

## Conformational Analysis of Bis-(*N,N*-Dimethylisoleucinato)-copper(II): Estimation of the Diastereoselectivity Effect by Means of two Approximate Methods

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Received May 11, 1984

The consistent force field (CFF) method was used to calculate the energies and geometries of the conformers of two diastereomeric species ( $[\text{Cu}(\text{l-ligand})_2]$  and  $[\text{Cu}(\text{l-ligand})(\text{D-ligand})]$  isomers) of bis-(*N,N*-dimethylisoleucinato)copper(II) complex. By means of two approximate methods (consistent within  $0.02 \text{ kJ mol}^{-1}$ ), it was possible to estimate the diastereoselectivity effect knowing the true energies of only 32 lowest conformers. The calculated diastereoselectivity effect is in rough accordance with the experimentally measured values and, besides, is equal to the value predicted for the analogous *N,N*-dimethylvalinato complexes.

### INTRODUCTION

The enantioselectivity — or, more generally, diastereoselectivity<sup>1</sup> — effect in coordination compounds of amino acids and their derivatives<sup>2</sup> can be caused by cis-trans isomerism, by a different ability of diastereomeric complex species to ligate solvent (water) molecules as well as by purely conformational factors (difference in strain, vibrational and solvation energies between diastereomeric conformers). In addition, the difference in stability constants of the MLL and MDL complexes (where L and D are enantiomeric ligands) can be also caused by kinetic, rather than thermodynamic factors.

Our interest in diastereoselectivity effects in copper(II) complexes with *N*-alkylated amino acids<sup>3-6</sup> is based on a simple fact that the enantioselectivity effect in these compounds, if measured in poorly solvating solvents incapable of coordination (*e. g.* chloroform<sup>4</sup>), can be explained in terms of conformational Gibbs energy difference between LL- and DL-diastereomers of the same (trans-) bonding isomer. All other factors can be neglected which makes these systems almost ideally suited for the evaluation and adaptation of the original empirical force field for the aminocidato complexes<sup>7</sup>.

In our previous paper<sup>8</sup> we made a conformational analysis of diastereomeric bis-(*N,N*-dimethylvalinato)copper(II) complexes and obtained a qualitatively good estimate of the enantioselectivity effect; in the present paper we chose a similar but a more complex system. Contrary to *N,N*-dimethylvalinato complexes, where only 21 conformers are possible, in *N,N*-dimethylisoleucinato complexes there are 18 predictable conformations of each chelate

ring and, consequently,  $18(18 + 1)/2 = 171$  predictable conformers of each diastereomeric complex. The excessive labour and computer time needed to calculate the energies of all those conformations forced us to develop approximate methods for estimating the conformational Gibbs energy of the molecule from the Gibbs energies of its conformers.

#### METHODS

The conformational (strain) energy was calculated from the basic formula:

$$\begin{aligned}
 V = & \frac{1}{2} \sum_i k_{b,i} (b_i - b_{0,i})^2 + \frac{1}{2} \sum_j k_{\theta,j} (\theta_j - \theta_{0,j})^2 \\
 & + \frac{1}{2} \sum_k V_{n,k} (1 \pm \cos n \varphi_k) \\
 & + \sum_l A_l \exp(-B_l r_l) - C_l r_l^{-6}
 \end{aligned} \quad (1)$$

composed of four terms representing conformational potentials caused by bond stretching, valence angle bending, torsional angle bending, and non-bonded interactions, respectively. The empirical parameters  $k_b$ ,  $b_0$ ,  $k_{\theta}$ ,  $V_n$ ,  $n$ ,  $A$ ,  $B$ ,  $C$ , defining the force-field, were chosen in advance while the variables (internal coordinates):  $b$  (bond length),  $\theta$  (valence angle),  $\varphi$  (torsional angle) and  $r$  (non-bonded distance), were modified during the computation in order to make  $V$  a minimum. All of the parameters were the same as used previously<sup>8</sup>, *i. e.* as in the published force field<sup>6</sup>, except those for the C—N—C bending which were taken to be equal to the parameters for the C—C—C bending.

Calculations were performed with the program developed by S. R. Niketić and K. J. Rasmussen<sup>9</sup>.

#### Calculation of the Average Gibbs Energy

The Gibbs energy of a molecular species with  $N$  interconvertible conformers can be calculated by taking the average over the accessible conformational states, weighted by appropriate Boltzmann factors:

$$\langle G \rangle = \frac{\sum_{i=1}^N G_i \exp(-G_i/RT)}{\sum_{i=1}^N \exp(-G_i/RT)} \quad (2)$$

where  $G_i$  denotes the Gibbs energy of the  $i$ -th conformer.

Introducing the symbolism  $G_i = G_i^0 + x_i$  the formula (2) can be rewritten as:

$$\langle G \rangle = \frac{\sum_{i=1}^m G_i \exp(-G_i/RT) + \sum_{j=m+1}^N (G_j^0 + x_j) \exp[-(G_j^0 + x_j)/RT]}{\sum_{k=1}^m \exp(-G_k/RT) + \sum_{l=m+1}^N \exp[-(G_l^0 + x_l)/RT]} \quad (3)$$

This formulation of the relation (2) enables the calculation of the approximate value of  $\langle G \rangle$  knowing the true values of the Gibbs energies of only  $m$  lowest minima. For the remaining  $N - m$  conformers, the approximate

( $G_i^0$ ) values were used. These were computed as sums of Gibbs energies of individual chelate rings (this was previously<sup>7</sup> shown to be a reasonable approximation). We used two kinds of approximation:

$$\left. \begin{aligned} \text{and} \quad & x_i = 0 \\ & x_i = \bar{x}_m = \ln \frac{1}{m} \sum_{i=1}^m \exp(-x_i/RT) = \ln \bar{X}_m \end{aligned} \right\} \text{for } m < i \leq N \quad \begin{matrix} (4a) \\ (4b) \end{matrix}$$

Obviously, the approximation (4a) is expected to hold when  $G_i \gg x_i$ .

Introducing new variables  $X_i = \exp(-x_i/RT)$  and writing the relations for true and approximate values of average Gibbs energy as  $\langle G \rangle = R/S$  and  $\langle G \rangle^* = R^*/S^*$ , respectively, the convergence of  $\langle G \rangle^* \rightarrow \langle G \rangle$  with approximation (4b) can be proved. The difference between the true and approximate values of  $S$  can be written:

$$\begin{aligned} S - S^* &= \sum_{i=m+1}^N \exp(-G_i^0/RT) X_i - \bar{X}_m \sum_{i=m+1}^N \exp(-G_i^0/RT) = \\ &= \sum_{i=m+1}^N \exp(-G_i^0/RT) (X_i - \bar{X}_m) \end{aligned} \quad (5)$$

For a molecular system with many energetically very close minima:

$$\lim (S - S^*) = 0 \quad (6)$$

$$\text{when } (G_i - G_{i-1}) \rightarrow 0.$$

Similarly, the difference between the true and approximate values of variable  $R$  can be written as:

$$\begin{aligned} R - R^* &= \sum_{i=m+1}^N \exp(-G_i^0/RT) (G_i^0 X_i + x_i X_i - G_i^0 \bar{X}_m - \bar{x}_m \bar{X}_m) = \\ &= \sum_{i=m+1}^N G_i^0 \exp(-G_i^0/RT) (X_i - \bar{X}_m) + \sum_{i=m+1}^N \exp(-G_i^0/RT) (x_i X_i - \bar{x}_m \bar{X}_m) = \\ &= \sum_{i=m+1}^N G_i^0 \exp(-G_i^0/RT) (X_i - \bar{X}_m) + \sum_{i=m+1}^N \exp(-G_i^0/RT) \bar{x}_m (X_i - \bar{X}_m) + \\ &\quad + \sum_{j=i+1}^N \exp(-G_i^0/RT) X_i (\bar{x}_m - X_j) \end{aligned} \quad (7)$$

For  $G_i \approx G_{i+1}$  the first two terms in relation (7) converge towards zero. The last term, for values of  $\exp(-G_i^0/RT)$  close to 1 ( $G_i$  is very large), can be written:

$$C = \sum_{i=m+1}^N \exp(-G_i^0/RT) X_i (\bar{x}_m - x_i) \approx \sum_{i=m+1}^N X_i (\bar{x}_m - x_i) \quad (8)$$

or

$$C = \sum_{i=m+1}^N [X_i \ln(\bar{X}_m) - X_i \ln X_i] = \ln \sum_{i=m+1}^N \left( \frac{\bar{X}_m}{X_i} \right) X_i \quad (9)$$

Relation (9) can be approximated with a Taylor series assuming  $C = \ln f(X_i)$ :

$$f(X_i) \approx f(\bar{X}_m) - \sum_{i=m+1}^N \frac{\partial f(\bar{X}_m)}{\partial X_i} (\bar{X}_m - X_i) + \frac{1}{2} \sum_{i=m+1}^N \frac{\partial^2 f(\bar{X}_m)}{\partial X_i^2} (\bar{X}_m - X_i)^2 + \\ + \frac{1}{2} \sum_{i=m+1}^N \sum_{j=i+1}^N \frac{\partial^2 f(\bar{X}_m)}{\partial X_i \partial X_j} (\bar{X}_m - X_i) (\bar{X}_m - X_j) \quad (10)$$

Assuming that all first-order differentials equal  $K$ , and the second-order ones  $K'$ , it is obvious that the first three terms of relation (10) converge to a minimum value:

$$f(\bar{X}_m) = 1 \quad (11a)$$

$$\sum_{i=m+1}^N K (\bar{X}_m - X_i) \rightarrow 0 \quad (11b)$$

$$\sum_{i=m+1}^N K (\bar{X}_m - X_i) \rightarrow \text{minimum} \quad (11c)$$

The fourth term in the Taylor series (10):

$$D = \frac{1}{2} K' \sum_{i=m+1}^N \sum_{j=i+1}^N X_i X_j \quad (12)$$

is dependent on the difference between the true and approximate values of variables  $G_i$  and converges to zero when  $m \rightarrow N$ .

#### RESULTS AND DISCUSSION

Contrary to crude predictions that there are 18 minima of the conformational energy of the chelate ring of bis-(*N,N*-dimethylisoleucinato)copper (II) complex, investigations of the conformational space of separate chelate rings showed that two of the predicted minima ( $\chi_1 \approx 180^\circ$ ,  $\chi_2 \approx -60^\circ$ ; for definition of  $\chi$  angles see Figure 1) are not possible. Initial conformations with the specified values of torsional angles had strain energies so high — obviously because of a very close contact of the ethyl and methyl groups bound to the nitrogen atom — that even minimization was impossible.

The Gibbs energies of the highest (No. 1) and lowest (No. 12) minima differ considerably ( $\approx 50$  kJ mol<sup>-1</sup>). The two lowest minima (12 and 15) are very close energetically, differing by less than 0.5 kJ mol<sup>-1</sup>, both in strain and Gibbs energies (Table I).

Only six conformations of the chelate ring (out of 16) have been found to induce an interannular strain and, thereby, give rise to the diastereoselectivity in MLL molecules; these are characterized by  $\varphi \approx 150^\circ$ ,  $\chi_1 \approx \pm 60^\circ$  (Figure 1). The conformation 14 induces so great a conformational strain that all combinations with other conformations inducing an interannular strain were impossible, with an exception of minimum 11—14 in which by far the greatest diastereoselectivity effect was observed (Table II).

The Boltzmann weights of LL and DL isomers (Table III) show that virtually all (97.6%) molecules of the DL isomer have one of the three energetically

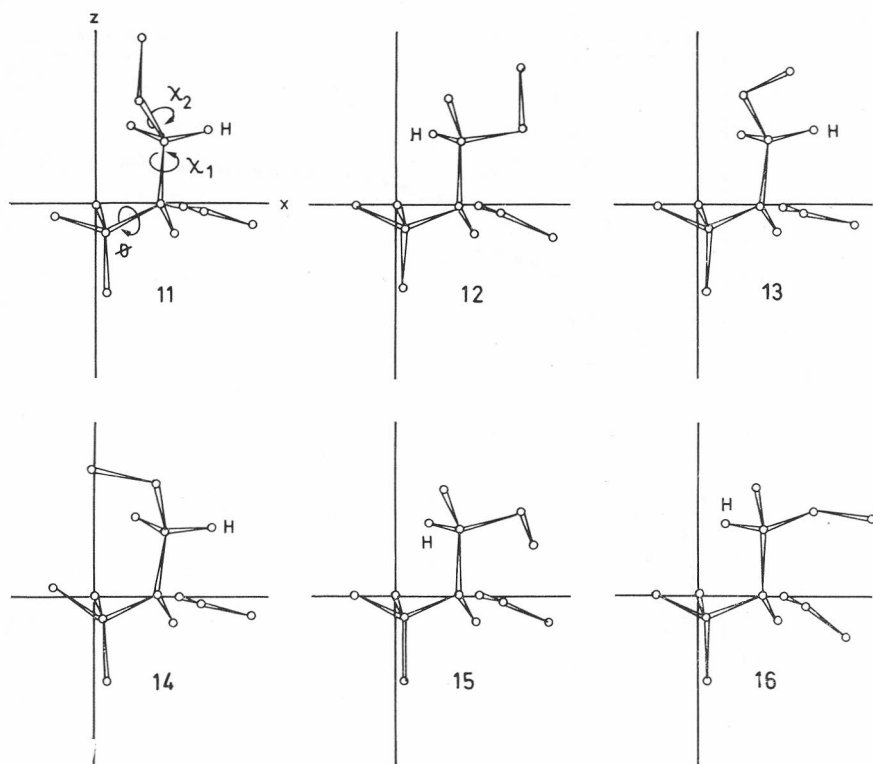


Figure 1. Ring conformations inducing interannular strain in bis-((*N,N*-dimethylisoleucinato)copper(II) complex (only one chelate ring is drawn). The relevant torsional angles are defined as:  $\chi_1$  (R & S) =  $\chi$  ( $C^{\gamma_2}$ ,  $C^{\beta}$ ,  $C^{\alpha}$ , N),  $\chi_2 = \chi$  ( $C^{\delta_1}$ ,  $C^{\gamma_1}$ ,  $C^{\beta}$ ,  $C^{\alpha}$ ),  $\varphi = \varphi$  (O, Cu, N,  $C^{\alpha}$ ).

TABLE I

Conformational Potential Minima of bis-((*N,N*-Dimethylisoleucinato)copper(II) Chelate Ring at  $T = 298.16$  K

No.	$\varphi/^\circ$	Torsional Angles*		$V/\text{kJ mol}^{-1}$	$G/\text{kJ mol}^{-1}$
		$\chi_1/^\circ$	$\chi_2/^\circ$		
1	-146.74	34.75	56.86	66.63	666.75
2	-146.70	-90.84	59.70	34.75	632.91
3	-143.48	54.28	-160.20	36.57	634.01
4	-140.07	57.81	-58.59	45.57	646.27
5	-145.42	-90.59	-176.93	29.86	626.34
6	-145.13	174.31	172.63	32.08	629.42
7	-144.29	177.94	61.87	32.43	632.02
8	-145.51	-91.13	-73.20	30.25	626.17
9	153.16	-151.64	-162.84	32.97	627.98
10	151.99	-156.84	53.00	35.51	631.10
11	153.70	73.22	-178.49	36.81	633.57
12	149.46	-84.38	-172.75	20.85	617.23
13	151.49	74.28	-93.29	45.48	642.12
14	154.39	67.60	79.53	60.15	659.09
15	150.41	-62.13	-62.37	20.75	617.59
16	150.01	-69.56	61.59	30.99	628.60

\* For definition see Figure 1.

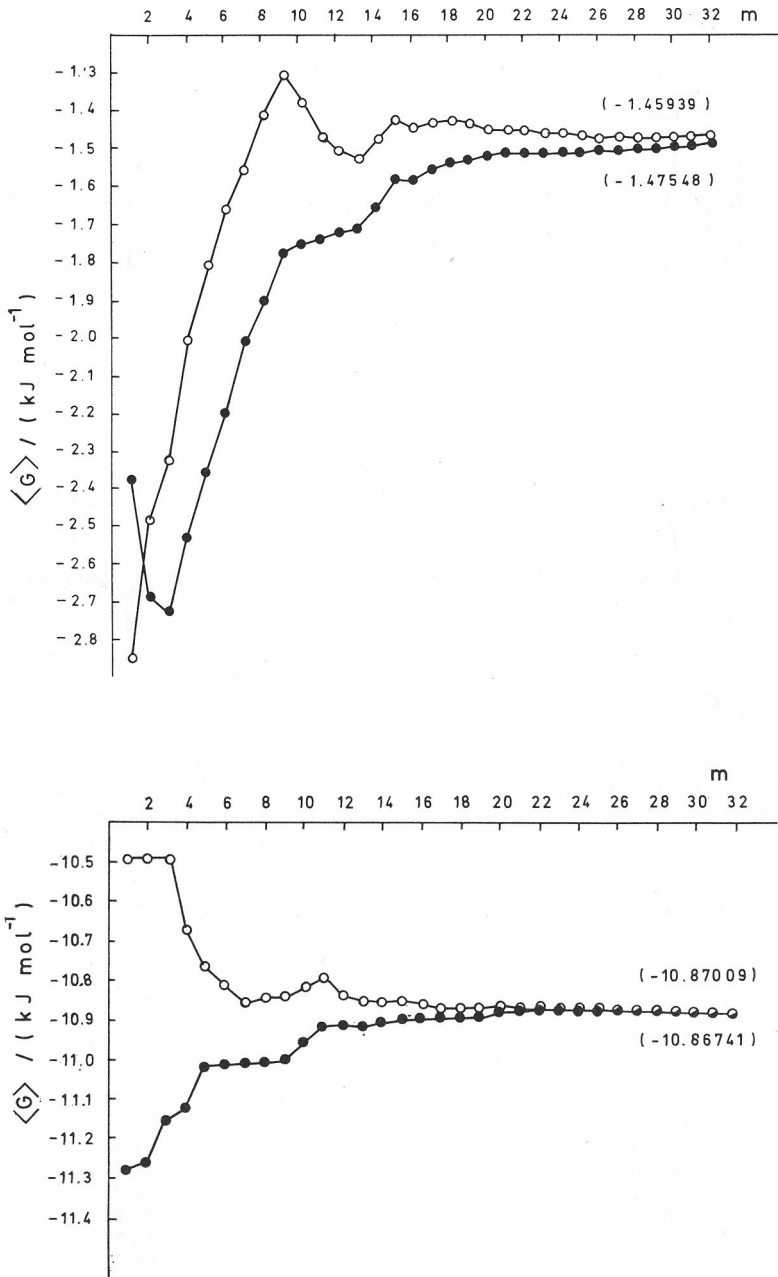


Figure 2. Iterative computation of the Gibbs energies of LL (upper diagram) and DL (lower diagram) isomers by means of two approximate methods (Eq. (4a): ●, Eq. (4b): ○). The final results are given in parentheses. The zero point for  $\langle G \rangle$  is taken equal to the lowest approximate  $G$  value ( $G_0 = 1234.454 \text{ kJ mol}^{-1}$ ).

TABLE II

Conformational Potential Minima of bis-(N,N-dimethylisoleucinato)copper(II) with Diastereoselective Effect Greater than 1.0 kJ mol<sup>-1</sup> at T = 298.16 K

Ring con- formations No.	LL-isomer		DL-isomer		Diastereoselective effect	
	V	G	V	G	$\Delta V$	$\Delta G$
	kJ mol <sup>-1</sup>	kJ mol <sup>-1</sup>	kJ mol <sup>-1</sup>	kJ mol <sup>-1</sup>	kJ mol <sup>-1</sup>	kJ mol <sup>-1</sup>
11 11	63.20	1261.14	58.83	1255.85	4.37	5.29
11 12	50.61	1246.33	43.18	1239.47	7.43	6.87
11 13	71.30	1269.30	67.32	1265.13	3.98	4.17
11 14	96.22	1297.32	80.06	1281.04	16.17	16.28
11 15	50.67	1247.10	42.95	1239.82	7.72	7.29
11 16	61.69	1259.10	53.48	1250.88	8.21	8.22
12 12	37.82	1230.60	27.50	1222.95	10.31	7.65
12 12	59.06	1254.83	51.63	1248.72	7.44	6.10
12 15	37.74	1231.98	27.28	1223.32	10.45	8.66
12 16	48.53	1242.17	37.88	1234.49	10.66	7.69
13 13	79.42	1278.23	75.75	1274.42	3.67	3.81
13 15	58.95	1255.72	51.42	1249.07	7.53	6.66
13 16	69.91	1267.63	61.98	1260.25	7.93	7.38
15 15	37.60	1233.00	27.06	1223.68	10.54	9.33
15 16	48.60	1245.06	37.64	1234.84	10.96	10.21
16 16	58.30	1254.54	48.21	1245.92	10.09	8.61

TABLE III

Gibbs Energies and Normalized Statistical Weights of bis-(N,N-Dimethylisoleucinato)copper(II) at T = 298.16 K with Approximation m = 32 (4b)\*

No.	LL-isomer		DL-isomer	
	G** kJ mol <sup>-1</sup>	Normalized Boltzmann Weight	G** kJ mol <sup>-1</sup>	Normalized Boltzmann Weight
12 12	0.000	0.371	0.000	0.374
12 15	1.378	0.213		
15 15	2.402	0.141		
9 12	5.048	0.048	Total: 0.976	
8 12	5.442	0.041		
9 15	5.581	0.039		
5 12	5.630	0.038		
8 15	5.761	0.036		
5 15	5.943	0.034		
10 15	8.866	0.010		
Total: 0.971				

\* Only conformations with a Boltzmann weight >0.01 are shown.

\*\* Relative to the lowest conformer.

very close conformations (12—12, 12—15, and 15—15). In the LL isomer, to the contrary, the lowest three conformers represent only  $\approx 70$  per cent of all possible conformers. This fact is, undoubtedly, closely connected with the diastereoselectivity effect.

Using the approximate methods described above it was possible, after ca. 20 »iterations«, to obtain results which were only slightly dependent on the  $m$  value chosen (Figure 2). Both approximate methods (Eqs. (4a) and (4b)) converged to the same values, the later having converged only slightly faster. However, the convergence of both polynomials to the same value seems to be a strong support of the validity of the approximate computation procedure. The estimated value for the diastereoselectivity effect ( $\langle G \rangle_{\text{MLL}} - \langle G \rangle_{\text{MDL}} = 9.4 \text{ kJ mol}^{-1}$ ) is about  $4.5 \text{ kJ mol}^{-1}$  greater than the one obtained experimentally<sup>4</sup>. Presumably, this disagreement is mainly due to a poor simulation of coordination polyhedron plasticity as was suggested previously<sup>8</sup>. It is interesting to note, that the estimated diastereoselectivity effect in *N,N*-dimethylvaline and *N,N*-dimethylisoleucine is virtually the same which is in good agreement with the experimental results<sup>4</sup>.

## REFERENCES

1. K. Bernauer, *Top. Curr. Chem.* **65** (1975) 1.
2. V. A. Davankov, A. A. Kurganov, and S. V. Rogozhin, *Usp. Khim.* **63** (1974) 1610.
3. V. A. Davankov, S. V. Rogozhin, and A. A. Kurganov, *Izv. Akad. Nauk. SSSR. Ser. Khim.* **204A** (1971) 204.
4. V. A. Davankov, S. V. Rogozhin, A. A. Kurganov, and L. Ya. Zhuchkova, *J. Inorg. Nucl. Chem.* **37** (1975) 369.
5. V. A. Davankov, S. V. Rogozhin, Yu. T. Struchkov, G. G. Alexandrov, and A. A. Kurganov, *J. Inorg. Nucl. Chem.* **38** (1976) 631.
6. A. A. Kurganov, V. A. Davankov, and L. Ya. Zhuchkova, *Koord. Khim.* **3** (1977) 988.
7. N. Raos, S. R. Niketić, and Vl. Simeon, *J. Inorg. Biochem.* **16** (1982) 1.
8. N. Raos and Vl. Simeon, *Croat. Chem. Acta* **56** (1983) 79.
9. *The Consistent Force Field: A Documentation*, S. R. Niketić and K. J. Rasmussen, Springer-Verlag, Berlin 1977.

## SAŽETAK

**Konformacijska analiza bis-(*N,N*-dimetilizoleucinato)bakra(II): procjena dijastereoselektivnog učinka s pomoću dviju približnih metoda**

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Metoda usklađenog polja sila (CFF) uporabljena je za proračun energija i geometrija konformerâ dviju dijastereomernih vrsta ( $[\text{Cu}(\text{l-ligand})_2]$  i  $[\text{Cu}(\text{l-ligand})(\text{o-ligand})]$ ) kompleksa bis-(*N,N*-dimetilizoleucinato)bakra(II). S pomoću dviju približnih metoda (skladnih unutar  $0,02 \text{ kJ mol}^{-1}$ ) bilo je moguće procijeniti dijastereoselektivni učinak na osnovi poznavanja točnih potencijalnih energija samo 32 energijski najniža konformera. Izračunani dijastereoselektivni učinak približno se slaže s eksperimentalno izmjerenim, a k tomu je jednak onomu koji se predviđa za analogne komplekse *N,N*-dimetilvalina.