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Influence of Alkali and Alkaline Earth Salts on the Internal Rotational Barriers in N,N-dimethylbiuret. Experimental and Theoretical Studies

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The effect of alkali and alkaline earth salts on the barriers to internal rotation about the C–NR$_2$ (R = H, CH$_3$) bonds in N,N-dimethylbiuret has been studied by means of ^{1}H n.m.r. line shape analysis. The 1:1 complexes of the ligand with the ions of Li, Na, K, Be, Mg and Ca have been investigated by ab initio *MO–SCF calculations with minimal GLO basis sets. The changes of the activation energies for the rotational barriers, the influence of methyl N-substitution on complex stability, and the geometry of the complexes are discussed on the basis of the theoretical results.*

Introduction

Recently, studies on the complex formation of alkali and alkaline earth metal ions with unsubstituted biuret have been carried out [1, 2]. Two different barriers to internal rotation about the C–NR$_2$ (R = H, CH$_3$) bonds in N,N-dimethylbiuret (DMB) have been found [3]. These two different barriers of rotation due to two different amido groups in the same molecule promised to give access to studies concerning the specificity of ligand binding sites, especially for coordination of alkali and alkaline earth metal ions at peptide groups, which play a very important role not only in chemistry but also in biological phenomena [4–8]. We intended to determine the values of the activation energies for these two rotational barriers of DMB under the influence of alkali and alkaline earth metal ions, using ^{1}H n.m.r. spectroscopy, as well as *ab initio* MO–SCF calculations with a minimal basis set, which have been successfully used in investigations on the partial double bond character of C–N bonds in the peptide groups of similar systems [8–11].

Experimental

N,N-dimethylbiuret was prepared as in the previous work [3], and purified by recrystallization from absolute alcohol. The purity was controlled by its melting point (175–180 °C) and standard spectroscopic methods. Anhydrous reagent grade alkali and alkaline earth metal salts (Merck, Fluka, and Alfa Ventron) were used without further purification. Anhydrous dimethyl sulphoxide (DMSO, Merck *p.a.*) and liquid sulphur dioxide, which was purified by several condensations, were used as solvents.

To avoid intermolecular interactions between ligand molecules and to obtain good n.m.r. signals, the optimal ligand concentration was found to be a constant concentration for all investigations of 0.51 *M* in both solvents. The n.m.r. spectra were obtained for a 1:1 metal ion to ligand ratio in DMSO for all alkali and alkaline earth metal ions, except MgCl$_2$. Due to the low solubility of salts in liquid SO$_2$, especially for the investigation at low temperature, only 1:10 metal iodide to ligand ratios were available. However, the experimental results show that the anion effect seems to be a minor effect concerning the change of the rotational barriers at low salt concentration [12].

All samples were prepared in standard n.m.r. tubes in a dry nitrogen atmosphere.

Measurement of the Internal Rotation Barriers

The rate of internal rotation around C–N bonds in DMB at each temperature was obtained by comparing the theoretical spectra, calculated according to the modified Bloch equations [13], with the experimental spectra. The activation energies of the rotation were evaluated according to the Arrhenius equation using the least squares method. The experimental spectral parameters in the temperature range of 23–30 °C and at –60 °C, where the well-separated ^{1}H n.m.r. signals of NH$_2$ and N(CH$_3$)$_2$ groups respectively could be observed, were used as input data for calculating the theoretical spectra.

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TABLE I. Calculated SCF Energies (a.e.u.).

M–DMB	*cis*-unrotated	*cis*-NH_2 rotated	*cis*-NR_2 rotated
DMB	−398.90029	−398.85409	−398.87114
Li^+–DMB			
Chelate	−405.41518	−405.36588	−405.35111
cis-unsubst.	−405.38882	−405.33451	−405.35850
cis-subst.	−405.38774	−405.34210	−405.35457
Na^+–DMB			
Chelate	−548.12361	−548.07520	−548.09083
cis-unsubst.	−548.09345	−548.04490	−548.06315
cis-subst.	−548.09254	−548.04665	−548.06026
K^+–DMB			
Chelate	−982.55223	−982.50476	−982.52047
cis-unsubst.	−982.51831	−982.47029	−982.48819
cis-subst.	−982.51763	−982.47176	−982.48580
Be^{2+}–DMB			
Chelate	−411.79130	−411.73775	−411.74832
cis-unsubst.	−411.74999	−411.69781	−411.71730
cis-subst.	−411.74981	−411.70545	−411.71051
Mg^{2+}–DMB			
Chelate	−584.76967	−584.71657	−584.72803
cis-unsubst.	−584.70237	−584.65171	−584.66989
cis-subst.	−584.70203	−584.65661	−584.66532
Ca^{2+}–DMB			
Chelate	−1059.13489	−1059.08303	−1059.09594
cis-unsubst.	−1059.07157	−1059.02156	−1059.03951
cis-subst.	−1059.07143	−1059.02579	−1059.03562

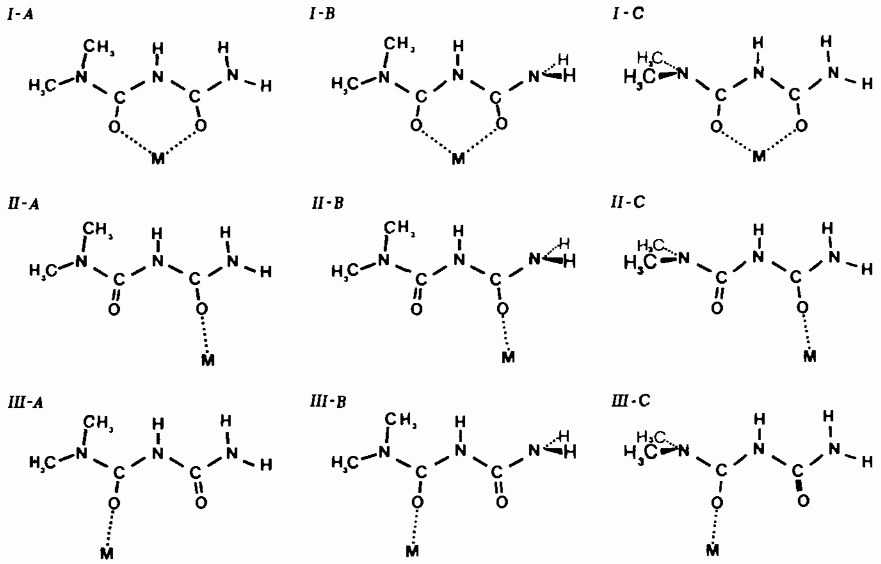

Fig. 1. 1:1 Complex geometries.

TABLE II. Stabilization Energies for the Different Geometries of the DMB Complexes with Metal Ions (in kcal mol^{-1}), and the Percent Chelate Energy Gain of 1:1 Chelate Complexes Compared with 1:1 *Cis* Complexes. (in parenthesis).

Ion	Biuret*	DMB		
		config. I-A	config. II-A	config. III-A
Li	64(+34%)	66(+33%)	49.3	48.6
Na	59(+47%)	60(+46%)	41.1	40.5
K	59(+56%)	60(+55%)	38.9	38.5
Be	190(+14%)	197(+15%)	171.3	171.2
Mg	159(+33%)	165(+34%)	122.8	122.6
Ca	133(+40%)	138(+41%)	98.0	97.9

*Data from reference 2.

The series of the temperature dependent spectra were recorded in the temperature range 23–80 °C, using a 60 MHz ^{1}H n.m.r. Varian EM 360 L and a 80 MHz-FT-NMR Bruker WP 80 spectrometer, and from –20 °C to 60 °C using a 60 MHz JEOL C 60 HL n.m.r. spectrometer. The details of the temperature measurement and the computer program are discussed in reference 14.

Ab initio *MO–SCF Calculations*

In the quantum theoretical calculations, nine configurations of 1:1 DMB complexes of Li^+, Na^+, K^+, Be^{2+}, Mg^{2+} and Ca^{2+} were considered, representing the chelate complex geometry (Fig. 1-I), and the two *cis*-complex geometries with the position of the metal ion along the axis of the C=O bond either at the non-substituted or at the substituted amido group (Fig. 1-III). The geometry of the ligand molecule [3] and metal ion–ligand distances were taken in analogy with biuret and its complexes [2]. The exponents of the GLO basis for cations and ligand have been given in the previous works [2, 3]. The activation energies of rotation about the C–N bonds were obtained from the different energy values of the corresponding non-rotated and rotated conformations.

All SCF calculations were performed on the CDC Cyber 74 computer of the Technical University of Vienna. The details of the computer program are given in reference 15.

Results and Discussion

The calculated SCF total energies of the 1:1 complexes are presented in Table I. From these results, the chelate geometry is indicated to be the most stable form in all species of the non-rotated isomers, except in the case of lithium ion/DMB system where the configuration II-C is more stable than the other rotated structure for the C–N$(CH_3)_2$ barrier (Fig. 1, I-C, III-C).

TABLE III. Calculated Percent Change of the Rotational Barriers in 1:1 Complexes.

		B_1 (%) NH_2	B_2 (%) $N(CH_3)_2$
Li^+	I	+7	–
	II	+7	+4
	III	–1	+2.5
Na^+	I	+4	+13
	II	+5	+4
	III	0	+11
K^+	I	+3	+9
	II	+4	+3
	III	0	+9
Be^{2+}	I	+16	+48
	II	+13	+12
	III	–9	+30
Mg^{2+}	I	+15	+43
	II	+10	+11
	III	–2	+26
Ca^{2+}	I	+12	+33
	II	+8	+10
	III	–1	+23

In order to compare the influence of the individual metal ions and the methyl-N-substitution effect on the formation of complex, the stabilization energies of the three different geometries of the non-rotated DMB complexes are summarized in Table II. The stabilization energies of the 1:1 cation–biuret chelate complexes [2]. are also given.

Generally, the stabilization energies of DMB complexes compared with those of the analogous biuret complexes in chelate structure indicate that the complex stability increases upon methyl-N-substitu-

TABLE IV. Calculated Rotational Barrier Changes in the 1:1 Chelate Complexes (kcal mol^{-1}).

Ion	B_1 (CO–NH$_2$)	B_2 (CO–N(CH$_3$)$_2$)
Li	+1.9	+0.2
Na	+1.3	+2.3
K	+0.8	+1.6
Be	+4.6	+8.7
Mg	+4.3	+7.8
Ca	+3.5	+6.1

tion for all ions, especially for divalent ions. As the data in Table II show, the chelate geometry seems to be the most stable structure for all cations. In the case of monovalent cations, an asymmetric energy surface of two *cis*-geometries (Fig. 1, II, III) is being observed ($E_u > E_s$). For divalent cations this evidence is not given ($E_u \approx E_s$). This asymmetry in the energy surface was a first indication of a difference in the bonding of alkali and alkaline earth cations to DMB.

The Theoretical Calculated Values of the Rotational Barriers

Table III lists the percent change of the rotational barriers in metal ion–DMB complexes for three geometries (Fig. 1), related to the corresponding barriers of free DMB. Positive values, which indicate an increase of the double bond character of the C–N bonds in DMB due to the complex formation, result for all cases except for geometry III (Fig. 1), where the calculations predict a decrease of the C–N double bond character of the CO–NH$_2$ group due to the coordination of the cation at the carbonyl oxygen of the substituted amido group.

In order to estimate the trends in the rotation barrier change due to the complex formation, the values for the most stable geometry (*i.e.* chelate structure) have been calculated (Table IV). The influence of cations on the rotational barriers depends not only on the charge but also on the size of ions. The smaller the ions and the greater their polarizing power, the larger the change of the rotational barriers. The Li–DMB complex, however, seems to be an exceptional case.

Experimental Results

The activation energies of the internal rotation barriers of the amido groups in DMB and in DMB under the influence of the salts are given in Table V. The rotational barrier of the CO–NH$_2$ group was evaluated by using the FT-NMR method at $E_a(NH_2)$ = 27.8 kcal mol^{-1} for the free DMB system, which is quite large compared with the value of $E_a(NH_2)$ = 19.7 kcal mol^{-1} obtained by CW-NMR technique. This difference is expected to result not only from the different NMR methods, but also to the different quality of the instruments. Slightly different linewidths obtained by the instruments for identical samples at the same temperature indicate some differences. The accuracy of these two different methods is not comparable, but the determined values by either of the methods were well reproducible. Thus, the relative changes of the rotational barriers in the salt/DMB systems by using the same technique as for the free DMB system can be used for the evaluation of the influence of the metal salts. The experimental results are summarized in Table VI.

As a general trend within the investigated salts, monovalent and divalent metal salts show a different behaviour concerning the relative change of the rotational barriers. For alkali earth ions a decrease of both rotational barriers is observed, while an increase of the CO–NH$_2$ barrier and a decrease of the CO–N(CH$_3$)$_2$ barrier have been found for alkali ions. It is supposed that the strong influence of Na$^+$ and Mg^{2+} on the double bond character in DMB is related to their complex stability (indicated by the calculated stabilization energy), and also by the stabilization constant which could be estimated

TABLE V. Activation Energies of Internal Rotation in DMB and Its Complexes in kcal mol^{-1}.

MX_n–DMB	E_a (NH$_2$)* a	E_a (N(CH$_3$)$_2$)* b
0.5 *M* DMB	27.8	11.4
Iodide (X = I)		
LiI–DMB	27.2	12.8
NaI–DMB	45.5	6.8
KI–DMB	33.1	8.9
RbI–DMB	35.8	7.2
CsI–DMB	34.4	10.4
BaI$_2$–DMB	21.5	–
Chloride (X = Cl)		
LiCl–DMB	25.6	–
MgCl$_2$–DMB	15.5**	7.4
CaCl$_2$–DMB	25.5	9.3
SrCl$_2$–DMB	26.6	–
BaCl$_2$–DMB	24.6	–

*[M]/[L] is 1:1 for the evaluation of $E_a(NH_2)$ and approximately 0.1 (in nearly saturated solution of salts in liquid SO$_2$) for $E_a(N(CH_3)_2)$. **[M]/[L] is 0.67 for MgCl$_2$–DMB system.

^{1}H NMR spectra were carried out using the spectrophotometers; a) 80 MHz-FT-NMR Bruker WP 80; b) 60 MHz-NMR JEOL C 60 HL.

TABLE VI. Changes of the Activation Energies of Internal Rotation in DMB under the Influence of Alkali and Alkaline Earth Metal Salts.

Salt	E_a (NH_2) [M]/[L] = 1.0	E_a ($N(CH_3)_2$) [M]/[L] = 0.1
NaI	+17.7	−4.6
KI	+5.3	−2.5
RbI	+8.0	−4.2
CsI	+6.6	−1.0
LiI	−0.6	+1.4
LiCl	−2.2	–
$MgCl_2$	−12.3*	−4.0
$CaCl_2$	−2.3	−0.1
$SrCl_2$	−1.2	–
$BaCl_2$	−3.2	–
BaI_2	−6.3	–

*[M]/[L] = 0.67.

from the chemical shift of the imido proton in analogy to biuret complexes [2, 12]. The results for the series of K^+, Rb^+, Cs^+ and Ca^{2+}, Sr^{2+}, Ba^{2+} also agree with this assumption to some extent. Again, lithium complexes represent an exceptional case. There is no doubt, however, that the changes of the rotational barriers due to complex formation depend not only on the complex stability, but also on the complex geometry, which will be discussed including the theoretical results.

Comparison of Experimental and Theoretical Results

Rotation about the C–N bond of the non-substituted amido group

As mentioned above, the experimental data show clearly different behaviour for monovalent and divalent ions, and the influence of the anions seems to be a minor effect in this case (*cf. e.g.* LiCl/LiI and $BaCl_2/BaI_2$). Lithium ion presents the obvious exception among alkali ions. It shows a similar behaviour as the divalent cations. This could be explained by the low shielding of its positive charge and its small ionic radius (similar to magnesium ion). From the relative change of the barrier, one can rank the interaction of the ions as in the following series:

For monovalent ions: Na > Rb > Cs > K
For divalent ions and Li^+: Mg > Ba > Ca > Li > Sr

These series correspond neither to the order of atomic numbers nor to that of ionic radii, but they show a specific interaction of individual ions with the ligand, based probably on the geometry and stability of the complexes.

According to the MO–SCF calculations of 1:1 complexes it is indicated that for ion coordination at the carbonyl group of the non-substituted part of DMB, an increase of the $CO–NH_2$ barrier should result, and that the opposite effect should be found for a coordination to the substituted amido group. This indicates the latter coordination to be preferred by the divalent ions and lithium, whereas the other alkali ions should be located rather at the chelate position or at the unsubstituted amino group. As the experimental data do not indicate significant anion effects in the case of this barrier, this conclusion from the theoretical data seems to be possible, although the simple 1:1 model cannot be expected to supply more than indications for the situation in solution.

Rotation about the C–N bond of substituted amido group

In this case, data were difficult to obtain due to the low solubility of salts in liquid SO_2, which was required instead of DMSO as solvent for the temperature range where this rotational barrier is observable. It can be found, however, that mono- and divalent ions interact in a similar way leading to a decrease of this barrier. Again, lithium ion shows a special behaviour, as it increases the rotation barrier.

The MO–SCF calculations of complex models indicate that there is no case which would lead to a decrease of this rotational barrier due to the complex formation with cations. Thus, the decrease of the barrier should be based on other effects. It could be possible that the anion effects have more influence on this barrier than on the $CO–NH_2$ barrier. The results of chemical shift investigations [12] with respect to the effect of chloride and iodide ions also confirm this assumption. It is also quite reasonable to assume that such anion–DMB interaction will affect the C–N bond character, too. Unfortunately, a comparison of different anions with identical cations could not be performed because of the low solubility of salts in liquid SO_2. Therefore no final interpretation of the metal ion effects on this barrier can be given at this time.

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