

Study of acid-base properties of *N,N'*-di(2-hydroxybenzyl)ethylenediamine-*N,N'*-diacetic acid and its chelates with lanthanides

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The *N,N'*-di(2-hydroxybenzyl)ethylenediamine-*N,N'*-diacetic acid (HBED) represents a polydonor ligand with phenolic functional group, which is suitable for chelation with M(III). The potentiometric measurements, UV spectrophotometry, and ¹H NMR spectroscopy were used for the study of acid-base properties. The study of complex formation with rare earth elements was performed by potentiometric method and paper electrophoresis. The stability constants of complexes of ML type, as well as the hydrogen complexes of MH₂L and MHL type at $I_c(\text{KNO}_3) = 0.1 \text{ mol dm}^{-3}$ and $T = 293.2 \text{ K}$ were evaluated from the neutralization curves.

N,N'-ди(2-гидроксibenзил)этилендиамин-*N,N'*-диуксусная кислота (HBED) представляет собой полидонорный лиганд с фенольной функциональной группой, подходящей для хелатообразования с M(III). Потенциометрические измерения, УФ-спектрофотометрия и ¹H ЯМР-спектроскопия были использованы для изучения кислотно-основных свойств. Исследование комплексообразования с редкоземельными элементами проводилось потенциометрически и с помощью электрофореза на бумаге. Константы устойчивости комплексов типа ML, а также водородсодержащих комплексов типов MH₂L и MHL при $I_c(\text{KNO}_3) = 0,1 \text{ моль дм}^{-3}$ и $T = 293,2 \text{ К}$ были определены из кривых нейтрализации.

The preparation and chelating properties of HBED were published by *Martell et al.* [1, 2]. They have determined the ionization constants by evaluation of the potentiometric and spectrophotometric measurements, and the stability constants of complexes with Mg(II), Zn(II), Ca(II), Ni(II), Cu(II), Cd(II), Pb(II), and Lu(III) by evaluation of the potentiometric neutralization curves. They paid the greatest attention to the study of very stable Fe(III) complexes. HBED forms very stable complexes with Ga(III) ion as well. These complexes together with other polydonor ligands were studied by *Harris and Martell* [3].

Experimental

HBED was prepared according to [1]. The pH measurements were performed on a PHM 26 (Radiometer) using a G202C glass electrode and saturated calomel electrode. The ionic strength of solutions ($I_c = 0.1 \text{ mol dm}^{-3}$) was adjusted by KNO_3 , temperature was maintained at 293.2 K, and solutions were saturated by purified gaseous nitrogen. The stock solutions of rare earths were made of their nitrates. The ionization constants K_{a1} and K_{a2} , as well as the basicity constants K_0 and K_{00} were evaluated from the neutralization curves of HBED obtained by titration with NaOH or HCl ($c = 0.1 \text{ mol dm}^{-3}$), respectively. The ionization constants K_{a3} and K_{a4} were obtained spectrophotometrically [4] by measuring the absorption curves of HBED solutions adjusted to various pH values. The overall ionic strength was adjusted by NaCl . The measurements were performed at concentration $c_L = 10^{-4} \text{ mol dm}^{-3}$ in the spectral range 256–333 nm using the UNICAM SP-700 spectrophotometer. With regard to the very close values of K_{a3} and K_{a4} the computation of their values was performed by multilinear regression.

The HBED—lanthanides chelate stability constants were evaluated from the neutralization curves of HBED solutions of concentration $c = 2 \times 10^{-3} \text{ mol dm}^{-3}$ containing the equimolar amounts of metal ions. The mathematical treatment was performed with the aid of programs based on the fundamental relationships for the computation of ionization constants and stability constants from the results of pH measurements [5]. The pH readout was recalculated to the concentration by subtracting 0.08.

^1H NMR spectra were measured on the NMR spectrometer Tesla BS 487 A operating at 80 MHz and 298 K. Probes of HBED for the NMR measurements were prepared by dissolving ligand in D_2O and adding KOD or DCl solutions. The concentration of HBED was $c = 5 \times 10^{-2} \text{ mol dm}^{-3}$. A deuterated *tert*-butyl alcohol (CH_3)₃CO_D (TBA) of $\varphi = 5 \text{ vol. \%}$ served as an internal standard. The pD values of solutions were determined from the pH readout according to the expression [6]

$$\text{pD} = \text{pH}_m + 0.40$$

The chemical shifts of the nonlabile proton signals are determined with an accuracy of $\pm 0.02 \text{ ppm}$ in the δ scale towards DSS ($\delta_{\text{TBA}} = 1.233 \text{ ppm}$).

The electrophoretic measurements were performed on an apparatus without electrode vessels using stock solutions containing the ligand in concentration $c = 2 \times 10^{-2} \text{ mol dm}^{-3}$, and chromatographic paper Whatman No. 2. The solution acidity of individual experiments was adjusted to the desired value of pH so as to differ approximately of a unit of pH from each other. The solutions of rare earth elements were sampled at concentration $c = 5 \times 10^{-2} \text{ mol dm}^{-3}$. The detection was performed by alcoholic solution of alizarine with subsequent drying in the vapours of ammonia. The experimental conditions, manner of the construction of mobility curves and their evaluation is described by Jokl [7, 8].

Results and discussion

Acid-base properties of HBED

After the isolation HBED was defined by the results of elemental analysis and potentiometric neutralization titration as $C_{20}H_{24}N_2O_6 \cdot HCl \cdot 2H_2O$, which differs from the formula in Ref. [1] describing HBED as the dihydrate dihydrochloride. Isolated monohydrochloride product (H_5L^+) successively splits off five protons (Fig. 1). Protons bound in the betaine structure on the lone electron pair of

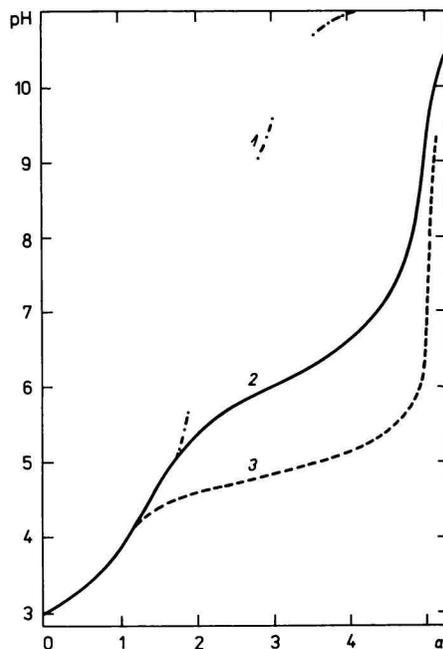


Fig. 1. Potentiometric neutralization curve of HBED·HCl alone and in the presence of La(III) and Lu(III).

1. $c_L = 1.5 \times 10^{-3} \text{ mol dm}^{-3}$; 2. $c_L : c_{La} = 1 : 1$;

3. $c_L : c_{Lu} = 1 : 1$.

$a = n(\text{NaOH})/n(\text{HBED} \cdot \text{HCl})$; $I_c(\text{KNO}_3) = 0.1 \text{ mol dm}^{-3}$.

nitrogen are ionized in the separated buffer areas. The ionization of phenolic hydroxyls takes place as far as in the strong alkaline area. The final values of ionization constants are listed in Table 1 and they are in good agreement with those reported by authors of [1]. Table 1 also contains the pK_0 and pK_{00} values representing the following equilibria

$$K_0 = \frac{[H_4L] \cdot [H^+]}{[H_5L^+]}$$

$$K_{00} = \frac{[H_3L^+] \cdot [H^+]}{[H_6L^{2+}]}$$

Table 1
Negative logarithms of ionization constants of HBED

pK	$I_c = 0.1 \text{ mol dm}^{-3}$ $T = 293.2 \text{ K}$	$I_c = 0.1 \text{ mol dm}^{-3}$ [1] $T = 298.2 \text{ K}$
pK_{00}	1.9	
pK_0	2.0	
pK_{a1}	4.64	4.64
pK_{a2}	8.32	8.32
pK_{a3}	11.19	11.00
pK_{a4}	12.41	12.46

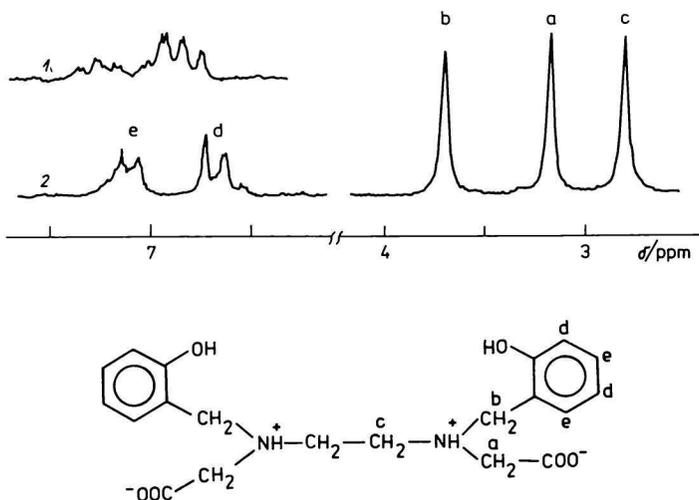


Fig. 2. ^1H NMR spectrum of the HBED solution in D_2O , $\text{pD} = 12.8$ (1).
Spectrum of the aromatic proton signals of HBED in solution at $\text{pD} = 10.4$ (2).
The labeling of nonlabile protons of HBED.

^1H NMR spectrum of HBED confirms its supposed structure (Fig. 2). The five signals of nonlabile protons with the same integral intensity are observed in the spectrum. Each signal belongs to the four protons and the molecule of HBED is symmetrical. In order to assign signals to the individual types of protons there were utilized the results obtained in the NMR study of *N*-(*o*-hydroxybenzyl)imino-diacetic acid (HBIDA) [9]. Spectra of HBED in D_2O solutions were measured in the range of $\text{pD} = 1.7$ – 13.8 . Acidifying the solution to $\text{pD} < 1.7$, HBED started to precipitate as hydrochloride. In the whole pD range measured the signals of protons of methylene groups were observed as singlets, those of aromatic protons

as two multiplets of the same intensity, with the exception at $pD = 9-12$ (Fig. 2). Fig. 3 shows the plot of chemical shifts of signals as dependence on pD .

This dependence and the values of ionization constants indicate that around $pD = 3$ the HBED is present as a H_4L form in the solution measured. In the spectra of solutions of lower pD the greatest changes of the chemical shift values are revealed by H^a protons. At these protons thus occurs the greatest decrease of electron density, which means that protons (better D^+ ions in D_2O solutions of deuterated acid) became bonded to the carboxylate groups of HBED. In the range of $pD = 4-6.5$ the upfield shift of all signals is observed, e.g. at all protons the electron density becomes higher. It is a consequence of the proton dissociation. The relative changes of chemical shifts in this region indicate that the proton dissociates from the nitrogen atom. The changes of chemical shifts of protons of methylene groups attached to nitrogen (H^a , H^b , H^c) are substantially greater than those of the protons of aromatic rings (H^d , H^e). In the range about $pD = 7$ the HBED in solution is present as a H_3L^- form. The unchanged number and shape of the HBED signals in this region indicates that the nondissociated proton from the nitrogen of

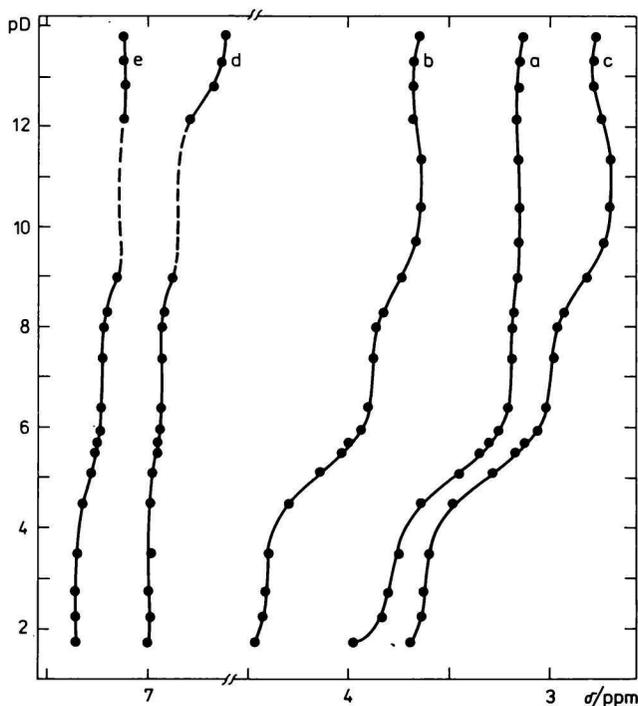


Fig. 3. Dependence of chemical shifts of nonlabile protons of HBED on pD of solution. $c = 5 \times 10^{-2} \text{ mol dm}^{-3}$; $T = 298.2 \text{ K}$.

amino group is either bound by both nitrogens or a rapid exchange of this proton between the nitrogens in question proceeds.

In the range up to $pD = 8$ there is observed such a course of the dependence of chemical shifts on pD as it was observed by authors who had firstly examined amines and amino acids in this way [10, 11]. As the functional group protons dissociate the electron density at nonlabile protons is increasing and therefore the signals are shifted upfield. In the range of $pD > 8$ certain "irregularities" in the dependence of chemical shifts on pD are observed (Fig. 3). We suppose that they are the consequence of magnetic anisotropy of aromatic rings of HBED. In the range of $8 < pD < 10$ the second proton dissociates from the nitrogen atom and on the δ dependence on pD a shift to lower δ values is observed. The shift of the signals of carboxymethyl group protons (H^a) is substantially smaller than those of the signals of protons of the other methylene groups also attached to the nitrogen atom. The changes of chemical shifts (Table 2) at the dissociation of two protons from nitrogens of HBED ($\Delta\delta_a = 0.64$ ppm, $\Delta\delta_b = 0.78$ ppm, and $\Delta\delta_c = 0.92$ ppm) are, however, approximately the same as in the case of other diaminetetracetic acids [10, 11]. For instance, the values in question for EDTA are $\Delta\delta_{a,b} = 0.75$ ppm and $\Delta\delta_c = 1.04$ ppm.

In the range of $9 < pD < 12$ the appearance of signals of the aromatic protons is changed from two signals of the same intensity through nonresolved and overlapped multiplets to the two signals with an intensity ratio 1 : 3 (Fig. 2,b). In this region the signals of H^c proton on each aromatic ring become overlapped by the H^d proton signals and so the chemical shifts of these protons could not be evaluated from the spectrum. At the values of $pD \sim 10$ the H_2L^{2-} form predominates in solution.

Further increase of pD of the HBED solutions causes successive dissociation of the phenolic group protons. As a consequence of this the $+M$ effect is increased and $-I$ effect is turned to $+I$ effect of phenolate group when compared with the phenolic one. The increase of electron density at the aromatic protons in *ortho* and

Table 2
Chemical shift values of nonlabile protons of HBED in various ionic forms
(for proton labeling see Fig. 2)

Ionic form	δ_a /ppm	δ_b /ppm	δ_c /ppm	δ_d /ppm	δ_e /ppm
H_4L					
$pD = 2.8$	3.79	4.41	3.61	7.00	7.36
H_3L^-					
$pD = 7.4$	3.18	3.93	2.97	6.92	7.21
H_2L^{2-}					
$pD = 10.4$	3.15	3.63	2.69	—	—
L^{4-}					
$pD = 13.8$	3.13	3.63	2.76	6.60	7.11

para position due to the effects mentioned above causes the changes of chemical shifts of H^d protons in alkaline region (Fig. 3). Similar changes of the chemical shifts of aromatic protons were also observed when the proton of phenolic group in HBIDA dissociates [9]. The change of chemical shifts of the methylene group protons at pD > 11.4 is, however, unexpected, because the dissociation of the phenolic group protons does not bring about higher shielding of the H^a, H^b, and H^c protons. Such "anomalous" changes of chemical shifts were observed for protons of ethylene groups of EDTA, ethylenediamine-*N,N'*-diacetic acid, and triethylenetetraaminehexaacetic acid, at pH < 4 when their carboxylate groups were protonated [12]. It was explained so that the —COOH group revealing remarkable magnetic anisotropy is getting closer to the protons of ethylene groups. The downfield shift of the HBED signals as seen in Fig. 3 for the H^b and H^c protons at 11.4 < pD < 12.8 is connected with the magnetic anisotropy of aromatic rings and it may be explained as follows: By comparing the p*K* values of HBED with those of similar compounds there might be supposed the existence of a hydrogen bond between the hydroxyl group and nitrogen of HBED in the H₂L²⁻ form [1]. The same type of hydrogen bond in the case of HBIDA was supposed according to its NMR study results [9]. Being in H₂L²⁻ form the HBED in solution probably possesses predominant conformation, in which the aromatic rings due to the repulsions are remarkably distant from each other. In the range 11.4 < pD < 12.8 the proton of phenolic group dissociates along with the formation of a HL³⁻ form, in which the rapid exchange of a proton between the two oxygen atoms proceeds. As a result of this there are observed averaged signals in the spectrum, e.g. a singlet for protons of two methylene groups as that for the other ionic forms of HBED. At the dissociation of proton from phenolic group a substantial change of the HBED conformation probably takes place. We suppose that the distance of aromatic rings is reduced, which allows the rapid proton exchange between two phenolic oxygens, as it was mentioned earlier. The H^b and H^c protons are thus placed to the environment with reduced shielding or higher deshielding effect of aromatic rings, which brings about the increase of chemical shifts (0.05 ppm and 0.1 ppm, respectively).

Stability constants of HBED complexes with lanthanides

According to the course of titration curves obtained for various ratios of the overall concentrations $c_M:c_L$ it was found that HBED forms with the ions of lanthanides only the complexes of the $n(\text{metal ion}):n(\text{ligand}) = 1:1$ ratio. This is also documented by the curves of the Bjerrum function $\bar{n} = f(p[L])$ for various concentrations c_M (Fig. 4). They have identical course, but they, however, do not follow the theoretical curve of this function indicating formation of the only binary complex ML. It means that in this case the more complicated equilibria are

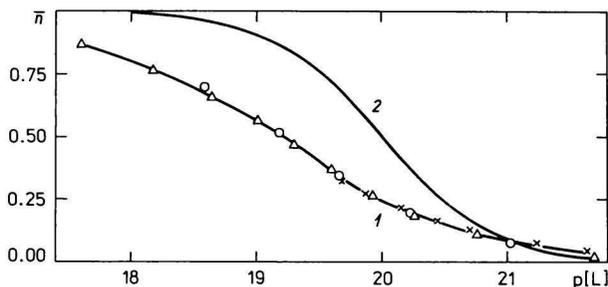


Fig. 4. $\bar{n} = f(p[L])$ for neutralization curves of systems containing HBED and Gd(III) at the various ratio of concentrations: $c_M:c_L = 1:1$ (Δ), $0.5:1$ (O), $2:1$ (x) (1).

The theoretical slope of the $\bar{n} = f(p[L])$ function for the formation of binary complex ML (2).

involved and the ML species formation proceeds through the successive formation of hydrogen complexes. Since also the H_3L^- anion is capable to form the complexes, one may expect the formation of hydrogen complexes of MH_3L^{2+} , MH_2L^+ , and MHL type. The formation of hydrogen complexes and ML complexes proceeds in a common buffer region (Fig. 1), and therefore for the computation of stability constants K_1 the protonated complexes must be included to the terms for the overall concentrations. The experimental data best fit the relationships [5], in which the formation of MH_2L^+ and MHL complexes is included. The hydrogen complexes formation constants K_{H1} and K_{H2} have been computed from the neutralization curves

$$K_{H1} = \frac{[MHL]}{[ML^-][H^+]}$$

$$K_{H2} = \frac{[MH_2L^+]}{[MHL][H^+]}$$

as the ionization constants of MH_2L and MHL species, respectively. The final values are listed in Table 3. The interval of reliability of given values is ± 0.04 for $\log K_1$ and ± 0.1 for $\log K_{H1}$ and K_{H2} , respectively.

The electrophoretic mobility curves of HBED complexes with individual lanthanides are of the same course and they reveal two clearly separated plateaus in the anodic region (Fig. 5). The first plateau at $pH = 5-7$ ($u = -0.30$) corresponds to the ML^- complexes, the second one in alkaline region may be assigned to the existence of hydroxo complexes $MOHL^{2-}$.

The 1H NMR study of the complex-forming properties of HBED with lanthanides was impossible to perform due to the low solubility of complexes formed.

According to the results of potentiometric measurements it may be stated that HBED forms stable complexes with lanthanides in which the agent acts as

Table 3
Stability constants of lanthanide complexes with HBED
 $I_c(\text{KNO}_3) = 0.1 \text{ mol dm}^{-3}$; $T = 293.2 \text{ K}$

M(III)	HBED		
	$\log \{K_1\}$	$\log \{K_{H1}\}$	$\log \{K_{H2}\}$
La	16.42	7.12	5.98
Ce	17.16	5.95	5.44
Pr	17.85	5.77	5.30
Nd	18.32	5.61	5.16
Sm	19.24	5.51	4.98
Eu	19.28	5.50	4.98
Gd	19.16	5.67	5.09
Tb	19.61	5.33	4.87
Dy	19.90	5.22	4.80
Ho	19.97	5.18	4.82
Er	20.15	5.06	4.71
Tm	20.31	5.02	4.65
Yb	20.50	4.95	4.49
Lu	20.70	4.86	4.43

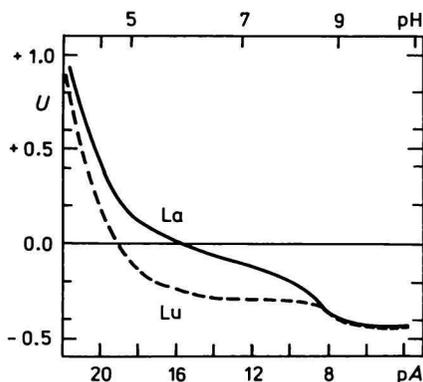


Fig. 5. Electrophoretic mobility curves of HBED complexes with La(III) and Lu(III). A = concentration of free ligand; U = relative electrophoretic mobility; $I_c(\text{KNO}_3) = 0.1 \text{ mol dm}^{-3}$; $T = 293.2 \text{ K}$.

a six-donor ligand after the proton dissociation of the carboxylic and phenolic groups even in the range of $\text{pH} = 4\text{--}7$. The dependence of $\log \{K_1\}$ on the proton number of lanthanides (Fig. 6) reveals the course as those of similar ligands. The scale of the La—Lu complex stability constants covers approximately four units of $\log \{K_1\}$ which is similar to that of EDTA. Though HBED and EDTA possess the same number of N and O donor atoms, the HBED differs from EDTA because it

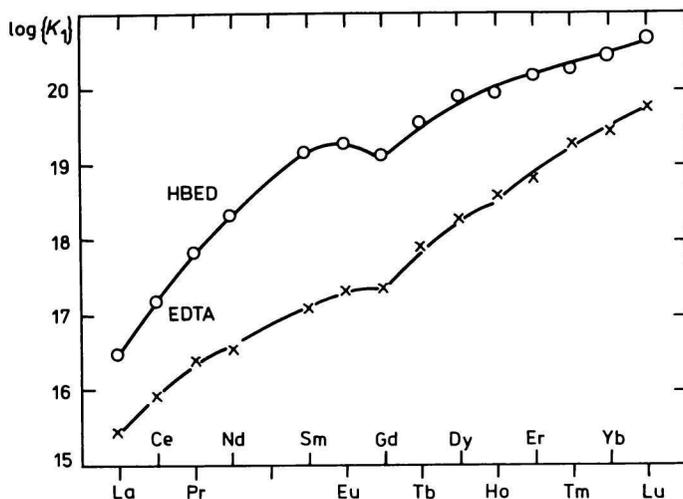


Fig. 6. Stability constants K_1 in dependence on the proton number of lanthanides.

reveals greater difference in the complex formation with light and heavier lanthanides expressed as a trend of the increase of complex stability constants with the decrease of the ionic radius of lanthanides.

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