Amide Conformation

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Switching and Conformational Fixation of Amides Through Proximate Positive Charges**

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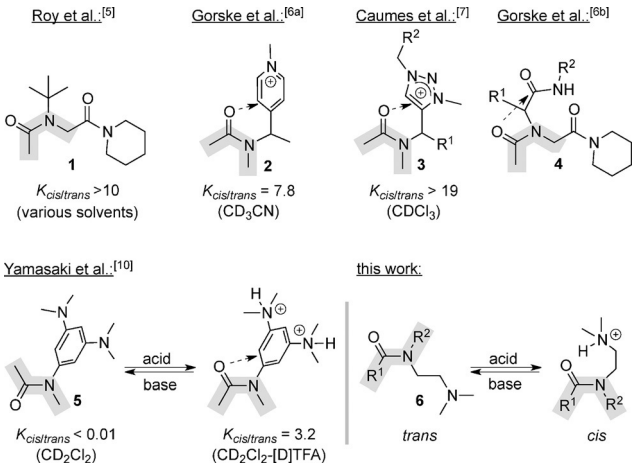
Dedicated to Professor Klaus Müller (Hoffmann-La Roche AG, Basel)

Abstract: *Tertiary amides, which usually occur as cis/trans mixtures, can be effectively shifted to the cis conformation by placing a positive charge in close proximity to the amide carbonyl. This effect was used to prepare cis-configured prolyl amides and to facilitate a strongly rotamer-dependent radical cyclization.*

Amide bonds represent the central and most important structural motif in peptides and many other natural and synthetic products.[1] The partial double-bond character is essential to achieving a high degree of conformational stability in small molecules, as well as in large macromolecular architectures including enzymes, transmembrane receptors, or ion channels.[2] Although the precision of such complex structures is a key element in selective molecular recognition, there has always been a considerable interest in how the conformational distribution of amide bonds could be influenced.[3] From a biological point of view, such insights into the *cis–trans* isomerization of amides can enable tuning of the activation barrier of receptors or ion channels, as has been recently reported for the 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) receptor.[4]

In general, and in the absence of special effects, secondary amides largely occur in the *trans* conformation, whereas *cis*/*trans* mixtures are usually observed for tertiary amides, with isomeric ratios depending on the nature and size of the substituents on the nitrogen atom.[2] By placing a bulky unit, such as a *tert*-butyl group, on the nitrogen atom of a secondary amide, the activation barrier for the isomerization of **1** is lowered and the equilibrium regarding the two original substituents is shifted towards the *cis* rotamer (Scheme 1).[5]

A stronger influence on the conformational distribution was observed for the pyridinium- and triazolium-substituted amides **2** and **3**.[6,7] These effects are explained by $n\rightarrow\pi^*_{Aryl}$ interactions between the carbonyl oxygen and an antibinding orbital of the adjacent electron-deficient aromatic ring system.[8a] As initially observed by Raines,[9] a second carbonyl unit (see amide **4**[6b]) can also provide the required π^* orbital. Alternatively, hydrogen bonds may be used to influence the ratio of rotamers.[8]



Scheme 1. Conformationally switchable and non-switchable amide derivatives.

An interesting extension of the principle to exploit $n\rightarrow\pi^*_{Aryl}$ interactions was developed by Yamasaki and Kagechika[10] (Scheme 1). Since the aromatic system of **5** can be switched from an electron-rich to a comparably electron-poor state through double protonation, the preferred conformation of the amide bond becomes pH dependent.

Against this background, we asked whether a conformationally pH-dependent tertiary amide unit might not be conceivable through a more biomimetic and structurally more simple modification, whereby the latter aspect could in turn allow broad applicability. Herein, we present first insights into the pH-dependent effects of simple aminoalkyl groups and related basic moieties on the conformation of tertiary amides, along with applications of the new type **6** conformational switches.

Inspired by an ongoing study on US28 receptor ligands,[11] which revealed a surprising pH dependence for the amide conformation, we prepared the structurally simplified amide **7** to study the underlying effects in detail (Table 1). As expected, amide **7** initially occurred as a *cis*/*trans* mixture with no clear preference for either rotamer in all of the solvents selected for the experiments.[12a] The slightly increased $K_{cis/trans}$ value found in methanol (entry 2) might be due to micelle formation, which was observed for this

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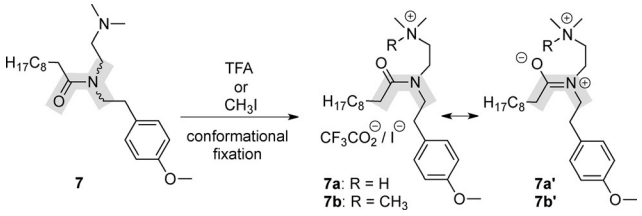
Table 1: Conformational fixation through protonation or quaternisation: Solvent effects.



Entry	Amine **7**[a] *cis*/*trans* ($K_{cis/trans}$)	Solvent	Ammonium salt[b] **7a** or **7b** *cis*/*trans* ($K_{cis/trans}$)
1	60:40 (1.5)	$CDCl_3$	>95:5 (>19) (**7a**)
2	67:33 (2.0)	CD_3OD	90:10 (9) (**7a**)
3	59:41 (1.4)	$(D_3C)_2SO$	90:10 (9) (**7a**)
4	59:41 (1.4)	C_6D_6	>95:5 (>19) (**7a**)
5	57:43 (1.3)	CD_3CN	>95:5 (>19) (**7a**)
6	–[c]	D_2O-CD_3OD	90:10 (9) (**7a**)
7	60:40 (1.4)	$CDCl_3$	>95:5 (>19) (**7b**)

[a] For the preparation of **7** see Ref. [11] and the Supporting Information. [b] Ammonium salts obtained through the addition of TFA (trifluoroacetic acid; 5–10 equiv) or CH_3I (1.0 equiv). [c] Not determined owing to low solubility. [d] Ratio of >95:5 assumed if minor isomer could not be detected by ^{1}H NMR.

solvent and mixtures containing up to 40% water, but not for dimethyl sulfoxide or acetonitrile (entries 3 and 5). Protonation to give **7a** (entries 1–6), or quaternization to give **7b** (entry 7), however, led to a clear predominance of the *cis* rotamers.[12b] In chloroform, benzene, and acetonitrile, the minor *trans* rotamers of **7a** and **7b** could no longer be detected by ^{1}H NMR spectroscopy (entries 1, 4, 5, and 7). Since slightly lower ratios were observed for dimethyl sulfoxide and methanol, as well as methanol in water, the overall trend is comparable to the solvent effects on the magnitude of $n\rightarrow\pi^*_{Aryl}$ interactions in triazolium-substituted amides **3** (Scheme 1).[7]

From a very general point of view, the two ammonium groups in amides **7a** and **7b** appear to strongly stabilize the *cis* rotamers through a form of ionic interaction. This interaction can be rationalized by assuming a greater participation of the multiply charged mesomeric forms **7a′** or **7b′**. Interestingly, the conformational fixation does not require the presence of a hydrogen bond, since the quaternary ammonium ion is able to exert a similar effect (compare entries 1 and 7).[13]

To investigate whether the remarkable conformational fixation induced by the ammonium alkyl side chain can also be achieved with other protonated moieties so that conformational switches could be designed for different ranges of pH values, we prepared the tertiary amides **8** and **9** (Figure 1).[14] The imidazole derivative **8** showed a relatively strong preference for the *cis* rotamer even before protonation, which is probably due to hydrogen bonding,[9b] and full conversion to the *cis* rotamer took place upon the addition of TFA.[12b–d] By contrast, the effect of the pyridylmethyl side chain was found to be similar to that of aliphatic amines in the unprotonated state (Table 1), but turned out to be slightly weaker in the protonated state, since a $K_{cis/trans}$ value of only 13 was reached.[12a–d] Slightly weaker effects were observed in

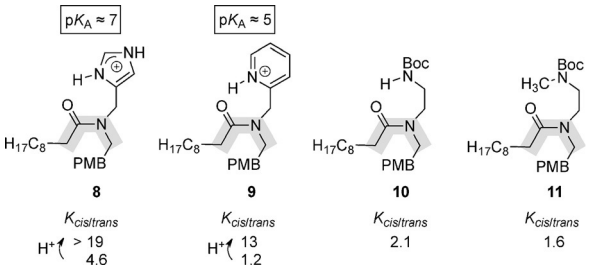


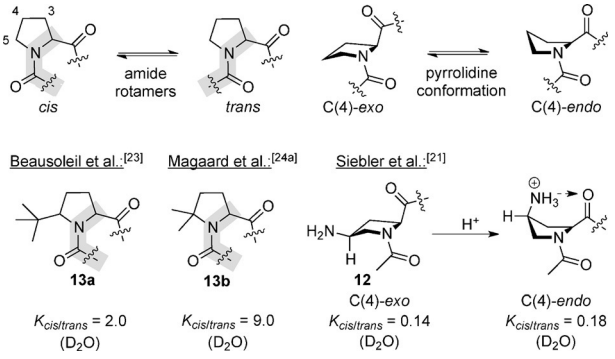
Figure 1. Influence of imidazolylmethyl, pyridinylmethyl, and *N*-Boc-aminoethyl side chains on the conformation of amides in $CDCl_3$. PMB = *para*-Methoxybenzyl. Boc = *tert*-Butyloxycarbonyl.

methanol, where protonation led to a change from $K_{cis/trans}=1.6$ to $K_{cis/trans}=6.7$ for imidazole **8**, and from $K_{cis/trans}=1.3$ to $K_{cis/trans}=6.7$ for pyridine derivative **9**, each time after the addition of two equivalents of TFA (see the Supporting Information for detailed titration experiments).

N-Boc-protection of the aminoethyl side chain, as in urethane **10**, demonstrated that a hydrogen bond alone has only a weak effect ($K_{cis/trans}=2.1$) without support from a positive charge.[12d] After methylation of **10**, compound **11** was found to occur in the usual ratio for unprotonated species.

Since proline plays an unique role in the folding and stability of proteins and peptides,[15] this amino acid was chosen for a first application. Proline, when incorporated in peptides, represents the only proteinogenic amino acid that occurs as a tertiary amide so that the *cis* as well as the *trans* rotamer should be observed.[16] However, only 10% of the peptidyl-CO-*N*-prolyl bonds in native proteins are present as *cis* rotamers (Scheme 2),[16c] and the conformation of the pyrrolidine ring was also found to have a strong effect on the stability and folding properties of peptides and proteins (Scheme 2). In this context, a number of 3- and 4-substituted prolines were prepared,[17,18] whereby the latter represents by far the more common approach and has frequently been used to tune the properties of collagen[9,19] and other biomolecules[20] (Scheme 2).

Not many approaches have yet appeared for developing switchable proline derivatives, however. A recent report with (4*S*)-amino-proline **12** demonstrated that an ionic interaction between a protonated amine and a carbonyl unit (see amide **7**, Table 1) can effectively be used to modulate the conformation

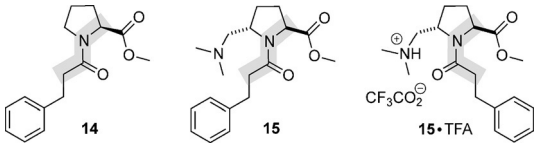


Scheme 2. Conformational studies on proline derivatives.

of the pyrrolidine ring, but this approach leaves the *cis*/*trans* ratio of the amide more or less unchanged.[21,22] Aiming at proline derivatives with a clear preference for the *cis* rotamer, only the introduction of sterically demanding substituents in 5-position, as in amides **13a**[23] and **13b**[24] (Scheme 2), or conformational fixation through the introduction of a covalent linkage have so far been successful.[25]

To study whether the directing effect of an aminoalkyl group might also be applicable to modulating the *cis*/*trans* ratio of prolyl amides, the derivatives **14** and **15** were prepared (Table 2 and the Supporting Information). The 3-phenylpropionyl unit was chosen to facilitate detection by UV

Table 2: Reference compound **14** and 5-(aminoalkyl)-substituted proline derivative **15**.



Entry	Solvent	cis/trans		
		14[a,c]	**15**[a–c]	**15**·TFA
1	$CDCl_3$	18:82	32:68	>95:5[e]
2	C_6H_6	15:85	25:75	>95:5[e]
3	CD_3CN	19:81	27:73	>95:5[e]
4	CD_3OD	19:81	36:64	95:5
5	D_2O	18:82[d]	33:67[d]	87:13

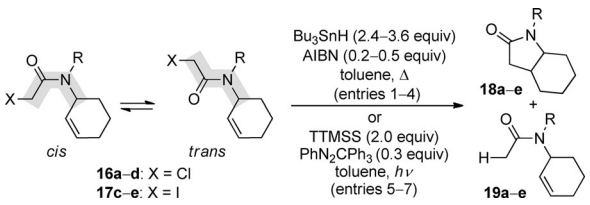
[a] For the preparation of **14** and **15**, see Supporting Information. [b] Ratio determined in the presence of K_2CO_3. [c] Assignment of *cis* and *trans* rotamers is in agreement with reported ^{13}C NMR data and NOESY experiments for compound **14**. See Refs. [12e] and [16a]. [d] Addition of 10% CD_3OD to increase solubility. [e] Ratio of >95:5 assumed if minor isomer could not be detected by ^1H NMR.

spectroscopy. Whereas the prolyl amide **14**, which served as a reference compound, and the unprotonated amino alkyl derivative **15** showed the expected predominance of the *trans* rotamers with very little dependence on the solvent, protonation of the aminoalkyl group in **15** led to more or less full conversion to the *cis* rotamer.[12e] The responsible ionic interaction was again slightly weakened by the protic solvents methanol and water (entries 4 and 5), but in chloroform, benzene, or acetonitrile, the *trans* rotamer could not be detected by ^1H NMR after protonation (entries 1–3; see Supporting Information for NMR titration experiments).

To investigate the synthetic applicability of the conformational fixation, we selected a group of radical cyclization reactions that are known to be highly dependent on amide conformation (Table 3). Since radicals usually have a short lifetime, with no reversible resting state, it is favorable with regard to cyclization if amide **16** is largely present as the *cis* rotamer or the barrier to rotation is lowered by elevated temperatures.[26] The unfavorable *trans* conformation, by contrast, can be expected to lead to reduction. It was thus not surprising that the secondary amide **16a**, which occurs solely as the *trans* isomer, was reduced to **19a** with no bicyclic amide **18a** being detected (entry 1).

The attachment of an *n*-butyl or a benzyl group to the amide (entries 2 and 3) led to improved *cis*/*trans* ratios for the

Table 3: Radical cyclization reactions.



Entry	Amide **16, 17**: R=	*cis*/*trans*[a]	**18**/**19**[b]	**18** %[c]	**19** %[c]
1	**16a**: H	<5:95	<5:95	–	68
2	**16b**: Bn	42:58	68:32	44	21
3	**16c**: Bu	60:40	76:24	57	18
4	**16d**: $(CH_2)_2NHBoc$	75:25	96:4	61	5
5	**17c**: Bu	54:46	50:50	39[d]	39[d]
6	**17d**: $(CH_2)_2NHBoc$	74:26	50:50	30[d]	29[d]
7	**17e**:[f] $(CH_2)_2NH_3^+$	>95:5	57:43	43[e]	32[e]

[a] Ratio determined for starting materials by ^1H NMR in $CDCl_3$. [b] Ratio determined by ^1H NMR ($CDCl_3$) for crude product mixtures. [c] Yields after purification by column chromatography. [d] Yields determined by addition of an internal standard (dimethyl terephthalate) to the crude product mixture. [e] Yields determined by addition of an internal standard (maleic acid) to the crude product mixture. [f] Amide **17e** prepared from **17d** through treatment with TFA. AIBN = azobisisobutyronitrile. TTMSS = tris(trimethylsilyl)silane.

reactants **16b** and **16c** and resulted in a predominance of the cyclic amides **18b** and **18c** over the reduced compounds **19b** and **19c**.[27] A further increase in selectivity could be achieved with an N-Boc-protected aminoethyl group (entry 4), which influences the *cis*/*trans* ratio of **16d** through hydrogen bonding.[9b,28] Since the reaction of **16d** had already given a high proportion of cyclized product **18d**, less favorable conditions were chosen to probe the effect of the protonated aminoethyl side chain. Specifically, the reaction temperature was lowered to room temperature[26] and the reductant tris(trimethylsilyl)silane[29] was no longer added by syringe pump but in one batch at the beginning. Under these conditions, the performance of the *n*-butyl and the NHBoc-ethyl derivatives **17c** and **17d** decreased, and 1:1 mixtures of **18c**/**19c** and **18d**/**19d** were obtained (entries 5 and 6). The strong conformational fixation induced by the protonated aminoethyl side chain in **17e** (*cis*/*trans* >95:5; entry 7), was then able to bring about the production of cyclized amide **18e** in a larger amount than the reduced product **19e**.

In summary, we have shown that the conformation of tertiary amides can be effectively modulated through a positive charge located in close proximity to the carbonyl oxygen atom. The underlying interaction of the carbonyl unit and the covalently attached ammonium ions turned out to be independent of the presence of a hydrogen bond. First applications of this effect include the preparation of prolyl amides with a strong preference for the *cis* conformation and the enhancement of radical cyclization reactions for converting amides into lactams. Future research is directed towards the introduction of the new and switchable amide derivatives into peptides and other biomolecules, as well as towards studies on the biological effects of this modification.[30]

Keywords: amide bond · ammonium ions · conformation · proline · rotamers

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