ORIGIN OF THE RING-RING INTERACTION IN CYCLIC DIPEPTIDES INCORPORATING AN AROMATIC AMINO ACID

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Abstract: Cyclic dipeptides comprising an aromatic amino acid residue
demonstrate the energetically most favored conformation in which an
aromatic ring stacks over the 2,5-dioxopiperazine ring. The communic-
ation is the first report providing a more detailed insight into the
mechanism of this stacking.

Cyclic dipeptides possessing an aromatic amino acid residue assume most frequently both in
solutions[1] and in the solid state[2] a conformation called folded (F), in which an aromatic side
chain ring stacks over the dioxopiperazine (DOP) ring, Fig. 1a. Kopple and Marr[3] who discovered
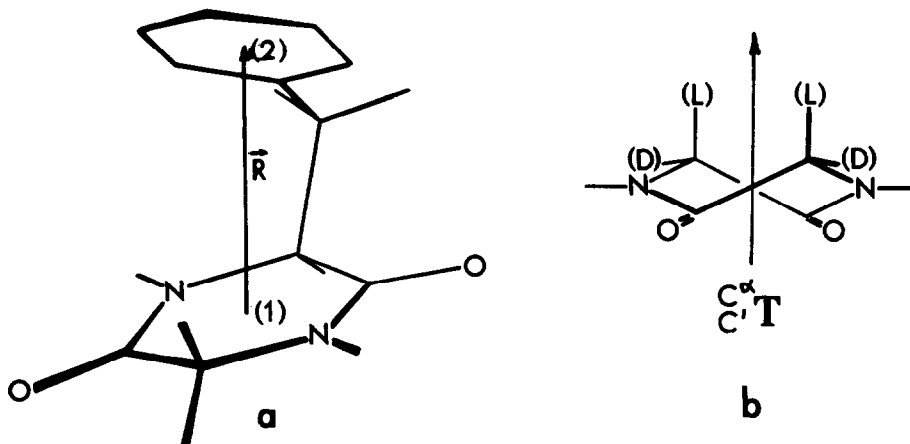

Figure 1. a: Folded, F, conformation of c/Gly-Phe/. b: $C_{C'}^{C^{\alpha}}$T pucker mode of the DOP ring approxim-
ately corresponding to the following peptide torsion angles relationship: $\psi_{1,2}$, $\psi_{1,2}$, $\omega_{1,2}$ [5]
equal to $-\phi$, 2ϕ, $-\phi$, respectively, where $\phi > 0°$. Pro-L and pro-D positions at C^{α} carbon atoms
are axial and equatorial, respectively, in $C_{C'}^{C^{\alpha}}$T.

this appearance estimated that the F conformation is favored by ca. 13 kJ/mole over other
possibilities in polar solutions (trifluoroacetic acid, dimethylsulphoxide and water[3]) and
proposed that the intramolecular dipole-induced dipole (μ-μ') should mainly contribute to the

stabilization of this form. On the other hand, Anteunis, upon an inspection of several relevant papers, suggested in his review[1b] dispersion forces to be the major contributor to this stacking. To our knowledge, no detailed study on the nature of this highly specific interaction has ever appeared.

We chose cyclo-/glycyl-L-phenylalanyl/, c/Gly-Phe/, as a model and carried out direct calculations of electrostatic, inductive and dispersion terms in three selected types of conformation. We adopted the DOP ring geometry approximating the crystal structure of c/Thr-His/[4], which we describe in terms of a set of the peptide torsion angles[5] as $\varphi_{1,2}=-6°$, $\psi_{1,2}=11°$ and $\omega_{1,2}=-5°$; hereafter given the nickname $^{C^\alpha}_{C'}T$ form, Fig. 1b. The latter stands for a twist conformation of the DOP ring in which both C^α atoms are above and both C' atoms below the mean plane of the ring, provided that the amino acid residues follow clockwise around the C_2 axis, Fig. 1b. We attached the benzyl group in the pro-L position at C_2^α carbon atom thus generating the L configuration of the Phe residue with its side-chain axial. We held the χ_2^2 torsion angle[5] fixed at 90° and allowed the χ_2^1 angle to vary in order to generate the folded conformation, $\chi_2^1=60°$ (F) and its both unfolded counterparts: the one extended to N, $\chi_2^1=-60°$ (EN) and the other extended to C=O, $\chi_2^1=180°$ (EO). Only F and, in two cases, EN have been observed in crystals[2].

For our computations we utilized a theory described by Buckingham[6]. The highest multipoles we considered were quadrupoles and we did not include contributions of induced field gradients (no superpolarizabilities were involved). Under these provisions our equations assumed the following forms:[6]

Electrostatic interactions:

$$U_{es} = U_{\mu^1-Q^2} + U_{Q^1-Q^2} = \frac{1}{D}\left(-\frac{1}{3}T_{\alpha\beta\gamma}\mu^1_\alpha Q^2_{\beta\gamma} + \frac{1}{9}T_{\alpha\beta\gamma\delta}Q^1_{\alpha\beta}Q^2_{\gamma\delta}\right) \qquad /1/$$

Inductive interactions:

$$U_{ind} = -\frac{1}{2D^2}\left(\alpha^2_{\alpha\beta}F^2_\alpha F^2_\beta + \alpha^1_{\alpha\beta}F^1_\alpha F^1_\beta\right) \qquad /2/$$

$$\text{where} \quad F^2_\alpha = T_{\alpha\beta}\mu^1_\beta - \frac{1}{3}T_{\alpha\beta\gamma}Q^1_{\beta\gamma}; \quad \text{and} \quad F^1_\alpha = \frac{1}{3}T_{\alpha\beta\gamma}Q^2_{\beta\gamma} \qquad /2a/;/2b/$$

Dispersion interactions:

$$U_{disp} = -\frac{1}{4D^2}\frac{I^1 I^2}{I^1+I^2}T_{\alpha\beta}T_{\gamma\delta}\alpha^1_{\alpha\gamma}\alpha^2_{\beta\delta} \qquad /3/$$

In these equations the superscripts 1 and 2 are labelling the interacting rings, DOP and phenyl, respectively. D^2 is an exception and it means the second power of the dielectric constant D. $\underline{\mu}$ and $\underline{Q}$ are the permanent dipole /a vector/ and the permanent quadrupole /a 2nd rank tensor/, respectively. F^2 is the electric field /a vector/ induced at /2/ by the permanent multipoles $\underline{\mu}^1$ and $\underline{Q}^1$ of /1/. For F^1 the opposite holds, yet there is no permanent dipole moment at /2/ so that the quadrupolar term only survives in Eqn /2b/, vide infra. I^i in Eqn /3/ stands for the ionization potential of the center /i/. The subscripts $\alpha=(x,y,z)$, $\beta=(x,y,z)$, etc., when repeated in product terms, imply Einstein's summation, i.e. $T_{\alpha\beta}\mu_\beta = T_{\alpha x}u_x + T_{\alpha y}u_y + T_{\alpha z}u_z$, etc., and the T tensors are defined in Eqn /4/:

$$T_{\alpha\beta\gamma\delta} = \nabla_\alpha T_{\beta\gamma\delta} = \nabla_\alpha\nabla_\beta T_{\gamma\delta} = \nabla_\alpha\nabla_\beta\nabla_\gamma\nabla_\delta R^{-1} \qquad /4/$$

where $\nabla_\xi = \dfrac{\partial}{\partial x} + \dfrac{\partial}{\partial y} + \dfrac{\partial}{\partial z}$ and $\underline{R}$ is a vector running from the geometrical center of /1/ to the geometrical center of /2/. $\underline{\underline{\alpha}}$ /a 2nd rank tensor/, entering Eqns /2/ and /3/ is the ground state polarizability.

In accordance with their definitions in Eqn /4/ the tensors $T_{\alpha\beta}$, $T_{\alpha\beta\gamma}$ and $T_{\alpha\beta\gamma\delta}$ vary with R^{-3}, R^{-4} and R^{-5}, respectively. Hence, in Eqn /1/ the U_{u-Q} term is proportional to R^{-4}, the U_{Q-Q} term - to R^{-5}; Eqn /2/, after substitution of /2a/ and /2b/ and expansion, involves one term in R^{-6}, one term in R^{-7} and two terms in R^{-8}; whereas U_{disp} in Eqn /3/ is proportional to R^{-6}.

We have introduced following simplifications in our calculations: (i) The point-multipole approximation is used throughout; it is intrinsic to the theory[6]. (ii) Both, the DOP ring and the phenyl ring have been considered as separate entities. Thus, we have used permanent multipoles and polarizabilities associated with $c/Gly/_2$ for the center /1/ and those associated with benzene for the center /2/; therefore $\underline{\mu}^2 = \underline{0}$ and terms involving $\underline{\mu}^2$ do not enter Eqns /1/ and /2b/. (iii) For $c/Gly/_2$ the CNDO/2-derived permanent multipoles[7] and the polarizability computed by the method of Applequist and coworkers[8] have been used in the calculations while for benzene the experimental values of $\underline{Q}$[9] and $\underline{\underline{\alpha}}$[10] have been employed. (iv) We have introduced the dielectric constant D to simulate an effect of an environment[11]. No consistent theory exists concerning the choice of D. However, in two most popular force fields for peptides either D is assumed constant[12] (usually equal to 2 - 4) or numerically equal to R, in $\text{\AA}$[13]; each choice having its own rationale[12,13]. From the inspection of Eqns /1/ through /3/ it is seen that the second option, D=R, disfavors U_{ind} and U_{disp} compared to U_{es}, with increasing R. This is because setting D=R converts all electrostatic R^{-n} terms into $R^{-(n+1)}$ ones while all inductive and dispersion R^{-n} terms into $R^{-(n+2)}$ ones. (v) CNDO/2-derived and exptl I's were used for $c/Gly/_2$ and benzene[16], resp..

We carried out calculations both ways and found that they lead to the same general conclusions. The results of the calculations for the F, EN and EO conformers with the DOP ring fixed in the $\begin{smallmatrix}C\alpha\\C\end{smallmatrix}$·T pucker mode are presented in Table 1.

Table 1. Electrostatic, U_{es}, inductive, U_{ind}, and dispersion, U_{disp}, energy contributions. (kJ/mole) to the stabilization of three conformers of c/Gly-Phe/ discussed in the text. Details of the computations (i.e. location of the coordinate system of reference and atomic coordinates as well as numerical values and directional properties of multipoles and polarizabilities involved) will be published elsewhere along with the results of conformational energy calculations for c/Gly-Phe/[14].

Conformer	R/Å/	U_{es}		U_{ind}; sum of 4 terms varying with R^{-6} to R^{-8}	U_{disp}	U_{tot}
		$U_{u^1-Q^2}$ R^{-4} term	$U_{Q^1-Q^2}$ R^{-5} term		R^{-6} term	
			Terms scaled by D = 2			
F	3.554	-0.98	-4.25	-2.15	-9.99	-17.37
EO	4.762	0.41	4.83	-0.38	-2.31	2.55
EN	4.817	0.39	-1.55	-0.45	-1.55	-3.17
Energy span[a]	-	1.39	9.08	1.77	8.44	19.92
			Terms scaled by D = R			

Table 1. Continuation

Conformer	R/Å/	U_{es}		U_{ind}; sum of 4 terms varying with R^{-8} to R^{-10}	U_{disp} R^{-8} term	U_{tot}
		U_{u1-Q2} R^{-5} term	U_{Q1-Q2} R^{-6} term			
F	3.554	−0.55	−2.39	−0.68	−3.16	−6.79
EO	4.762	0.17	2.03	−0.07	−0.41	1.73
EN	4.817	0.16	−0.64	−0.05	−0.27	−0.80
Energy span[a]	−	0.73	4.42	0.63	2.90	8.52

a/ For each contribution, the highest difference in energy amoung three conformers.

The enrgy spans amoung the three conformers are given in order to visualize their relative importance. The following conclusions can be drawn:

1. The quadrupole-quadrupole and dispersion interactions mainly contribute to the ring-ring folding in c/Gly-Phe/. It is likely that the same holds in DOPs comprising other aromatic amino acids, unless ionized states are involved.

2. Despite of their different origins, the leading terms in both approaches appear to be those covering the region spanned between R^{-5} to R^{-8} of dependency on inverse power of R, in good agreement with present theories[15]. In this respect both strategies seem to be mutually consistent.

3. The first approach $\left(D=\acute{c}onst\right)$, as adjustable, enables better, even exact, agreement with the experiment.

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