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Structure-lipophilicity relationships of peptides and peptidomimetics

Minireview Article

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Summary. Understanding the physicochemical and structural properties of peptides are important prerequisites for the rational design of bioactive peptides and peptidomimetics. The present contribution reviews methods used for the assessment and prediction of lipophilicity (or hydrophobicity) and their correlation with structural elements of peptides and closely related peptidomimetics.

Keywords: Amino acids – Lipophilicity prediction – Peptides – Peptidomimetics

Introduction

Bioactive peptides, such as peptide hormones, immunomodulators and growth promoters, have been found to modulate a wide variety of biological functions such as immunity, blood pressure, pain and memory (Hurby et al., 1990). The potency and specificity of these peptides make it clear that peptide design will be among the major issues of drug research. Indeed, the peptidomimetic approach has recently led to the successful development of a new nonpeptidyl secretagogue for growth hormone (Smith et al., 1993) and several selective conformationally constrained opioid peptides (Hurby and Pettitt, 1989), potent RGD antagonists of the fibrinogen receptor GP IIb/IIIa (Callahan et al., 1992), antagonists of angiotensin II (Carini et al., 1990) and various inhibitors of enzymes including renin (Raddatz et al., 1992) and the angiotensin-converting enzyme.

Peptides and their constituent amino acid residues show a wide range of properties. Amino acid side-chains contain polar and non-polar groups, charged and uncharged groups, and have a range of size and flexibility. Understanding the relationship between chemical structure and physicochemical properties of peptides and peptidomimetics are important topics in peptide and protein

research because it has been demonstrated that the biological properties of bioactive peptides can be rationalized if the structure-related properties of its constituent amino acid residues are precisely known. Furthermore, a better understanding of physicochemical properties of peptides are important for the improvement of separation and purification of peptides in biochemistry and molecular biology. In this context, lipophilicity and H-bonding parametrization of peptides are of major importance. At this point it seems warranted to define the term lipophilicity. Lipophilicity is a measure for the partitioning of organic compounds between an organic or lipidic environment and an aqueous compartment. It encodes structural information such as molecular volume, H-bonding and surface accessibility (see Part I, Van de Waterbeemd et al., 1994). It is well-known that this property is correlated to absorption, distribution and plasma protein binding of drugs. In peptide and protein chemistry the terms hydrophobicity and hydropathicity are being used, which are often considered as equivalent (Trumpp-Kallmeyer et al., 1992). However, as we explained previously (Van de Waterbeemd et al., 1994), hydrophobicity can be used in a more restricted way and may be reserved to express expulsion from aqueous environments. Thus one may define that

$$\text{lipophilicity} = \text{hydrophobicity} + \text{polarity} \quad (1)$$

Using different approaches, it has been shown that partition coefficients expressed as log P, can be split into two terms, namely a volume term and a term related to the polarity of the molecule, including e.g. H-bonding effects (Van de Waterbeemd and Testa, 1987).

Determination of the lipophilicity of peptides

Both experimental and theoretical approaches have been proven useful for the characterization of amino acid and peptide lipophilicity. Recently we have reviewed the main progress in the field of amino acid lipophilicity (Van de Waterbeemd et al., 1994). In the present paper we focus on peptides and closely related peptidomimetics. In principle the lipophilicity of peptides can be determined by:

- experimental methods:
  - shake flask partitioning between two liquid solvents
  - chromatography (HPLC, TLC, CPC)
- theoretical approaches:
  - using fragmental additivity schemes
  - from HPLC or TLC retention times
  - using QSAR equations

Experimental techniques

The classical technique of measuring partition coefficients consists of the so-called shake flask procedure, in which a solute is distributed between two immiscible solvents by simple shaking. This approach has several disadvantages,

e.g. the compounds most be pure and stable, requires milligram amounts of compound and above all is rather tedious. Alternative methods have been developed and discussed (Dearden and Bresnen 1988). Most practical for routine measurements are chromatographic methods, such as thin-layer chromatography (TLC) (Dross et al., 1993), reversed-phase high performance liquid chromatography (RP-HPLC) (El Tayar et al., 1985) and centrifugal partition chromatography (CPC) (El Tayar et al., 1991). Meek (1980, 1981) defined HPLC retention coefficients of amino acid residues and was able to predict the retention of small peptides (20 residues or less). A similar approach was followed by Hodges (Guo et al., 1986; Mant et al., 1988) and Hearn (Wilce et al., 1991) and their coworkers. It was noticed that the additivity principle only works for small peptides up to ca 15 amino acids. For larger peptides, where secondary and tertiary structural features become more important, greater deviations of experimental retention times from calculated values are observed. A new prediction model has recently been proposed in which the contribution to peptide retention of each amino acid residue is not a constant but a decreasing function of peptide length (Chabanet and Yvon, 1992). Linear gradient elution of peptides and the correlation between retention and log P values calculated with Rekker's fragmental system (see below) have been studied (Sasagawa et al., 1982). For zwitterionic peptides, lipophilicity measurements should be performed at a pH near their isoelectric points in order to obtain a standard scale of lipophilicity (Akamatsu et al., 1989). Thin layer chromatography has been used for the determination of the lipophilicity of bioactive compounds and peptides (Cserhati and Szögyi, 1990). Statistical analysis of the retention data using principal component analysis showed that the presence of a ring structure in the peptides has the greatest impact on their retention behavior (Cserhati and Szögyi, 1990). Retention time measurements on RP-HPLC of positional isomers by 'walking' e.g. a proline through the alanines of H-Lys-$(Ala)^{18}$-Lys-NH_2 showed a clear effect of conformation of the peptide (Büttner et al., 1990). It is believed, that at least in part, the solid support induces a specific secondary structure in peptides. HPLC can thus be used to obtain conformational information on peptides (Funasaki et al., 1993; Lebl, 1993).

Theoretical approaches: addivity schemes from log P values

Using an additive fragmental approach, 1-octanol/water partition coefficients can be calculated with the program CLOGP (Daylight CIS Inc. or BioByte Corp., formerly the MedChem project) based on the work of Hansch and Leo (1979) at Pomona College in Claremont, USA, by the equation:

$$\log P = \Sigma a_i \cdot f_i + \Sigma b_j \cdot F_j \qquad (2)$$

where f_i are fragmental values (e.g. the lipophilicity increment for a -COOH group), and F_j are correction terms (e.g. for interaction between polar groups); a_i and b_j represent the number of occurrences of fragments and interaction factors, respectively. Some fragments are not parametrized in CLOGP. In such cases the calculation has to be completed ad hoc by estimates for missing fragment values or interaction effects. A similar fragmental system has been

developed by Rekker and De Kort (1979; Rekker and Mannhold, 1992). In computerized form this approach is available in the PROLOGP program (Darvas, 1986).

In principle, log P values of peptides can be calculated using Rekker's or Leo's fragmental methods (Leo, 1991). In both methods correction terms account for intramolecular effects, such as neighboring or proximity effects of polar groups. However, in peptides we have a particular situation where the constituting amino acids form repetitive units. The side chains are in close contact and can interact with each other. In many cases peptides are charged. Longer chains can produce secondary and tertiary structures. Therefore log P calculations of peptides meet with serious difficulties, which can be summarized as follows:

- solvent accessibility and hydrophobic collapse
- polar group interactions
- ionized groups, e.g. zwitterions
- conformational effects
- intramolecular H-bonding
- bound water molecules

One of the factors not properly accounted for in traditional log P calculations are through-space interactions, present in highly folded conformations, which have been called hydrophobic collapse. (El Tayar et al., 1993, Rich, 1993; Wiley and Rich, 1993), as depicted in Fig. 1. This hydrophobic clustering of groups leads to a reduction of exposed molecular surface, which has an important impact on the lipophilicity of a compound.

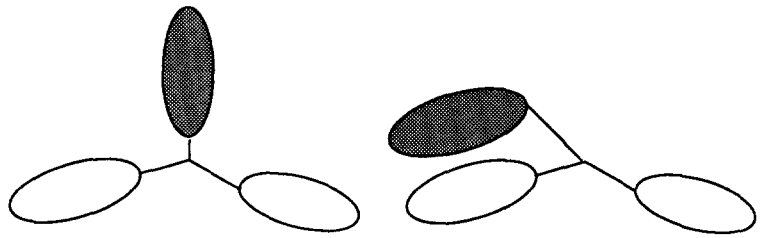


Fig. 1. The lipophilicity of a tripeptide. On the left no interactions between side-chains are considered, which is the case in traditional log P calculations. In reality, due to hydrophobic collapse (clustering) or intramolecular H-bonding, a molecule may be folded in solution, thus influencing the overall lipophilicity of the molecule

Since it appears to be inappropriate to use the "normal" fragment values for NH_2 and COOH in amino acids, Abraham and Leo (1987) have extended the CLOGP approach by defining a superfragment for amino acids. Proximity effects between this superfragment and other polar side-chain groups are treated in a well-defined way.

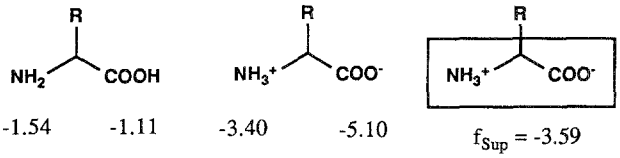


Fig. 2. The definition of an amino-acid superfragment (Abraham and Leo, 1987)

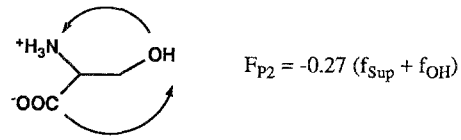


Fig. 3. Proximity effects between polar groups in an amino acid (Abraham and Leo, 1987), resulting in a correction for the lipophilicity by a factor F_{P2}

Some amino acids behave rather unexpectedly. Arg has a log P somewhat higher than calculated. Crystal structures show that the guanidine nitrogen and carboxylate oxygen atoms are bridged by two water molecules, increasing the log P by $3 \times (0.63) = 1.89$ (Abraham and Leo, 1987). Intramolecular H-bond formation or bridging hydration may explain higher than expected experimental lipophilicity values for amino acids and peptides. Tightly bound water might considerably alter the hydrophilic/hydrophobic nature of parts of a peptide or protein.

Despite the wide use of amino acid side-chain hydrophobicity scales (see part I, Van de Waterbeemd et al., 1994), it must be assumed that the side-chain hydrophobicity varies as a function of neighboring groups to which H-bonds or water bridges can be formed. Therefore a general classification of an amino acid as hydrophobic or hydrophilic might be misleading. For example, the calculated log P value of cyclosprin A, a cyclic undecapeptide, is very high and unrealistic (CLOGP = 14) compared to the observed value (log P = 2.92) (El Tayar et al., 1993). In more recent work, Leo (personal communication) has further improved these approaches, by introducing bulk factors for the side-chains in the calculation. It seems that nonpolar side-chains require a negative correction and that polar side-chains may cancel a negative bulk effect.

Several attempts to account for conformational flexibility in log P calculations of peptides have been published. Specific hydration of polar groups able to participate in hydrogen bonding gave new fragment values useful in the prediction of log P values of di- and tripeptides (Richards et al., 1992). Since this approach seems of limited use, an alternative has been suggested using AM1 quantum chemical calculations (Alkorta and Villar, 1992). Using this method, it was possible to distinguish between diastereoisomers.

Theoretical approaches: QSAR equations

Quantitative structure-activity relationship (QSAR) studies are widely used in the design of bioactive compounds such as potential drugs and agrochemicals. Using similar approaches physicochemical properties can be described as a

linear combination of other properties. Aqueous solubility e.g. can be correlated to the log P and melting point of a compound. Such methods have also been used to factorize partition coefficients into more fundamental properties (Taft et al., 1985).

Akamatsu and Fujita have studied the partitioning behavior of di- to pentapeptides and introduced various correction and indicator terms to predict a log P value (Akamatsu et al., 1989, 1992). An interesting aspect of their approach consists in defining a new correction term derived from the Chou-Fasman potential of each amino acid to account for β-turns. These Japanese authors also introduced an effective hydrophobicity scale of side-chains. N-terminal residues behave differently from C-terminal and internal chain residues. The pH-corrected distribution coefficient (log D) in octanol/water of zwitterionic peptides was shown to form a plateau over several pH units and to drop outside this pH range due to the increased population of positively or negatively charged species. The highest log D value was considered as the distribution coefficient of the zwitterionic peptides. Their quantitative model for the prediction of the lipophilicity of linear free di- to pentapeptides is as follows:

$$\begin{aligned}\log D = {} & 0.942(\pm 0.064)\Sigma\pi - 0.582(\pm 0.096)I_{pep} + 0.546(\pm 0.089)E_s'^{c}(R_N) \\ & + 0.295(\pm 0.071)[\Sigma E_s'^{c}(R_M) + E_s'^{c}(R_C)] + 0.516(\pm 0.172)I_{turn} \\ & + 0.764(\pm 0.211)\log f_{i+2} + 0.144(\pm 0.089)I_Y + 0.378(\pm 0.106)I_W \\ & + 0.659(\pm 0.165)I_M + 1.581(\pm 0.197)(I_S + I_T) - 0.807(\pm 0.225)I_P(N) \\ & - 0.346(\pm 0.118)I_P(\#\,pep) - 3.866(\pm 0.190) \\ n = 124;\ r = 0.967;\ s = 0.209;\ F = 134 \end{aligned} \quad (3)$$

In this equation, log D is the distribution coefficient (the log P value at a certain pH), n is the number of compounds, r is the correlation coefficient, s is the standard deviation of the regression, and F is the Fisher test for significance of the equation. In parentheses are the 95% confidence intervals of the regression coefficients. $\Sigma\pi$ is the sum of the intrinsic π values for individual amino acids (π is the contribution of each amino acid side-chain to the overall lipophilicity of the peptide), I_{pep} is zero for dipeptides and one, two and three with ascending numbers of peptide bonds, R_N and R_C stand for the side-chain of amino acids at the N- and C-termini, respectively, R_M stands for the side-chains of the central amino acids, $E_s'^{c}(R_i)$ represents the steric parameter of R_i substituents, I_{turn} is zero for di- and tripeptides and unity for tetra- and pentapeptides. I_Y, I_W, I_M, I_S, I_T and $I_P(N)$ are indicator variables, zero or unity, depending on the absence or the presence, respectively, of such component polar amino acids as tyrosine, tryptophan, methionine, serine, threonine and N-terminal proline. $I_P(\#\,pep)$ is the number of proline residues in the peptide. The log f_{i+2} term expresses the relative frequency of occurrence of amino acid i + 2 in a β-turn substructure, i.e. a conformational factor which takes into account the probability of an amino acid in position i + 2 to form a β-turn structure. Despite their usefulness, several important limitations inherent in this model restrict considerably their potential applications. The large number of indicator variables for polar amino acid

residues is an important limitation. These have no information on physicochemical properties of the peptides. The use of π and E_s variables, in spite of their apparent non-orthogonality, in the same equation is another severe drawback. A lipophilicity parameter such as π encodes both steric bulk and polar information (Van de Waterbeemd et al., 1994). Certainly, this may induce redundant information in the model.

A further attempt to derive more simple QSAR equations for log P calculations of peptides has been reported by Lien and coworkers (Gao et al., 1993). The following equation was obtained:

$$\log P = 2.985(\pm 0.131) \log MW + 0.633(\pm 0.080) \log P_{aa} + 1.099(\pm 0.325) N + 0.074(\pm 0.043)\,\mu + 0.265(\pm 0.167)\, F_\beta - 9.158(\pm 0.58)$$
$$n = 124;\ r = 0.939;\ s = 0.274;\ F = 11.22 \qquad (4)$$

where MW is the molecular weight of the peptide, $\log P_{aa}$ the hydrophobicity of component amino acids, N the number of amino acids in the peptide, μ the calculated dipole moment and F_β the frequency of β-turn formation of the peptide. This equation is derived for the same set as used by Akamatsu et al. Its validity is restricted to peptides with no ionizable side chains.

Preliminary results of Vallat (1992) demonstrate that the H-bonding descriptor Λ (see Part I, Van de Waterbeemd et al., 1994) may be useful to predict log D values of di- to pentapeptides (equation 5).

$$\log D = 1.78(\pm 0.10)\Sigma V/100 + 0.654(\pm 0.148)\Lambda(R_N) + 1.10(\pm 0.12)\Sigma[\Lambda(R_M) + \Lambda(R_C)] \cdot 0.431(\pm 0.057) I_{pep} + 0.725(\pm 0.197) \log f_{i+2} \cdot 3.84(\pm 0.13)$$
$$n = 142;\ r = 0.959;\ s = 0.237;\ F = 314 \qquad (5)$$

where $\Sigma V/100$ represents the sum of the volume of the side-chains (divided by 100 in order to have a similar magnitude of the scale compared to other parameters) and $\Lambda(R_i)$ the polarity of R_i substituents (see below for discussion on the term Λ). R_N and R_C stand for the side-chain of amino acids at the N- and C-termini, respectively, R_M stands for the side-chain of central amino acids. I_{pep} is an indicator variable which represents the number of peptidic bonds (1 for dipeptides and 2 for tripeptides). This model seems satisfactory, at least, for the prediction of log D values of di- to pentapeptides. However, it cannot appropriately detect the deviant peptides with high probability to fold and to form a stable β-turn structure. To better understand the deviations of a simple additive model, Vallat (1992) has used the model for di- and tripeptides to predict the lipophilicity of tetra- and pentapeptides. The analysis of residuals (deviation from additivity) was shown to be related to intramolecular effects and could provide information concerning conformational event occurring in tetra- and pentapeptides.

Molecular lipophilic potentials

A useful tool in molecular modeling studies is the visualization of physicochemical properties of molecules. Thus molecular electrostatic potentials (MEP) and molecular lipophilic potentials (MLP) can be displayed in most commercial modeling packages. The distribution of hydrophobic and hydrophilic regions over a peptide is mostly rendered visible by attributing a color to the hydrophobic residues and another color the hydrophilic ones. As seen in part I, it is by no means clear to which category certain amino acids belong. An attempt to develop a more sophisticated lipophilic surface are the MLP (Furet et al., 1988) and HINT (Kellogg et al., 1992) approaches. Molecular lipophilic potentials have also successfully been used to calculate conformation-dependent log P values of small organic molecules (Gaillard et al., 1993).

Lipophilicity of peptidomimetics

Peptidomimetics design is still a formidable challenge (Olson et al., 1993; Wiley and Rich, 1993). The probability of success depends on the reliability of structural information available and also on the creativity and ingenuity of the medicinal chemist. As far as peptidomimetics design is concerned, the most important structural modifications of bioactive peptides can be classified into three groups: backbone, building block and turn mimetics. We briefly discuss the impact of certain structural modifications on the lipophilicity.

Backbone mimetics

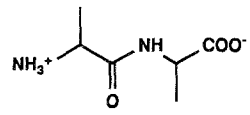
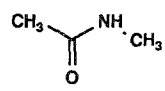
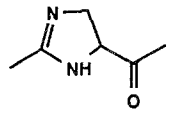
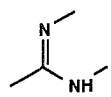
The essential structural features of a peptide chain are determined by the planar amide units (CONH) constituting the backbone of the chain. A compilation of peptide bond mimetics is summarized in Table 1 (Roark et al., 1993). As can be seen, the environment of a modified bond plays a role as well in the resulting effect of a modification on the lipophilicity of the molecule.

In addition to peptide bond surrogates, numerous studies have been devoted to configuration changes at the α-carbon atom by replacement of an L by a D-residue or by the introduction of an α-aza-amino acid (where the α-CH is replaced by N).

Turn inducers, mimetics and stabilizers

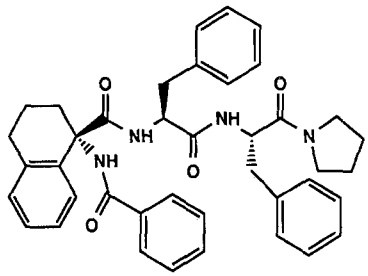
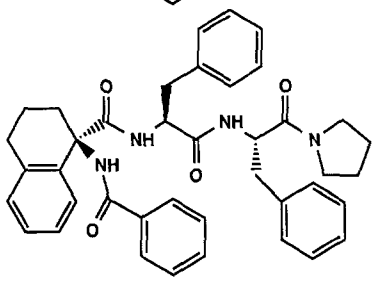
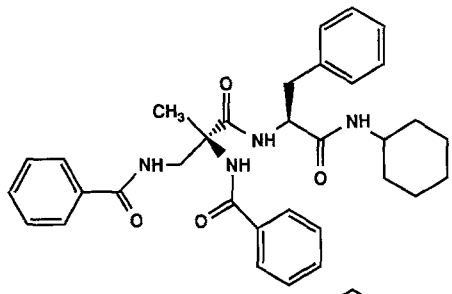
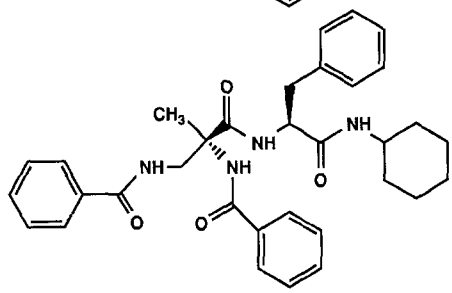
In the last two decades, a large number of building blocks aimed at replacing the classical protein-coded amino acids of biologically active peptides became available. α,α-Disubstituted amino acids are known for their propensity to induce secondary structures. For example, in the synthesis of a series of new α,α-disubstituted amino acids, intermediate peptides 1–4 (see Table 2) have been obtained (Obrecht et al., 1992; Karajiannis, 1994). The resolution of racemates such as compound 1, 2 could routinely be done by chromatographic methods. Experimental lipophilicity measurements on TLC and RP-HPLC confirmed these differences in retention behavior which is related to configurational, but

Table 1. Peptide bond mimetics: effect on lipophilicity

		Ala-Ala	Me-CONH-Me
			
Amide	-CONH-	0.0	0.0
Methyleneamino	-CH_2NH-	0.45	1.09
Retroamide	-NHCO-	0	0
Carbamate	-NHCOO-	0.24	0.92
Thiocarbamate	-NHCOS-	0.26	1.01
Urea	-NHCONH-	0.14	0.53
Ester	-COO-	0.32	1.22
N-methylamide	-$CONCH_3$-	0.63	0.28
Amide homologue	-$CONHCH_2$-	-0.08	0.53
Urea homologue	-$CH_2NHCONH$-	0.44	1.06
Ketomethylene	-$COCH_2$-	0.26	1.34
Thioamide	-CSNH-	0.19	0.71
Cis-olefinic double bond	-CH=CH-	0.88	3.34
Ethylene	-CH_2CH_2-	0.92	3.89
Thiolester	-COS-	0.42	1.61
Sulfonamide	-SO_2NH-	0.06	0.21
Hydroxyethylene	-CH(OH)CH_2-	-0.46	1.68
Cyanomethyleneamino	-CH(CN)NH-	-0.40	0.35
Methylenesulfoxide	-$SOCH_2$-	-0.21	0.23
4,5-Dihydro-1,3-thiazole		0.5	2.1
		-0.2	0.7
		-1.1	2.1

The values correspond to the difference in log P calculated by the CLOGP program version 3.55 and the reference structures Ala-Ala (CLOGP= -3.14) and N-methylacetamide (CLOGP = -1.08).

Table 2. Lipophilic properties of diastereomeric peptides from α,α-disubstituted α-amino acids

No.	Compound	CLOGP	TLC R_f	HPLC log kw (ABZ)	HPLC log k_W (ODS)
1		6.04	0.28*	4.86	6.48
2		6.04	0.51*	4.34	5.50
3		4.51	0.11**	4.10	4.84
4		4.51	0.21**	4.54	5.33

Experimental lipophilicity data: RP-HPLC ODS (Stagroma, LiChrosorb RP-18) and end-capped (Supelco ABZ) and TLC * Et_2O/i-PrOH 92:8, ** Hexane/AcOEt 1:2 (Karajiannis, 1994)

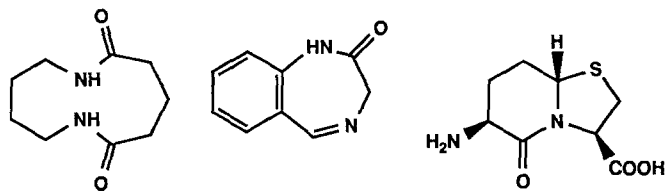


Fig. 4. β-Turn mimetics: bis-lactam (CLOGP = −1.69), benzodiazepine (CLOGP = −0.38) and bicyclic thiazolidine lactam (CLOGP = −2.20) ringsystems

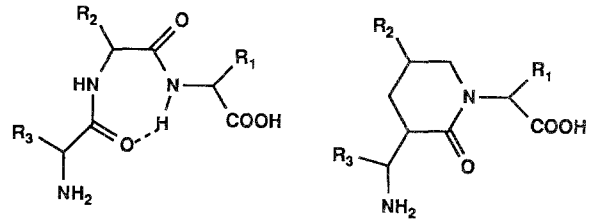


Fig. 5. Comparison of the lipophilicity of a γ-turn (CLOGP = −4.32) to a lactam mimetic (CLOGP = −2.61) for $R_1 = R_2 = R_3 = H$

also to conformational effects. X-ray structures of these compounds indeed revealed large differences in conformation, which may also exist in solution (Obrecht and Karajiannis, 1994).

Peptides can adopt extended, helical or other folded conformations. A turn is defined as a site where the polypeptide chain reverses its overall direction. The terms β- and γ-turns have more restricted definitions and describe turns of four and three residues, respectively. These turns may or may not be stabilized by an intraturn hydrogen bond; in β-turns, the C=O of residue i may be hydrogen bonded to the NH of residue i + 3, while in γ-turns, the C=O of residue i may be hydrogen bonded to the NH of residue i + 2. Ring structures such as bis-lactam (Khan et al., 1988), bicyclic thiazolidine lactam (Baca et al., 1993) and benzodiazepine (James et al., 1993) (Fig. 4) were shown to provide an excellent foundation for the development of a variety of a β-turn mimetics (Hinds et al, 1991). The effect of γ-turn fixation (Sato et al., 1992) on the lipophilicity of the mimetic must be taken into account in the design of such compounds (see Fig. 5). 1,8-Disubstituted structures such as phenothiazines have been proposed for loop and β-turn stabilization (Müller et al., 1993).

All these structural modifications have shown potential value in changing the physicochemical (solubility, lipophilicity, etc) and the pharmacokinetic character of bioactive peptides while retaining their pharmacodynamic properties. Today, there is an important need for structural information on the factors which favor formation and stabilization of turn structures. Understanding these factors would be a major improvement in non-peptides design using turn mimetics. For example, a β-turn mimetic was reported where the conversion of α-melanotropin, Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH2, a linear 13-amino acid peptide, to a cyclic conformationally constrained β-turn structure, provided a superpotent, prolonged acting, superagonist (Sawyer et al., 1980). Unlike tetrapeptides, benzodiazepine peptidomimetics enter cells to exert its action (James et al., 1993).

Another application involves the modification of enzymes. The introduction of a β-turn mimetic in the HIV-1 protease, using chemical synthesis, led to the formation of more conformationally stable enzyme while retaining the same affinity and specificity of the native one (Baca et al., 1993).

Cellular permeability of peptides

The increasing interest in small peptides and derived peptidomimetics as potential drugs requires a better understanding of peptide drug delivery and transport

problems. Several investigations have shown that the lipophilicity of drugs might not be the only key factor in cellular permeability (Young et al., 1988; Van de Waterbeemd and Kansy, 1992). H-bonding donor capacity was also recently considered as an important factor for peptide permeability through the epithelial cells (Conradi et al., 1991). Indeed, it has been shown that N-methylation of the peptide bonds of a series of peptides significantly increases their passive absorption compared to the parent oligomer. Conradi and coworkers have suggested that the abolishment of the strong H-bond donor capacity of the CONH group upon methylation would be the principal factor of improved cellular permeability.

Conclusions

The lipophilicity of peptides can be assessed by experimental and theoretical methods. Models for the prediction of the lipophilicity of short peptides have been developed with a certain success. More experimental work is required to unravel factors which relate the effect of conformation of small peptides to lipophilicity (Dyson and Wright, 1991). Low oral bioavailability and metabolic stability of many peptides is a major drawback of some of the compounds presently under development. Progress in the reliable estimation of the physicochemical property lipophilicity will benefit to a more rational design of peptides and peptidomimetics. The restricted conformation of turn mimetics has also considerable impact on the lipophilicity and the distribution properties of such compounds.

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