554 BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 554—557 (1972) [Vol. 45, No. 2

Synthesis of Chelating Agents. VIII. Synthesis and Acid Dissociation of 3,3-Dimethylbutane-1,2-dinitrilo-*N*,*N*,*N'*,*N'*-tetraacetic Acid[1]

Yuzo Yanagihara,* Tairoku Yano, Hiroshi Kobayashi, and Keihei Ueno

Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Hakozaki, Fukuoka

(Received July 12, 1971)

3,3-Dimethylbutane-1,2-dinitrilo-*N*,*N*,*N'*,*N'*-tetraacetic acid (BEDTA) has been synthesized by the carboxymethylation of 3,3-dimethylbutane-1,2-diamine (BEDA). The stepwise acid dissociation constants determined by the potentiometric method were found to be $pK_{a1}=6.26$ and $pK_{a2}=9.78$ for BEDA and $pK_{a1}=2.1$, $pK_{a2}=3.62$, $pK_{a3}=5.29$, and $pK_{a4}=11.6$ for BEDTA at 25°C and an ionic strength of 0.1 (KCl). The values were discussed in relation to molecular structures.

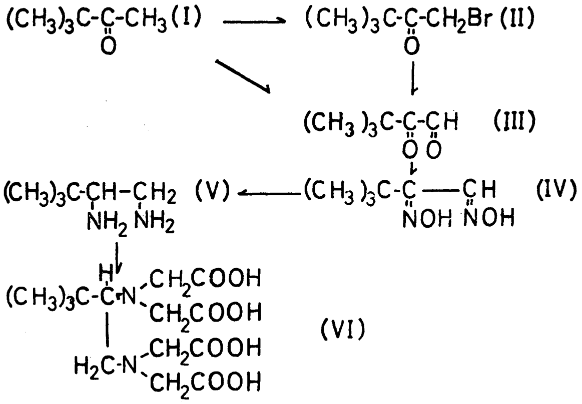
In previous papers we have reported on the effect of phenyl-substitution on either 1- or 2-carbons of ethylenedinitrilotetraacetic acid (EDTA) or both,[2] and on the effect of benzene ring fused to 4,5-positions of *trans*-cyclohexane-1,2-dinitrilo-*N*,*N*,*N'*,*N'*-tetraacetic acid (CyDTA), on the chelating behavior of these ligands.[3] The major factors governing the chelate stability constant were found to be the ease of taking a *skew* conformation with respect to two nitrilodiacetate groups, as well as the inductive effect which may increase the basicity of nitrogen atoms of the nitrilodiacetate groups.

Introduction of alkyl groups on the ethylene bridge of EDTA would cause a steric effect favorable for chelate formation and also an electron-releasing effect to increase the basicity of nitrogen. Relatively higher chelate stability constants of propane-1,2-dinitrilotetraacetic acid (MEDTA)[4] and butane-2,3-dinitrilotetraacetic acid (BDTA)[5] can thus be understood.

From the results we were interested in the synthesis of EDTA derivatives, in which *t*-butyl groups were introduced on either 1- or 2-carbons of ethylene bridge in EDTA or both. Such bulky groups might cause a highly steric effect in favor of metal chelate formation.

This paper reports on the synthesis and acid dissociation behaviors of 3,3-dimethylbutane-1,2-diamine (BEDA) as well as 3,3-dimethylbutane-1,2-dinitrilotetraacetic acid (BEDTA).

3,3-Dimethylbutane-1,2-diamine (V), which was obtained as dihydrochloride, was synthesized from pinacolone (I) through *t*-butylglyoxal (III) and *t*-butylglyoxal dioxime (IV). 3,3-Dimethylbutane-1,2-dinitrilotetraacetic acid (VI) was synthesized by the carboxymethylation of the diamine (V). The acid dissociation behaviors of diamine (V) and tetraacetic acid (VI) were investigated by the potentiometric method, and the results were discussed in relation to their molecular structures.



Scheme

Experimental

IR spectra were measured with JASCO DS-301 and DS-403G spectrophotometers. NMR spectra were recorded on a Varian A-60 instrument using acetonitrile as an internal standard, its signal being set at 120 Hz downfield from TMS.

Synthesis of the Ligands. *t-Butylglyoxal (III)* was synthesized by two independent procedures.

(A) Oxidation of pinacolone with selenium dioxide.[6] *t*-Butylglyoxal was obtained in 47% yield according to the procedure in literature, bp 52—71°C/100 mmHg (lit, bp 114—115°C).

(B) Oxidation of bromopinacolone with dimethylsulfoxide. A solution of 78 g of bromopinacolone obtained by the bromination of pinacolone[7] in 400 m*l* of dimethylsulfoxide, was heated at 80—90°C for 3 hr and the reaction mixture was poured into 1 *l* of water. The aqueous solution was extracted with 200 m*l* ether several times. The combined ether extracts were washed with water, then dried over magnesium sulfate. After the solvent evaporated off, the residue was distilled under reduced pressure to give a fraction boiling at 45—50°C/55 mmHg. Yield was 9.3 g (29% from bromopinacolone). The purity of glyoxal (III) was a decisive factor on the yield of glyoxal dioxime (IV). The sample subjected to prolonged standing after the syntheses became inactive for oxime formation because of the hydration of glyoxal by atmospheric moisture. Furthermore, the dioxime from impure glyoxal crystallized with difficulty, resulting in a poor yield. Although procedure (A) gave better yield, procedure (B) was preferred because of a purer

---

[1] Contribution No. 248 from the Department of Organic Synthesis, Kyushu University. Part VII: T. Yano, H. Kobayashi, and K. Ueno, This Bulletin, **43**, 3167 (1970).

* Present Address: Research Laboratories, Kawasaki Plant, Asahi Kasei Co., Ltd., Kawasaki, Kanagawa 210.

[2] N. Okaku, Y. Toyota, Y. Moriguchi, and K. Ueno, This Bulletin, **40**, 2326 (1967).

[3] T. Yano, H. Kobayashi, and K. Ueno, *ibid.*, **43**, 3167 (1970).

[4] J. H. Grimes, A. J. Huggard, and S. P. Wilford, *J. Inorg. Nucl. Chem.*, **25**, 1225 (1963).

[5] H. M. N. H. Irving and K. Sharpe, *ibid.*, **33**, 203 (1971).

[6] R. C. Fuson, H. Gray, and J. J. Gouza, *J. Amer. Chem. Soc.*, **61**, 1937 (1939).

[7] J. H. Boyer and D. Strau, *ibid.*, **74**, 4506 (1952).

product.

t-Butylglyoxal Dioxime (IV). To a solution of 12.6 g (0.18 mol) of hydroxylamine hydrochloride in 30 m*l* of water was added, successively a solution of 2 g (0.0175 mol) of freshly prepared glyoxal (III) in 10 m*l* of ethanol and a solution of 10.1 g of potassium hydroxide in 10 m*l* of water. The mixture was kept standing at room temperature for a few days. An oily layer separated and solidified gradually to afford a pasty mass, from which a solid product was collected by filtration under suction and was recrysrallized from ethanol-water, mp 101—102°C (lit, mp 101—102°C).[5] Yield was 1.3 g (51% of the theoretical). IR: ν_{OH}, 3200—3300 cm^{-1}, ν_{NO}, 950 cm^{-1}.

Found: C, 49.99; H, 8.44; N, 19.23%. Calcd for $C_6H_{12}O_2N_2$: C, 49.99; H, 8.39; N, 19.43%.

3,3-Dimethylbutane-1,2-diamine Dihydrochloride (V). Of the reduction methods including sodium in ethanol, aluminum lithium hydride, hydrogenation with Raney nickel or platinum oxide, tin-hydrochloric acid and zinc-acetic acid, the first one gave the best result in the preparation of diamine(V) from dioxime(IV).

Metallic sodium (5.8 g) was added portionwise from the top of a condenser to a refluxing solution of 3.3 g of dioxime (IV) in 60 m*l* of ethanol. After the added sodium metal was consumed, 60 m*l* of water was added to the solution, and ethanol was distilled off through a fractionating column. The residue which separated into two layers was extracted with ether, and the ethereal layer was washed with a small amount of water and dried over anhydrous potassium carbonate. To the dried ether solution, dry hydrogen chloride gas was passed to precipitate the diamine dihydrochloride, which was then recrystallized from ethanol. Mp above 270°C. Yield: 1.8 g (42%). IR: $\nu_{NH_3^+}$ 2400—3300 cm^{-1}. NMR (τ in D_2O): 8.99(9H), 6.60—6.80(3H).

Found: C, 37.98; H, 9.49; N, 14.89; Cl, 37.57%. Calcd for $C_6H_{18}N_2Cl_2$: C, 38.10; H, 9.54; N, 14.81; Cl, 37.96%.

3,3-Dimethylbutane-1,2-dinitrilotetraacetic Acid (VI). A solution of 1.0 g (0.048 mol) of diamine dihydrochloride(V) in 3 m*l* of water, was neutralized with a calculated amount of 7 N sodium hydroxide solution. To this solution were added a solution of 3.7 g (0.267 mol) of bromoacetic acid in 5 m*l* of water, which had been neutralized to phenolphthalein with 7 N sodium hydroxide below 10°C, and 30 m*l* (0.21 mol) of 7 N sodium hydroxide solution. The mixture was heated at 100°C for 10 hours under carbon dioxide free atmosphere. The resulting solution was acidified with 6 N hydrochloric acid so that its pH was 1.8—2.0, and was kept in a refrigerator overnight to precipitate the crude tetraacetic acid. The white precipitates were collected by filtration and recrystallized from water. Mp 225°C (decomp.).

Yield: 0.42 g (23%). IR: ν_{COOH} 1763, 1730 cm^{-1}.

Found: C, 47.64; H, 6.60; N, 7.66%. Calcd for $C_{14}H_{21}N_2O_8$: C, 48.27; H, 6.94; N, 8.04%.

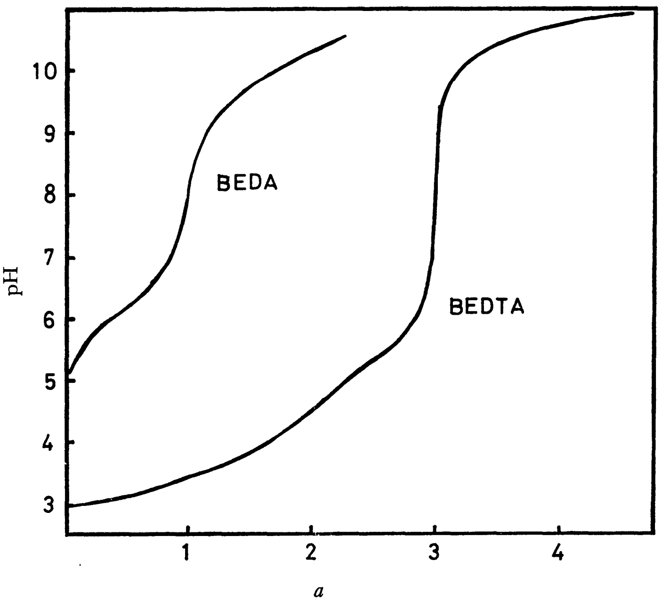


Fig. 1. The pH titration curves of BEDA and BEDTA at 25°C in 0.1 M KCl.

Determination of Acid Dissociation Constants. The same apparatus as that described previously was employed.[8] Measurements were carried out at 25.0±0.1°C in an aqueous solution under ionic strength, μ=0.10, with potassium chloride. For the determination of acid dissociation constants, 100 m*l* of 2×10^{-3} M of diamine(V) or of 1×10^{-3} M of tetraacetic acid (VI) was titrated with a solution of 0.1 N potassium hydroxide freed from carbonate ion.

Calculation

The titration curves of BEDA dihydrochloride (V) and BEDTA (VI) are shown in Fig. 1. As the titration curve of BEDA dihydrochloride represents a typical curve of dibasic acid, it can be treated by the standard procedure of Schwarzenbach.[9] The final equations for the procedure are:

$$g + (g-1)[\mathrm{H}^+]/K_{a2} + (g-2)[\mathrm{H}^+]^2/K_{a1}K_{a2} = 0 \quad (1)$$

$$g = (2-a) + \{[\mathrm{OH}^-]-[\mathrm{H}^+]\}/C_A \quad (2)$$

where a represents the number of moles of alkali added per mole of the ligand, C_A the total ligand concentration, and K_{a1} and K_{a2} the first and second acid dissociation constants, respectively. In the neighbourhood of a=0.5, equation (1) can be simplified as

$$(g-1) + (g-2)[\mathrm{H}^+]/K_{a1} = 0 \quad (3)$$

and in the neighbourhood of a=1.5 as

$$g + (g-1)[\mathrm{H}^+]/K_{a2} = 0 \quad (4)$$

Thus, by computing each five sets of experimental values near a=0.5 and a=1.5 into Eqs. (3) and (4), the values of K_{a1} and K_{a2} were obtained, respectively.

As regards BEDTA (VI), the dissociation of the first three steps are clearly separated from the fourth step, as is shown in Fig. 1. Thus, the calculation of the acid dissociation constants can be carried out by the standard procedure of Bjerrum modified by McIntyre. The procedure is essentially the same as described previously.[3] The results of calculations on diamine (V) and tetraacetic acid (VI) are summarized in Tables 1 and 2, respectively, along with the values of related compounds.

Results and Discussion

Acid dissociation constants of diamines. As shown in Table 1, the characteristic of BEDA is its relatively low pK_{a1} value compared with those of other ethylenediamines. We see that the pK_{a1} value of the ethylene-

---

[8] T. Ando, This Bulletin, **36**, 1593 (1963)

[9] G. Schwarzenbach, A. Willi, and R. O. Bach, *Helv. Chim. Acta*, **30**, 1303 (1947)

TABLE 1. ACID DISSOCIATION CONSTANTS OF 1,2-DIAMINES

Diamine	pK_{a1}	pK_{a2}	ΔpK_a
BEDA[a]	6.26±0.01	9.78±0.01	3.52
trans-Cyclohexane-1,2-diamine[b, 10]	6.72	9.89	3.17
cis-Cyclohexane-1,2-diamine[b, 10]	6.41	9.99	3.58
Ethylenediamine[b, 10]	7.48	10.18	2.70
Propane-1,2-diamine[c, 11]	7.13	10.00	2.87
dl-Butane-2,3-diamine[c, 11]	6.91	10.00	3.09
meso-Butane-2,3-diamine[c, 11]	6.92	9.97	3.05
2,3-Dimethylbutane-2,3-diamine[c, 11]	6.56	10.13	3.57

a) measured at 25.0±0.1°C and μ=0.10 (KCl)
b) measured at 20°C and μ=0.1 (KCl)
c) measured at 25°C and μ=0.5 (KNO_3)

TABLE 2. ACID DISSOCIATION CONSTANTS OF BEDTA AND RELATED COMPLEXANES MEASURED AT 25.0±0.1°C AND μ=0.10 (KCl)

Complexane	pK_{a1}	pK_{a2}	Δp$K_{a(2-1)}$	pK_{a3}	pK_{a4}
EDTA	2.1±0.1	3.62±0.04	1.5	5.29±0.03	11.6±0.3
EDTA[12]	1.99	2.67	0.68	6.16	10.23
MEDTA[a, 4]	2.60	3.03	0.43	6.20	10.84
PEDTA[b, 2]	1.87	3.21	1.34	5.42	9.60

a) Propane-1,2-dinitrilo-*N,N,N',N'*-tetraacetic acid measured at 30°C.
b) 1-Phenylethylenedinitrilo-*N,N,N',N'*-tetraacetic acid measured at 20°C.

diamine homologue decreases with the increasing number of methyl groups introduced on ethylene carbons, and that pK_{a1} values of cyclohexanediamines are also relatively low.

The first dissociation step of 1,2-diammonium ion might be affected by the extent of electrostatic repulsion between the two ammonium groups as well as by the stereochemical ease of hydrogen-bond formation of the amine nitrogen resulting from the first deprotonation of an ammonium group with vicinal ammonium hydrogen. The effects can be evaluated by comparing pK_{a1} values or ΔpK_a (=pK_{a2}−pK_{a1}) values, since the pK_{a2} values of these diamines do not differ greatly.

In a bisprotonated stage of 1,2-diamines, in which the rotation of amino groups around the ethylene linkage is not restricted, the stable conformation will be a *trans* form with respect to the amino groups, relieving electrostatic repulsion between the vicinal ammonium groups. Ethylenediamine and *C*-methylated ethylenediamines can take this conformation. Thus, two ammonium groups of such diamines are so remote that less electrostatic repulsion operates between the ammonium groups, and dielectric interaction between the ammonium groups and polar solvent molecules favorably stabilize the highly polarized ammonium groups against the first deprotonation process. Thus the relatively higher pK_{a1} values or relatively smaller ΔpK_a values of ethylenediamine and propane-1,2-diamine can be explained. However, another effect might operate on highly methylated ethylenediamines, where the ammonium groups are embedded in nonpolar hydrocarbon moiety and the polar solvent molecules are restricted to gain access to the ammonium group. This effect would become more significant with the increasing number of methyl groups introduced on ethylene linkage.

In order to explain the significant difference between ΔpK_a values of *cis*- and *trans*-cyclohexane-1,2-diamines, Schwarzenbach[10] proposed the dielectric effect by polar solvent molecules which shielded electrostatic repulsion between the vicinal ammonium groups.

In highly methylated ethylenediamines the dielectric shielding of the ammonium groups by polar solvent molecules is less effective than in ethylenediamine, where the polar solvent molecules are easily accessible to ammonium groups. The effect is responsible for the relatively lower pK_{a1} values of highly methylated ethylenediamines, in spite of the fact that the distance between the two ammonium groups does not differ in both types of ethylenediamines.

In the case of BEDA, two ammonium groups can not take *trans* conformation due to the steric hindrance between *t*-butyl and ammonium groups, but take a stable *skew* conformation with respect to ammonium groups. Thus, the distance between two ammonium groups is comparable to those of cyclohexane-1,2-diamines. At the same time, since one of the ammonium groups is located in the close neighborhood of *t*-butyl group, the polar solvent molecules are less easily accessible. The electrostatic repulsion between two ammonium groups is, therefore, less effectively shielded in BEDA. Simultaneous operation of the conformational and dielectric shielding effects might

---

10) G. Schwarzenbach and R. Bauer, *Helv. Chim. Acta*, **39**, 722 (1956)

11) F. Basolo, R. K. Murmann, and Y. T. Chen, *J. Amer. Chem. Soc.*, **75**, 1478 (1953)

12) G. Schwarzenbach and G. Anderegg, *Helv. Chim. Acta*, **40**, 1773 (1957)

be responsible for the lower pK_{a1} value and higher ΔpK_a value of BEDA.

It is interesting to note in this connection that pK_{a2} of diamines do not differ greatly. Although the pK_{a2} value is expected to reflect the basicity of nitrogen atom, introduction of alkyl groups on nitrogen or adjacent carbon does not cause any appreciable increase of the value. The result might indicate that the inductive effect of alkyl groups plays a minor role in determining the pK_{a2} values of 1,2-diamines.

Dissociation Constants of BEDTA. In the acid dissociation of EDTA and related tetrabasic complexane-type ligands, deprotonation of the first two and last two steps correspond to the dissociation of carboxylic protons and ammonium protons, respectively. The pK_a values of BEDTA and some related ligands are shown in Table 2.

In previous papers,[2,3] we classified the complexane-type ligands into two groups. The first are those in which the rotation of nitrilodiacetate group is not hindered sterically and two nitrilodiacetates prefer a *trans* conformation due to electrostatic repulsion. This type is characterized by a relatively low Δp$K_{a(2-1)}$ value. The second are those in which two nitriloacetate groups sterically favor a *skew* conformation, and this group is characterized by a relatively high Δp$K_{a(2-1)}$ value.

The Δp$K_{a(2-1)}$ value for BEDTA clearly suggests that this ligand prefers a *skew* conformation with regard to the nitrilodiacetate groups. This can be ascribed to the steric effect by *t*-butyl group, and is in line with the preceeding discussion on BEDA.

The values of pK_{a3} and pK_{a4} are related to the deprotonations of ammonium nitrogens. Thus, a relatively lower value of pK_{a3} can be understood from the low pK_{a1} value of BEDA.

As regards the pK_{a4}, the potentiometric titration of 10^{-3} M solution of the ligand at high pH region might include a considerable error. Thus, the observed pK_{a4} value might not be accurate enough for quantitative discussion, however, pK_{a4} value of BEDTA is obviously higher than the other, the order of magnitude being comparable to that of *trans*-CyDTA (pK_{a4}=12.35).[13]

As discussed previously on the pK_{a2} values of methylated ethylenediamines, the introduction of alkyl groups on nitrogen or adjacent carbon does not appreciably contribute to increase of the basicity of nitrogen. The unusually high pK_{a4} value of BEDTA or *trans*-CyDTA might thus be related to some kind of steric and electrostatic effects of deprotonated species.

The authors are grateful to the Ministry of Education for financial support in this work.

---

[13] G. Anderegg, *Helv. Chim. Acta*, **46**, 1833 (1963)