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Original Scientific Paper

Conformational Analysis of Bis-(*N,N*-dimethylvalinato)copper(II): a Possible Explanation of the Enantioselectivity Effect

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The conformational space of the stereoisomers of bis-(*N,N*-dimethylvalinato)copper(II) was investigated by the consistent force field (CFF) method. The calculated enantioselectivities, defined as Gibbs energy differences between M(L-ligand)₂ and M(L-ligand)(D-ligand) complexes, qualitatively agree with the experimentally observed values.

INTRODUCTION

In the solution of complexes of racemic amino acids an equilibrium takes place among optically pure and racemic complex species:



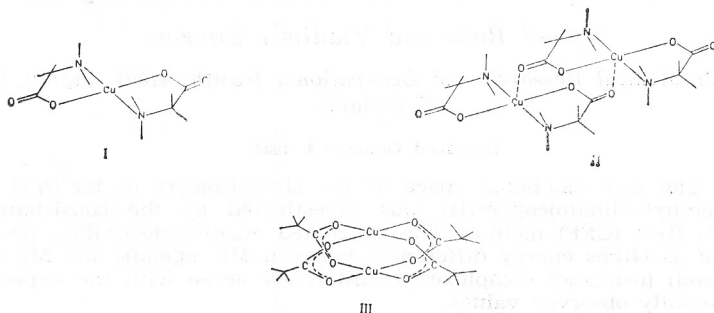
The equilibrium constant, *K*, defined as:

$$K = \frac{[\text{MDL}]^2}{[\text{MLL}] [\text{MDD}]} \quad (2)$$

is a measure of the enantioselectivity effect. If it is equal to 4 (lg *K* = 0.6), the enantioselectivity effect is absent (i. e. optically pure and »meso« complex species are equally stable); if lg *K* < 0.6, optically active species are more stable (negative effect), if lg *K* > 0.6, the reverse is true (positive effect).

The enantioselectivity effect is seldom observed in ML₂ complexes with bidentate amino acids.^{1,2} Thus, no stereoselectivity was observed in complexes of alanine and phenylalanine³, and those of proline and valine.⁴ In fact, it cannot be expected unless amino acids have bulky side-chains. However, in complexes with *N*-alkylated amino acids considerable enantioselectivity effects — both positive and negative — were observed. Deviation of lg *K* from 0.6 was first observed in copper(II) complexes with *N*-benzylproline.⁵ Later it was observed with other *N*-alkylated amino acids, mainly with derivatives of proline, valine and isoleucine.⁶ Interesting to note, the enantioselectivity effect is very dependent on the solvent: in water, it is mainly due to the steric hindrance between the amino acid side-chain and the apically coordinated water molecule.⁷ In apolar solvents, incapable of coordinating, different values for constant *K* were found.⁶

The aim of this paper is to explain the difference in stability constants of bis-(*N,N*-dimethylvalinato)copper(II) complexes measured in chloroform solution.⁶ Such a system is very suitable for consistent force field (CFF) calculations⁸ for three reasons: (1) there are not too many atoms in the molecule, (2) the molecule is rather simple conformationally, i. e. there is a small number of conformers, and (3) the solvent effect, which would otherwise considerably affect the metathetic constant (K)⁹ can be expected to be very small. However, the problem is to some extent complicated by a complex equilibrium between ML_2 complex (I), dimeric (polymeric) species (II), and »acetato-like« structure (III)¹⁰ which exists in chloroform solutions:



In the »acetato-like« structure there is obviously no significant enantioselectivity effect; according to our preliminary calculations, in structure (II) DL-isomers would be preferred because of the steric repulsion between the side-chain and oxygen atom placed in different chelate rings. In structure (I) a positive enantioselectivity effect can be predicted due to side-chain — side-chain interactions.

The overall enantioselectivity effect is determined by contributions of all complex species present in the equilibrated solution. However, it seems that the amount of species (III) and (II) in chloroform solution is very small¹⁰, so almost all enantioselectivity effects can be attributed to the monomeric complex (I).

METHODS

Conformational (strain) energy was calculated from the basic formula:

$$V = \frac{1}{2} \sum_i k_{b,i} (b_i - b_{o,i})^2 + \frac{1}{2} \sum_j k_{\theta,j} (\theta_j - \theta_{o,j})^2 + \frac{1}{2} \sum_k V_{n,k} (1 \pm \cos n\Phi_k) + \sum_l A_l \exp(-B_l r_l) - C_l r_l^{-6} \quad (3)$$

in which b , θ , and Φ stand for bond lengths, valence and torsional angles, respectively; r is non-bonded distance. k_b is empirical parameter for bond stretching, and k_θ is parameter for valence angle bending. Torsional interactions were determined with parameters V_n and n , and non-bonded interactions were computed from Buckingham function with parameters A , B and C . All parameters were the same as previously,¹¹ except those for C—N—C bending which were taken to be equal to the parameters for C—C—C bending.

The average Gibbs energy of diastereomer was calculated from the formula:

$$G = \sum_i w_i G_i / \sum_i w_i \quad (4)$$

where G_i denotes the Gibbs energy of the i -th conformer, and w_i stands for the statistical weight calculated from Boltzmann formula. Details of calculations were given elsewhere.¹¹

Calculations were performed with the program developed by S. R. Niketić and K. J. Rasmussen.¹²

RESULTS AND DISCUSSION

It can be expected that each of the rings in bis-(*N,N*-dimethylvalinato) copper(II) chelate has six possible conformers, so that the whole molecule should have a total of 21 conformers. By minimizing the strain energy, we obtained all of the expected minima (Tables I and II).

Contrary to copper(II) complexes with isoleucine and threonine,^{9,11} where there are many energetically close minima, Tables I and II clearly show that minimum No. 6 is really the global one: it is even 10 kJ mol⁻¹ lower than the lowest of the remaining minima (No. 3, Table I). The conformer of LL-isomer with the lowest energy is depicted in Figure 1.

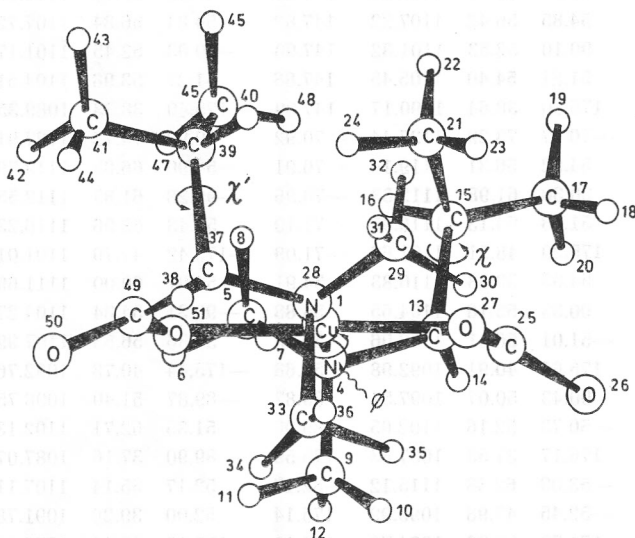


Figure 1. Minimized conformation of bis-(*N,N*-dimethyl-L-valinato) copper(II) with the lowest strain energy (minimum No. 6-6 in Table II). Torsional angles: Φ (O_{27}, Cu_1, N_4, C_5), χ ($C_{17}, C_{15}, C_{13}, N_4$), χ' ($C_{41}, C_{39}, C_{37}, N_{28}$).

TABLE I
Conformational Potential Minima of bis-(*N,N*-dimethylvalinato)copper(II)
Chelate Ring

No.	Torsional $\Phi/^\circ$	Angles* $\chi/^\circ$	Strain Energy/ (kJ mol ⁻¹)	Gibbs Energy/ (298 K) (kJ mol ⁻¹)
1	-145.35	148.35	28.65	553.15
2	-143.42	-71.49	36.16	561.82
3	-144.88	54.46	27.54	552.29
4	152.85	87.88	29.42	552.74
5	153.86	-51.85	34.12	558.19
6	150.11	174.41	18.69	543.41

* For definition see Figure 1.

TABLE II
 Conformational Potential Minima of bis-(N,N-dimethylvalinato)copper(II)
 at $T = 298.15$ K

No.	LL-isomer				DL-isomer				Stereoselective effect		
	Torsional Angles*		Strain Energy/ (kJ mol ⁻¹)	Gibbs Energy/ (kJ mol ⁻¹)	Torsional Angles*		Strain Energy/ (kJ mol ⁻¹)	Gibbs Energy/ (kJ mol ⁻¹)	ΔV / (kJ mol ⁻¹)	ΔG / (kJ mol ⁻¹)	
	χ^0	χ^0			χ^0	χ^0					
1	1	147.87	147.87	53.82	1103.90	147.87	-147.87	54.08	1104.19	-0.26	-0.29
1	2	147.83	-70.99	63.42	1115.53	147.83	70.95	63.75	1115.90	-0.33	-0.37
1	3	147.83	54.85	56.42	1107.22	147.82	-54.84	56.84	1107.72	-0.42	-0.50
1	4	147.91	90.10	52.53	1101.32	147.90	-90.03	52.45	1101.17	0.08	0.15
1	5	147.79	-51.61	54.40	1105.45	147.86	51.27	53.98	1104.51	0.42	0.94
1	6	147.86	175.30	38.64	1090.17	147.89	-175.40	38.33	1089.35	0.31	0.82
2	2	-70.97	-70.97	73.29	1127.44	-70.92	70.92	73.72	1127.91	-0.43	-0.47
2	3	-70.97	54.92	66.31	1119.14	-70.91	-54.90	66.85	1119.79	-0.54	-0.65
2	4	-70.96	90.30	61.98	1112.83	-70.96	-90.28	61.85	1112.55	0.13	0.28
2	5	-71.07	-51.63	64.13	1116.95	-71.19	51.43	63.56	1116.23	0.62	0.72
2	6	-71.02	175.20	48.21	1101.66	-71.09	-175.42	47.79	1101.01	0.42	0.65
3	3	54.93	54.93	59.33	1110.83	54.91	-54.91	60.00	1111.69	-0.67	-0.86
3	4	54.79	90.33	55.16	1104.65	54.88	-90.31	54.84	1104.27	0.32	0.38
3	5	55.00	-51.01	56.51	1108.06	54.55	51.36	56.53	1107.99	-0.02	0.07
3	6	54.93	175.66	40.91	1092.98	54.68	-175.44	40.78	1092.76	0.13	0.22
4	4	90.43	90.43	50.07	1097.54	89.87	-89.87	51.40	1098.75	-1.33	-1.21
4	5	90.62	-50.73	52.16	1102.65	89.98	51.35	52.71	1102.13	-0.55	0.52
4	6	90.33	176.17	37.53	1087.83	175.59	-89.90	37.16	1087.07	0.37	0.76
5	5	-53.09	-53.09	62.68	1115.12	-52.17	52.17	55.14	1107.11	7.54	8.01
5	6	174.31	-52.45	47.98	1099.99	175.14	52.00	39.26	1091.78	8.72	8.21
6	6	174.70	174.70	33.86	1084.76	175.19	-175.19	23.44	1076.40	10.42	8.36

* For definition see Figure 1.

Among 21 possible conformers, a considerable (positive) enantioselectivity effect was observed only in three cases (Nos. 5—5, 5—6, and 6—6, Table II). Differences in strain energy (V) or Gibbs energy (G) among LL- and DL-isomers of the remaining conformers are randomly positive or negative, never but once reaching a value of 1 kJ mol⁻¹. Such differences are presumably not caused by stereospecific interactions at all: rather, they can be attributed to the inaccuracy of energy calculations.

The strongest enantioselectivity effect was observed at the lowest minimum, i. e. No. 6—6. Table III shows that the repulsion among the side-chains of the two chelate rings disturbs the distribution of conformers: in DL-isomer almost all (97.8%) conformers belong to No. 6—6 type; considerably fewer (68.9%) molecules of LL-isomer have such a conformation.

TABLE III

Normalized Statistical Weights of bis-(N,N-dimethylvalinato)copper(II) at $T=298.15$ K

Conformer No.	1-1	1-4	1-6	2-6	3-6	4-4	4-6	5-6	6-6
DL-isomer									
Relative Gibbs Energy/(kJ mol ⁻¹)	16.954	10.677	12.954					15.379	0.000
Statistical Weight from Gibbs Energy	0.001	0.013	0.005					0.002	0.978
Relative Strain Energy/(kJ mol ⁻¹)			14.889				13.725	39.260	0.000
Statistical Weight from Strain Energy			0.002				0.004	0.002	0.991
LL-isomer									
Relative Gibbs Energy/(kJ mol ⁻¹)			5.402		8.214		3.070	15.233	0.000
Statistical Weight from Gibbs Energy			0.078		0.025		0.200	0.001	0.689
Relative Strain Energy/(kJ mol ⁻¹)			4.780	14.344	7.045	16.206	3.670	14.112	0.000
Statistical Weight from Strain Energy			0.1001	0.002	0.040	0.001	0.158	0.002	0.694

Calculating the average Gibbs energy (Eq. 4) a value of more than 7 kJ mol⁻¹ above the measured energy was obtained when the vibrational contribution to Gibbs energy was neglected (approximation $G_i \approx V_i$). Considerably better results were obtained when Gibbs energy was computed properly, i. e. by taking molecular vibrations into account. In an attempt to improve the agreement between the theory and the experiment, we estimated the energy of non-bonded interactions between the side-chains which, in fact, should be a correction for non-bonded interactions through chelate rings; obviously, such interactions do not exist in DL-conformers. In this way slightly better results were obtained.

TABLE IV

Calculated and Experimental Values for Gibbs Energy Differences Between LL- and DL-isomer of bis (N,N-dimethylvalinato)copper(II) at $T = 298.15$ K

	ΔG /(kJ mol ⁻¹)	
Calculated from	G	V
Theoretical	9.47	11.75
Theoretical corrected ^a	9.12	
Experimental ^b	2.9 ... 4.0	

^a The non-bonding potential between side-chains in DL-isomer was subtracted from conformational energy

^b Reference 6

The described calculations give systematically higher values than the experimental ones. This could be attributed to the imperfections of the force field used (especially to the errors in the parameters for central atom interactions). The conformational influence of the chelate rings (mainly due to non-bonded interactions among the *N*-methyl groups and coordinated oxygen in the other ring) is very large, varying even by 15 kJ mol⁻¹ among the DL-conformers, but deformation of the coordination polyhedron was never observed. This could mean that »too strong« parameters, holding the chelate rings firmly in plane, have been chosen. In order to clarify this point we have estimated the effects of tetrahedral distortion and ring puckering upon the

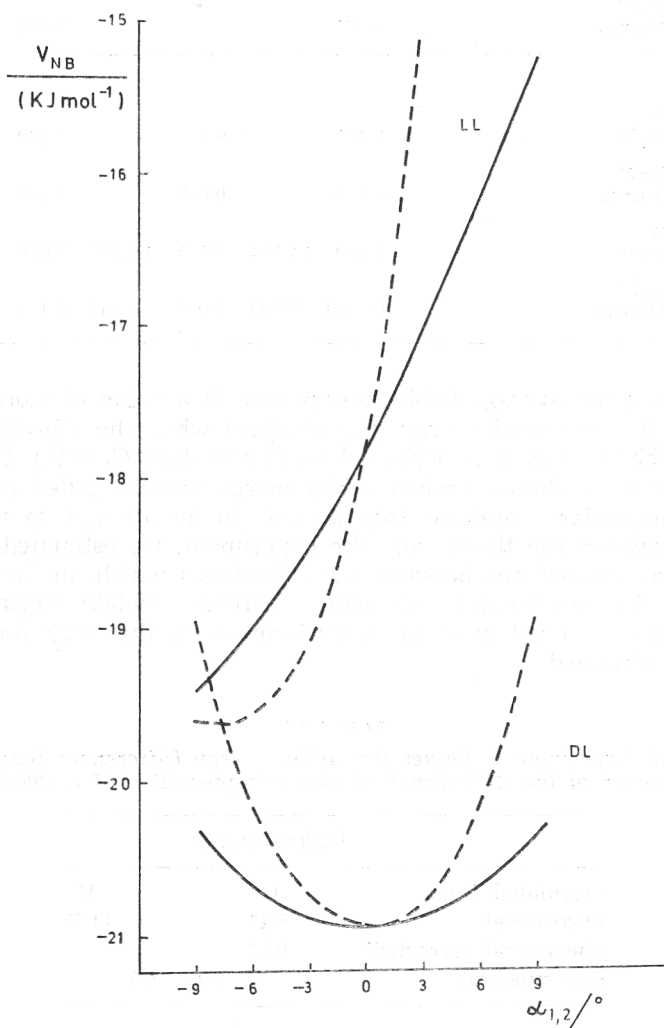
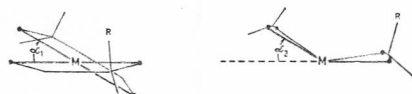


Figure 2. The influence of coordination polyhedron deformation on non-bonding potential of the two most abundant conformers: 6-6 LL (upper curves) and 6-6 DL (lower curves). Deformation was brought about by varying the angles α_1 (—) and α_2 (---) (see Formula 4).

energy of the two lowest conformers of MLL and MLD species. This was done by systematically varying the angles α_1 and α_2



IV

(see Formula 4), keeping all parameters unchanged without performing any minimization. In the case of MLD species such deformations brought about a net increase of non-bonding energy while, to the contrary, they seem to be energetically favourable with MLL (see Figure 2). Although such computations are rather crude approximations, falling outside the scope of the orthodox CFF methodology, it seems that the results depicted in Figure 2 call for an improvement of the force field.

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SAŽETAK

Konformacijska analiza bis-(N,N-dimetilvalinato)bakra(II): objašnjenje enantioselektivnog učinka

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Izvršeno je pretraživanje konformacijskog prostora bis(N,N-dimetilvalinato) bakra(II) primjenom metode usklađenog polja sila (CFF). Izračunane vrijednosti enantioselektivnog učinka, definiranoga kao razlika Gibbsovih energija kompleksa $M(L\text{-ligand})_2$ i $M(D\text{-ligand})(L\text{-ligand})$, kvalitativno se slažu s eksperimentom određenim vrijednostima.