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, CD_3CN) δ = 131.51, 131.16, 130.41, 61.80, 55.19, 53.18, 37.89, 25.14, 20.76 ppm.

1-Benzyl-1-azoniabicyclo[3.1.0]hexane tetrafluoroborate (13 b)

Was prepared according to the general procedure (reaction time: 168 h) from (3*R*)-1-benzyl-3-chloropiperidine (**4-*R***; 52 mg, 0.25 mmol) and silver tetrafluoroborate (49 mg, 0.25 mmol) yielding the title compound as an orange oil. ^{1}H NMR (400 MHz, CD_3CN) δ = 7.53–7.45 (m, 5H, aromatic C*H*), 4.52 (d, J = 13.6 Hz, 1H, ArCH_2), 4.32 (d, J = 13.6 Hz, 1H, ArCH_2), 3.81–3.74 (m, 1H, C*H*), 3.42–3.29 (m, 2H, CH_2), 3.09 (dd, J = 7.8, 4.5 Hz, 1H, N$^+$CH_2CH), 2.95 (dd, J = 6.4, 4.4 Hz, 1H, N$^+$CH_2CH), 2.39–2.28 (m, 1H, CH_2), 2.19 (dd, J = 13.9, 7.9 Hz, 1H, CH_2), 2.07–1.99 (m, 1H, CH_2), 1.80–1.70 (m, 1H, CH_2) ppm; ^{13}C NMR

(101 MHz, CD_3CN) $\delta = 131.51$, 131.19, 131.16, 130.41, 61.79, 55.16, 53.18, 37.88, 25.13, 20.76 ppm.

1,1-Diethylaziridnium perchlorate (18a)

Was prepared according to the general procedure (reaction time: 2.5 h) from 2-chloroethyl diethylamine (**5**; 68 mg, 0.5 mmol) and silver perchlorate (104 mg, 0.5 mmol) yielding the title compound as a colourless solid. ^{1}H NMR (400 MHz, CD_3CN) $\delta = 3.13$ (q, $J =$ 7.2 Hz, 4H, CH_2CH_3), 2.92 (s, 4H, CH_2), 1.27 (t, $J = 7.2$ Hz, 6H, CH_2CH_3) ppm; ^{13}C NMR (101 MHz, CD_3CN) $\delta = 53.61$, 40.20, 9.90 ppm. These data are consistent with published data.[27]

1,1-Diethylaziridnium tetrafluoroborate (18b)

Was prepared according to the general procedure (reaction time: 2.5 h) from 2-chloroethyl diethylamine (**5**; 68 mg, 0.5 mmol) and silver tetrafluoroborate (97 mg, 0.5 mmol) yielding the title compound as a colourless solid. ^{1}H NMR (400 MHz, CD_3CN) $\delta = 3.12$ (q, $J = 7.2$ Hz, 4H, CH_2CH_3), 2.91 (s, 4H, CH_2), 1.27 (t, $J = 7.2$ Hz, 6H, CH_2CH_3) ppm; ^{13}C NMR (101 MHz, CD_3CN) $\delta = 53.62$, 40.19, 9.89 ppm.

Deposition Numbers 2100817 (for **10a**) and 2100818 (for **11**) 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 www.ccdc.cam.ac.uk/structures.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Alkylation · Antitumor agents · Aziridinium ions · Kinetics · Structure-Activity relationship

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