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π-π Stacking assisted binding of aromatic amino acids by copper(II)–aromatic diimine complexes. Effects of ring substituents on ternary complex stability

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This paper is dedicated to Professor Dr. Bernhard Lippert of University of Dortmund on the occasion of his 60th birthday, with the very best wishes for his health and future activities.

Ternary Cu(II) complexes containing an aromatic diimine (DA = di(2-pyridylmethyl)amine (dpa), 4,4'-disubstituted 2,2'-bipyridine (Y_2bpy; Y = H (bpy), Me, Cl, $N(Et)_2$, $CONH_2$, or COOEt), or 2,2'-bipyrimidine) and an aromatic amino acid (AA = *p*-substituted L-phenylalanine (Xphe; X = H (phe), NH_2, NO_2, F, Cl, or Br), L-tyrosine, L-tryptophan (trp), or L-alanine) were studied by X-ray diffraction, spectroscopic, and potentiometric measurements. The structures of $[Cu(dpa)(trp)]ClO_4 \cdot 2H_2O$ and $[Cu((CONH_2)_2bpy)(phe)]ClO_4 \cdot H_2O$ in the solid state were revealed to have intramolecular π-π interactions between the Cu(II)-coordinated aromatic ring moiety, Cu(DA) (Mπ), and the side chain aromatic ring of AA (Lπ). The intensities of Mπ–Lπ interactions were evaluated by the stability constants of the ternary Cu(II) complexes determined by pH titrations at 25 °C and I = 0.1 M (KNO_3), which revealed that the stability enhancement of the Cu(DA)(AA) systems due to the interactions is in the order $(CONH_2)_2$bpy < bpy < Me_2bpy < $(Et_2N)_2$bpy with respect to DA. The results indicate that the π-electron density of coordinated aromatic diimines influences the intensities of the stacking interactions in the Cu(DA)(AA) systems. The Mπ–Lπ interactions are also influenced by the substituents, X, of Lπ and are in linear relationship with their Hammett σ_p values with the exception of X = Cl and Br.

Keywords: Copper(II) complexes; π-π stacking; Stability constants; Substituted bipyridines; Aromatic amino acids

Introduction

Noncovalent or weak interactions involving aromatic rings attract much attention for their importance in molecular recognition, stabilization of protein structures, and supramolecular architecture in chemistry and biology.[1-4] Studies on benzene and porphyrin dimers showed that the edge-to-face and offset face-to-face interactions between the aromatic molecules are more effective than the face-to-face interactions,[5,6] and a survey of protein structures revealed that the former type of interactions are most common for phenylalanine residues.[3] Cozzi and Siegel reported that the intensities of face-to-face interactions are influenced by ring substituents; electron-withdrawing groups strengthen the interactions while electron-donating groups weaken them.[7] On the other hand, cation-π interactions have been revealed for various systems including proteins, where the cationic groups of amino acid side chains such as guanidinium and ammonium groups were found to be located close to the aromatic rings of aromatic amino acid residues.[8] Both gas-phase experiments and theoretical calculations indicated that alkali metal ions bind strongly to aromatic rings in the gas phase.[8,9]

Metalation of porphyrin is known to enhance the π-π interaction between two porphyrin molecules due to intramolecular polarization of the metal ion and the porphyrin.[5,10] We have been studying aromatic ring stacking interactions in ternary Cu(II) and Pd(II) complexes, [M(DA)(AA)] (M = Cu(II) or Pd(II); DA = aromatic diimines such as 1,10-phenanthroline (phen); AA = aromatic amino acids such as L-tyrosine (tyr)); we found that metal-coordinated DA effectively stacks with the side chain aromatic ring of coordinated AA[11] and that the ring substituent in the interacting ring of AA has influence on the stacking.[11,12] While 2N1O-donor tripod-like ligands containing one pyridine and one phenol ring and a pendent indole ring were found to undergo only weak intramolecular indole-pyridine interactions in CH_3CN, their Pd(II) complexes exhibited much stronger interactions as evidenced by the ^1H NMR upfield shifts due to the ring current effect and the methylene proton signals showing a fixed side chain conformation.[13] The adduct formation between planar Pt(II) complexes, Pt(DA)(L') (L' =

ethylenediamine or amino acids), and mononucleotides was revealed to be enthalpically driven mainly through stacking interactions by the relevant thermodynamic parameters[14] and decrease the electron density of the Pt(II) center as seen from and the downfield shift of the ^{195}Pt NMR signal.[15] The adduct stability sequence due to DA, 3,4,7,8-tetramethyl-1,10-phenanthroline > 1,10-phenanthroline ≈ 5-nitro-1,10-phenanthroline, reflected the effects of the DA substituents on stacking. In this connection, Kohzuma et al. reported that the Cu center of the plastocyanin from a fern *Dryopteris crassirhzoma* has a phenylalanyl residue stacked with a coordinated histidine (His90) and, probably as a result of this, exhibits a higher redox potential than that of higher plant plastocyanins.[16]

These observations suggested that factors, such as the substituents on DA and AA and the electron density difference between them, may affect the interactions involving aromatic rings. In order to obtain further information on the stabilization and reactivity of metal complexes due to aromatic rings, we now carried out synthetic, spectroscopic, X-ray crystallographic, and potentiometric studies on the ternary Cu(II) complexes containing DA with various substituents and aromatic amino acids AA.

Experimental

Materials

Di(2-pyridyl)amine (dpa) and 2,2'-bipyrimidine (bpm) were purchased from Tokyo Kasei and Lancaster, respectively. The reagents used for preparation of the derivatives of 2,2'-bipyridine (bpy) were purchased from Nacalai Tesque, Tokyo Kasei, and Kanto Chemicals. L-Tryptophan (trp), tyr, L-phenylalanine (phe), and *p*-substituted derivatives of phe (Xphe: L-nitrophenylalanine, NO_2phe; L-aminophenylalanine, NH_2phe; DL-fluorophenylalanine, Fphe; DL-chlorophenylalanine, Clphe; DL-bromophenylalanine, Brphe) were obtained from Nacalai Tesque.

Preparation of ligands

4,4'-Dimethyl-2,2'-bipyridine (Me_2bpy), 4,4'-bis(diethylamino)-2,2'-bipyridine ($(NEt_2)_2bpy$), diethyl 2,2'-bipyridine-4,4'-dicarboxylate ($(COOEt)_2bpy$), 4,4'-dichloro-2,2'-bipyridine (Cl_2bpy), 4,4'-dicarbamoyl-2,2'-bipyridine ($(CONH_2)_2bpy$) were prepared according to the literature.[17]

Synthesis of Cu(II) complexes

Cu(dpa)Cl_2.[18] $CuCl_2$ (0.13 g, 1.0 mmol) in methanol (10 ml) and dpa (0.17 g, 1.0 mmol) in methanol (10 ml) were mixed, and the mixture was kept standing overnight. Green crystals which separated were collected and dried. Yield, 0.24 g (79 %). *Anal.* Found: C, 39.45; H, 2.99; N, 13.73. Calc. for $C_{10}H_9N_3Cl_2Cu$: C, 39.29; H, 2.97; N, 13.74%.

Cu(bpm)$(NO_3)_2$•H_2O.[19] bpm (0.16 g, 1.0 mmol) dissolved in methanol (10 ml) was added to $Cu(NO_3)_2$•$3H_2O$ (0.24 g, 1.0 mmol) in H_2O (10 ml). The resulting solution was concentrated under deduced pressure and kept overnight. Light-blue crystals which separated from the solution were collected and dried in the air. Yield, 0.30 g (87 %). *Anal.* Found: C, 26.33; H, 2.15; N, 23.06. Calcd. for $C_8H_8N_6O_7Cu$: C, 26.42; H, 2.22; N, 23.11%.

$Cu(Me_2bpy)(NO_3)_2$, $Cu((NEt_2)_2bpy)(NO_3)_2$, $Cu((COOEt)_2bpy)(NO_3)_2$•H_2O, and $Cu(Cl_2bpy)(NO_3)_2$ were prepared in a similar manner.

Cu(Me_2bpy)$(NO_3)_2$. Blue crystals. Yield, 0.29 g (78 %). *Anal*. Found: C, 38.75; H, 2.84; N, 14.90. Calcd. for $C_{12}H_{12}N_4O_6Cu$: C, 38.77; H, 3.25; N, 15.07%.

Cu($(NEt_2)_2$bpy)$(NO_3)_2$. Greenish-blue crystals. Yield, 0.35 g (72 %). *Anal.* Found: C, 44.39; H, 5.52; N, 17.35. Calcd. for $C_{18}H_{26}N_6O_6Cu$: C, 44.49; H, 5.39; N, 17.29%.

Cu((COOEt)$_2$bpy)(NO$_3$)$_2$•H$_2$O. Light-blue crystals. Yield, 0.39 g (77 %). *Anal.* Found: C, 38.10; H, 3.47; N, 11.12. Calcd. for $C_{16}H_{18}N_4O_{11}Cu$: C, 37.99; H, 3.59; N, 11.08%.

Cu(Cl$_2$bpy)(NO$_3$)$_2$. Blue crystals. Yield, 0.33 g (80 %). *Anal.* Found: C, 29.03; H, 2.05; N, 13.48. Calcd. for $C_{10}H_8N_4O_6Cl_2Cu$: C, 28.97; H, 1.94; N, 13.51%.

[Cu(dpa)(trp)]ClO$_4$•2H$_2$O (1). $Cu(ClO_4)_2 \cdot 6H_2O$ (0.37 g, 1 mmol) and dpa (0.17 g, 1.0 mmol) dissolved in methanol (20 ml) were mixed with trp (0.20 g, 1.0 mmol) dissolved in 1 M aq KOH (1 ml). The resulting solution was concentrated under deduced pressure and kept standing for a few days. Green crystals which separated were collected and dried. Yield: 0.18 g (31 %). *Anal.* Found: C, 44.29; H, 3.96; N, 11.84. Calcd. for $C_{21}H_{24}N_5O_8ClCu$: C, 43.99; H, 4.22; N, 12.20%.

[Cu((CONH$_2$)$_2$bpy)(phe)]ClO$_4$•H$_2$O (2). This complex was prepared in a manner similar to the above as blue crystals. Yield: 0.11g (19 %). *Anal.* Found: C, 42.88; H, 3.50; N, 11.85. Calcd. for $C_{21}H_{22}N_5O_9ClCu$: C, 42.94; H, 3.77; N, 11.92%.

Spectral measurements

Absorption spectra were measured at room temperature with a Shimadzu UV-3101PC recording spectrophotometer. All the samples were prepared as 1 mM aqueous solutions by dissolving binary Cu(DA) complexes and AA, and pH values were adjusted to 6-8 by aq NaOH.

X-ray structure determinations

The X-ray experiment for complex **2** was carried out on a Rigaku AFC–5R four-circle automated diffractometer with graphite monochromated Cu Kα radiation (λ = 1.54178 Å) and a rotating

anode generator. The crystal was mounted on a glass fiber. The cell constants were obtained by least-squares refinement using 25 carefully centered reflections with appropriate intensities. The data were collected by the ω-2θ scan method. Reflection intensities were monitored by three standard reflections at every 150 measurements, and the decays of the intensities for all the crystals were within 2 %. Refraction data were corrected for both Lorentz and polarization effects, and empirical absorption corrections were applied by using the DIFABS program.[20]

The experiments for complexes **1** was carried out on a Rigaku Mercury CCD system with graphite monochromated Mo Kα radiation (λ = 0.71070 Å). The crystal was mounted on a glass fiber. For determination of the cell constant and orientation matrix, 6 oscillation photographs were taken for each frame with the oscillation angle of 0.5 ˚ and the exposure time of 10 sec. Intensity data were collected by taking oscillation photographs, and the refraction data were corrected for Lorentz and polarization effects.

Crystal data and experimental details of the data collection for all the complexes analyzed are summarized in Table 1. The structures were solved by the direct method and expanded by Fourier techniques using the DIRDIF-99 program.[21] The non-hydrogen atoms were refined anisotropically by full-matrix least-squares calculations. Atomic scattering factors and anomalous dispersion terms were taken from the literature.[22] Hydrogen atoms for all the structures were located at the calculated positions with d(C–H) = 0.95 Å and were not refined. All the calculations were performed by using TEXSAN program package.[23]

CCDC reference numbers 611926 and 611927.

See http://www.rsc.org/suppdata/dt/xxxx for crystallographic data in CIF or other electronic format.

pH titrations

pH titrations were carried out at 25±0.05 ˚C and I = 0.1 M (KNO_3) under a nitrogen atmosphere according to the procedure reported earlier.[24] pH values were measured with a Fisher-Scientific

Accumet model 15 pH meter equipped with a Beckman 39321 glass electrode and a Beckman 39419 double junction reference electrode. The NIST standard buffers (4.008, 7.413, 9.180 at 25 ˚C) were used for calibration of the pH meter. For determination of the acid dissociation constants of dpa, Me_2bpy, and $(NEt_2)_2$bpy, their solutions (ca. 1.25 mM) containing an excessive amount of HNO_3 were titrated with standard 0.1 M KOH. Titrations of the binary Cu(II)–dpa, Cu(II)–Me_2bpy, and Cu(II)–$(NEt_2)_2$bpy systems were carried out in a similar manner for solutions with the Cu(II):ligand ratios of 1:1 and 1:2 and the Cu(II) concentration of 0.2–1.5 mM. Due to precipitation occurring in the 1:1 Cu(II)–$(NEt_2)_2$bpy system at high pH, only the data taken at low pH were used for calculations. Titrations of the ternary systems with DA = dpa, Me_2bpy, or $(NEt_2)_2$bpy were performed for solutions of 1:1:1 Cu(II)–DA–AA with the Cu(II) concentration of 0.2–1.5 mM. All the systems were titrated 3–8 times for reproducibility. The stability constants β_{pqrs} defined by eqn. (1) (charges are omitted for clarity) were calculated from the titration data by the least-squares treatment using SUPERQUAD:[25]

$$\mathrm{pCu + qDA + rAA + sH} \overset{\beta_{pqrs}}{\rightleftharpoons} \mathrm{Cu_p(DA)_q(AA)_rH_s}$$

$$\beta_{pqrs} = \frac{[\mathrm{Cu_p(DA)_q(AA)_r H_s}]}{[\mathrm{Cu}]^p[\mathrm{DA}]^q[\mathrm{AA}]^r[\mathrm{H}]^s} \quad (1)$$

where DA, AA, and H refer to free DA, free AA, and proton, respectively. Conversion of pH meter readings to hydrogen ion concentrations was made by the conversion factor $f = 10^{-pH}/[H^+] = 0.855$, and $pK_w' = 13.96$.[26] For systems involving bpm, $(COOEt)_2$bpy, and Cl_2bpy, the stability constants, K_{qrs}, defined by eqn. 2 were calculated on the assumption that Cu(II)–DA does not dissociate in the pH range considered:

$$\mathrm{pCu(DA) + rAA + sH} \overset{K_{prs}}{\rightleftharpoons} \mathrm{\{Cu(DA)\}_p(AA)_rH_s}$$

$$K_{prs} = \frac{[\mathrm{\{Cu(DA)\}_p(AA)_r H_s}]}{[\mathrm{Cu(DA)}]^p[\mathrm{AA}]^r[\mathrm{H}]^s} \quad (2)$$

Results and discussion

Absorption spectra of ternary systems in the near UV region

Absorption spectra of Cu–Me_2bpy–AA in the region 280-400 nm are depicted in Fig. 1. The spectra of Cu–DA–AA containing aromatic amino acids except NO_2phe, which has a strong absorption caused by the electronic transition within the nitrophenyl ring at ~300 nm, exhibited an increase of absorption at >320 nm. The spectral changes are seen from the difference between the spectra for the ternary systems and those calculated from the spectra for Cu–DA–ala (ala = L-alanine) and AA (Fig. 2). The difference spectra for Cu–Cl_2bpy–AA and Cu–Me_2bpy–AA containing aromatic amino acids show an absorption decrease at ~300 nm and an increase at 310-380 nm, which is especially evident for AA = trp, tyr, and NH_2phe. The absorption for the Cu–$(NEt_2)_2$bpy–AA systems decreased at 310-350 nm and increased at 360-400 nm, and the largest changes were observed for AA = NO_2phe, suggesting that the electron density difference between the aromatic rings of DA and AA affects the spectral behavior and that these spectral changes are caused by intramolecular π-π interactions between them.[12,27]

Structures of ternary complexes

The molecular structures of [Cu(dpa)(trp)]ClO_4•$2H_2O$ (**1**) and [Cu($(CONH_2)_2$bpy)(phe)]ClO_4•H_2O (**2**) in the solid state are shown in Figs. 3 and 4, respectively, and the bond lengths and angles around Cu(II) and interatomic distances between the Cu–DA moiety and the side chain aromatic ring of AA are summarized in Tables 2 and 3, respectively. Each complex has a Cu(II) ion in a distorted square-planar or a square-pyramidal geometry formed by two aromatic nitrogens of DA and an aliphatic nitrogen and a carboxylate oxygen of AA. Complex **1** (Fig. 3) has the indole ring of trp located close above the Cu–dpa coordination plane (Cu–C(15) = 3.06, C(5)–C(21) = 3.29, and N(1)–C(21) = 3.40 Å) (Table 2), indicating that the indole ring interacts mainly with the Cu(II) ion and the pyridine ring trans to the amino group with the angle of 18.6˚. A similar close contact was disclosed for **2** (Fig. 4) between the aromatic ring of AA and the Cu(DA) moiety with

the closest Cu(II)–C distance of 3.17 Å and the N–C and C–C distances of 3.24-3.43 Å as shown in Table 3. All the C(II)–ligand bond lengths are comparable with our previous observations on analogous ternary Cu(bpy)(AA) complexes.[12a,27,28] The structures show a strong distortion of the Cu(II) coordination plane, reflecting the aromatic-aromatic and probably Cu(II)–aromatic interactions. Similar observations have been made for ternary Cu(II) complexes with stacking,[11] and all these observations suggest that there exist bonding interactions between them. Whereas the coordinated bpy derivatives are nearly planar in **2** and **3**, the pyridine rings of dpa are not coplanar with the Cu(II) coordination plane, and this may affect the stacking ability of dpa and thus the stability of complexes.

Affinity of Cu(DA) for aromatic amino acids

The stability constants, log β_{pqrs}, for $Cu_p(DA)_q(AA)_rH_s$ and the log K_{prs} values for $\{Cu(DA)\}_p(AA)_rH_s$ determined at 25 ˚C and I = 0.1 M (KNO_3) are summarized in Tables 4 and 5, respectively. The affinity of the binary complex Cu(DA) for AA to form Cu(DA)(AA) may be evaluated by eqn. 3[29] from the successive stability constants, log $K^{AA}_{Cu(DA)(AA)}$, for the systems with DA = dpa, Me_2bpy, and $(NEt_2)_2$bpy and AA (except tyrOH):

$$Cu(DA) + AA \underset{}{\overset{K^{AA}_{Cu(DA)(AA)}}{\rightleftharpoons}} Cu(DA)(AA)$$

$$\log K^{AA}_{Cu(DA)(AA)} = \log \beta_{1110} - \log \beta_{1100} \qquad (3)$$

For the systems with DA = bpm, Cl_2bpy, and $(COOEt)_2$bpy, it is evaluated by log K_{110} (eqn. 2). Eqns. 2 and 3 were corrected for the protonation constant for the tyr phenol OH group as follows:

$$\log K^{AA}_{Cu(DA)(AA)} = \log K_{111} - \log K_{011}$$

$$= \log \beta_{1111} - \log \beta_{1100} - \log \beta_{0011} \qquad (3')$$

Table 6 shows that the log $K^{AA}_{Cu(DA)(AA)}$ values decrease with DA in the order $(COOEt)_2$bpy > Cl_2bpy > Me_2bpy > $(NEt_2)_2$bpy, which reflects the electron withdrawing effects of the substituents of bpy on the Cu(II) ion. Most of the Cu(DA)(AA) systems are more stable than Cu(DA)(ala),

suggesting that aromatic residues of AA contribute to the stabilization of ternary complexes by intramolecular stacking.

Stabilization due to ligand–ligand interactions

Stability enhancement of Cu(DA)(AA) due to ligand-ligand interactions relative to the complexes without them, i.e., Cu(DA)(ala), Cu(en)(AA), and Cu(en)(ala), may be evaluated by the following hypothetical equilibrium:

$$\text{Cu(DA)(ala)} + \text{Cu(en)(AA)} \overset{K}{\rightleftharpoons} \text{Cu(DA)(AA)} + \text{Cu(en)(ala)} \qquad (4)$$

where the coordination structures and ligand fields are maintained nearly equal for all the complex species, and therefore the K value greater than 1 indicates that Cu(DA)(AA) is stabilized maily due to ligand-ligand interactions. The log K values are calculated by eqn. 5:

$$\log K = \log \beta_{(\text{Cu(DA)(AA)})} + \log \beta_{(\text{Cu(en)(ala)})} - (\log \beta_{(\text{Cu(DA)(ala)})} + \log \beta_{(\text{Cu(en)(AA)})}) \qquad (5)$$

where $\log \beta_{\text{Cu(DA)(AA)}}$ (= log β_{1110} or β_{1111}) is replaced by $\log \beta_{\{\text{Cu(DA)}\}\text{(AA)}}$ (= log K_{110} or log K_{111}) for DA = bpm, Cl_2bpy, and $(COOEt)_2$bpy. The positive log K values in Table 7 indicate that the Cu(DA)(AA) complexes are stabilized by intramolecular stacking interactions. The log K values of the ternary complexes involving DA with electron-donating groups are larger than those with electron-withdrawing groups, and therefore the stacking is more effective in such complexes. As mentioned earlier, coordinated dpa is not coplanar with the coordination plane (Fig. 3), and this results in slightly lower stability of Cu(dpa)(AA) as compared with Cu(bpy)(AA). This decrease in stability is probably caused by the bent structure (Fig. 3) and a smaller area of interaction for the separated aromatic rings of dpa as compared with planar bpy.

The Cu(DA)(trp) and Cu($(NEt_2)_2$bpy)(NO_2phe) systems having a large log K value showed a large spectral change in the near UV region, indicating that the interactions between Cu(DA) and the side chain aromatic ring have electronic effects. In addition, large stabilization observed for the Cu(dpa)(trp) system corresponds well with the stacked solid state structures of **1**

shown in Fig. 3.

Effects of substituents on the aromatic-aromatic interactions

The interactions between aromatic rings in aqueous solution are considered to involve such forces as 1) hydrophobic interactions, 2) van der Waals forces, 3) quadrupole interactions, 4) bonding interactions between π-electrons, and 5) electrostatic attraction and repulsion.[5,30] Hunter and Sanders[5] and Cozzi and Siegel[7] reported that aromatic ring interactions are mainly governed by electrostatic or quadrupole interactions. Our previous observations that the intramolecular aromatic ring stacking interactions in Pd(II)-peptide complexes[31] and Pt(II) complex–nucleotide adducts[11a,32] are enthalpy-driven support that the interactions are bonding interactions and are in line with the non-classical hydrophobic effect.[4] The log *K* values for the Cu(bpy)(AA) systems were considerably larger than those for the Cu(bpm)(AA) systems (Table 7), and since the sizes of bpy and bpm are very similar, lower stability of the bpm-containing systems is not ascribed to the differences in hydrophobic interactions or van der Waals forces but to the low π-electron density of bpm as compared with bpy. The log *K* values seem to be influenced by the electronic conditions of the aromatic rings as have been pointed out before.[11] They are in a nearly linear relationship with the Hammett σ_p values[33] of the substituents on the aromatic rings of AA for the systems with AA = NH_2phe, tyr, phe, Fphe, and NO_2phe (Fig. 5). The systems except DA = $(NEt_2)_2$bpy have negative slopes, showing that the electron-rich aromatic ring of AA, Lπ, interacts with the Cu–DA moiety, Mπ, more strongly than the electron-deficient Lπ, so that the pyridine rings coordinated to metal ions can be regarded as comparable with the *N*-methylpyridinium ring in the systems by Hunter et al.[34] and the perfluorobenzene ring in the systems by Cozzi and Siegel,[7] in both of which the electrons are strongly withdrawn by the substituents.[30] These relationships indicate that DA in Cu(DA)(AA) except $(NEt_2)_2$bpy with an electron-donating diethylamino group is π-deficient due to the Lewis acidity of Cu(II).

Comparison of the log *K* values for various DA's indicates that the electron-rich aromatic

ring of coordinated NH_2phe and tyr interact with the Cu((NEt_2)$_2$bpy) moiety more strongly than with the Cu((COOEt)$_2$bpy) moiety, contrary to the expectation from the organic systems.[5,7,30] In the present and other ternary complexes,[11] π-π interactions involve metal-coordinated aromatic ring and a side chain aromatic ring of different nature and may not be directly comparable with the mentioned systems. The present results imply that intramolecular interactions in Cu(DA)(AA) involve interactions between Cu(II) and the aromatic ring of AA, so that the interactions may better be considered as Mπ–Lπ interactions.

Halo-substituents in aromatic amino acids

Figure 5 shows that the ternary systems containing the *p*-halo derivatives of phe, Xphe (X = F, Cl, or Br) exhibit anomalous log *K* values, which are much higher than expected from the σ values. Although the differences between the electron-withdrawing properties of F, Cl, and Br expressed in terms of the σ values are small (<0.2), the differences in the log *K* values of the relevant systems were found to be in the order Fphe << Clphe < Brphe. A close look at Fig. 5 reveals that deviations of the plots from the straight lines are smallest with F and largest with Br, suggesting that the observed deviations are due to the van der Waals forces between DA and Br or Cl reflecting the atomic radii of the halogen atoms. The log *K* values for Fphe are close to those expected from the linear relationship, which is because the F atom is the smallest.

Among the aromatic amino acids investigated, those with a haloaryl side chain group are clearly exceptional in stabilization of Cu(DA)(AA), suggesting that their high affinity for Cu(DA) is probably due to the combined effects of aromatic-aromatic interactions and aromatic-halogen van der Waals interactions. It is noteworthy in this connection that some aromatic halo compounds such as dioxins and polychlorinated biphenyls are known as endocrin-disrupting chemicals,[35] and the present finding indicate that halogenated aromatic rings may have a strong tendency to stack with other aromatic rings and thus affect the hormonal activity.

Conclusions

We prepared bpy derivatives with various substituents and the ternary Cu(II) complexes with these diimine ligands (DA) and aromatic amino acids (AA), Cu(DA)(AA). The structures of [Cu(dpa)(trp)]ClO_4•$2H_2O$ (**1**) and [Cu($(CONH_2)_2$bpy)(phe)]ClO_4•H_2O (**2**) in the solid state revealed that in these complexes there exist Mπ-Lπ interactions between the Cu(DA) moiety and the uncoordinated aromatic ring of AA. The contribution of the interactions to the stability of ternary Cu(II) complexes was evaluated by the log *K* values calculated from the stability constants determined by pH titrations. The stability enhancement was found to be in the order of DA bpy < Me_2bpy < $(NEt_2)_2$bpy, which indicates that the intensity of the Mπ–Lπ interactions increases with the increase of the electron density of DA. The log *K* values were found to be nearly linearly correlated with the σ_p values of the substituents of the uncoordinated aromatic rings, indicating that the electron density of both the coordinated and side chain aromatic rings affect the Mπ–Lπ interactions. The tendencies of complex stabilization as summarized in Fig. 5 indicate that a more effective Mπ–Lπ interaction is achieved by a larger electron density difference between the interacting aromatic ring; thus, an electron-deficient side chain aromatic ring of AA prefers an electron-rich DA. The results appear to be in contrast with the reported stability sequence for aromatic–aromatic interactions, π-deficient–π-deficient > π-deficient–π-rich > π-rich–π-rich. An anomalously large stability enhancement was observed for AA with a haloaryl side chain probably due to the contribution of the polarizability and van der Waals interactions of the halogen atoms, which may indicate unique properties of the halogen atoms incorporated into aromatic rings. Taken together, the present observations indicate the electronic nature of π-π interactions in metal-coordinated systems.

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Table 1 Crystallographic data

		1	**2**
Formula		$C_{21}H_{24}N_5O_8CuCl$	$C_{21}H_{22}N_5O_9CuCl$
Formula Weight		571.43	587.43
Crystal Color, Habit		deep blue, needle	blue, prism
Crystal Dimensions (mm)		0.35x0.15x0.10	0.05x0.02x0.01
Crystal System		orthorhombic	monoclinic
Lattice Parameters	*a* (Å)	6.7769(10)	9.9415(8)
	b (Å)	10.96900(10)	11.9758(7)
	c (Å)	31.0900(3)	10.0268(8)
	β (˚)		94.766(7)
	V (Å^3)	2311.1(3)	1189.6(2)
Space Group		$P2_12_12_1$	$P2_1$
Z value		4	2
D_{calc} (g/cm^3)		1.642	1.640
F(000)		1172	602
Radiation		Mo $K\alpha$ (λ = 0.71070 Å)	Cu $K\alpha$ (λ = 1.54178 Å)
μ (cm^{-1})		11.198	28.956
$2\theta_{max}$ (˚)		55.2	120.1
Index ranges		$0 \le h \le 8$	$0 \le h \le 11$
		$0 \le k \le 14$	$0 \le k \le 13$
		$0 \le l \le 40$	$-11 \le l \le 11$
Range of transmission factors		0.8941-0.8941	0.5661-0.9715
Observed reflections		3037	1985
Independent reflections		3018	1866 (R_{int} = 0.160)
Reflections used		3011	1839
No. Variables		327	354
Goodness of fit		1.001	1.010
p-factor		0.0103	0.0031
Final *R* indices [$I > 2\sigma(I)$][a]		R_1 = 0.0629	R_1 = 0.0472
R indices (all data)[b]		*R* = 0.0642; R_w = 0.2048	*R* = 0.0494; R_w = 0.1256

[a] $R_1 = \Sigma||Fo| - |Fc|| / \Sigma|Fo|$ for $I > 2\sigma(I)$. [b] $R = \Sigma||Fo| - |Fc|| / \Sigma|Fo|$, $R_w = \{\Sigma\omega(Fo^2 - Fc^2)^2 / \Sigma\omega(Fo^2)^2\}^{1/2}$; $\omega = [\{pFo^2 + \sigma(Fo^2)\}/4Fo^2]^{-1}$.

Table 2 Selected bond lengths (Å), bond angles (°) and interactomic distances (Å) of **1**

a) Selected bond lengths

Cu–O(1)	1.958(3)	Cu–N(1)	1.967(4)
Cu–N(3)	1.968(4)	Cu–N(4)	1.995(4)

b) Selected bond angles

O(1)–Cu–N(1)	95.0(1)	O(1)–Cu–N(3)	160.8(2)
O(1)–Cu–N(4)	82.5(1)	N(1)–Cu–N(3)	92.1(2)
N(1)–Cu–N(4)	162.7(2)	N(3)–Cu–N(4)	95.7(1)

c) Selected interactomic distances

Cu•••C(15)	3.06	Cu•••C(16)	3.21
N(1)•••C(21)	3.40	N(2)•••C(19)	3.39
C(5)•••C(21)	3.29		

Table 3 Selected bond lengths (Å), bond angles (°) and interactomic distances (Å) of **2**

a) Selected bond lengths

Cu–O(3)	1.923(4)	Cu–N(1)	2.008(6)
Cu–N(2)	1.994(6)	Cu–N(5)	1.990(6)

b) Selected bond angles

O(3)–Cu–N(1)	173.9(2)	O(3)–Cu–N(2)	93.4(2)
O(3)–Cu–N(5)	83.7(2)	N(1)–Cu–N(2)	82.3(2)
N(1)–Cu–N(5)	101.7(2)	N(2)–Cu–N(5)	161.4(2)

c) Selected interactomic distances

Cu•••C(16)	3.17	Cu•••C(17)	3.23
N(1)•••C(19)	3.43	C(1)•••C(20)	3.24

Table 4 Stability constants (log β_{pqrs}) for $Cu_p(DA)_q(AA)_r(H)_s$ at 25 ˚C and I = 0.1 M (KNO_3)[a]

		DA		
AA	pqrs	dpa	Me_2bpy	$(NEt_2)_2$bpy
	0101	7.069(1)	5.344(1)	8.619(6)
	0102	8.49(4)		14.020(7)
	1100	7.505(9)	8.33(3)	11.413(2)
	1200	12.683(9)	14.53(3)	20.890(4)
	110-1	0.187(4)	1.33(8)	
	110-2	-10.40(1)	-8.27(1)	
ala	1110	15.414(3)	16.025(6)	19.040(8)
phe	1110	15.755(4)	16.579(1)	19.761(3)
trp	1110	16.605(2)	17.490(1)	20.916(8)
tyr	1111	25.987(3)	27.014(3)	30.139(5)
	1110	15.816(6)	17.172(5)	20.421(6)
NO_2phe	1110		16.354(1)	19.883(3)
NH_2phe	1110		16.930(1)	19.957(2)
Brphe	1110		16.806(3)	20.186(1)
Clphe	1110		16.732(4)	20.058(4)
Fphe	1110		16.406(4)	19.672(3)

[a] Values in parentheses denote estimated standard deviations.

Table 5 Successive stability constants (log K_{prs}) for $[Cu(DA)]_q(AA)_r(H)_s$ at 25 ˚C and I = 0.1 M (KNO_3)[a]

		DA		
AA	prs	bpm	$(COOEt)_2$bpy	Cl_2bpy
	10-1	-6.878(9)	-6.875(6)	-7.157(9)
	10-2	-15.46(1)	-15.40(2)	-16.39(2)
ala	110	8.048(7)	7.962(2)	7.902(2)
phe	110	8.213(3)	8.476(2)	8.295(1)
trp	110	9.200(10)	9.585(1)	9.402(2)
tyr	111	18.389(8)	18.777(4)	18.729(3)
	110	8.74(2)		8.418(9)
NO_2phe	110	7.258(2)	7.696(5)	7.577(4)
NH_2phe	110	8.424(3)	8.646(3)	8.543(2)
Brphe	110	8.017(3)	8.412(3)	8.323(2)
Clphe	110	7.855(1)	8.375(2)	8.235(3)
Fphe	110	7.707(1)	8.047(3)	7.939(2)

[a] Values in parentheses denote estimated standard deviations.

Table 6 The log $K^{AA}_{Cu(DA)(AA)}$ values of Cu–DA–AA systems

	DA					
AA	dpa	bpm	Me_2bpy	$(NEt_2)_2bpy$	$COOEt_2bpy$	Cl_2bpy
ala	7.91	8.05	7.70	7.63	7.96	7.90
phe	8.25	8.21	8.25	8.35	8.48	8.30
trp	9.10	9.20	9.16	9.50	9.59	9.40
tyrOH	8.34	8.25	8.54	8.58	8.64	8.59
$tyrO^-$	8.31	8.74	8.84	9.01		8.42
NO_2phe		7.26	8.02	8.47	7.70	7.58
NH_2phe		8.42	8.60	8.54	8.65	8.54
Brphe		8.02	8.48	8.77	8.41	8.32
Clphe		7.86	8.40	8.65	8.38	8.24
Fphe		7.71	8.08	8.26	8.05	7.94

Table 7 The log *K* values of Cu–DA–AA systems[a]

	DA							
AA	dpa	bpm	Me_2bpy	$(NEt_2)_2$bpy	$COOEt_2$bpy	Cl_2bpy	bpy[b]	phen[b]
phe	0.54	0.37	0.76	0.92	0.72	0.60	0.60	0.64
trp	1.06	1.02	1.34	1.75	1.49	1.37		
tyrOH	0.75	0.42	1.17	1.28	0.99	1.00	0.90	1.05
$tyrO^-$	-0.11	0.19	0.63	1.36		0.00		
NO_2phe		-0.01	1.11	1.62	0.51	0.45	0.68	0.65
NH_2phe		0.64	1.17	1.18	0.94	0.84	0.70	0.92
Brphe		0.73	1.54	1.90	1.21	1.12	1.07	1.13
Clphe		0.45	1.35	1.66	1.06	0.98	0.82	0.90
Fphe		0.24	0.96	1.21	0.66	0.61	0.53	0.63

[a] Calculated according to eqn. 5. [b] Data taken from ref. 12.

Legends for Figures

Fig. 1 Absorption spectra of Cu–Me_2bpy–AA systems in water. AA = ala, black broken line; phe, black solid line; trp, black thick line; tyr, blue sold line; NO_2phe, red solid line.

Fig. 2 Difference absorption spectra of Cu–DA–AA systems in water: a) Cl_2bpy; b) Me_2bpy; c) $(NEt_2)_2$bpy. AA = phe, black solid line; trp, black thick line; tyr, blue sold line; NH_2phe, blue broken line; NO_2phe, red solid line; Fphe, green solid line; Clphe, brown solid line; Brphe, brown broken line.

Fig. 3 ORTEP view of [Cu(dpa)(trp)]ClO_4•$2H_2O$ (**1**). Thermal ellipsoids are drawn at the 50% probability level, and the hydrogen atoms, counter ion and water molecules are omitted for clarity.

Fig. 4 ORTEP view of [Cu($(CONH_2)_2$bpy)(phe)]ClO_4•H_2O (**2**). Thermal ellipsoids are drawn at the 50% probability level, and the hydrogen atoms, counter ion and water molecule are omitted for clarity.

Fig. 5 Relationships between log *K* values and σ_p values of substituents on AA.

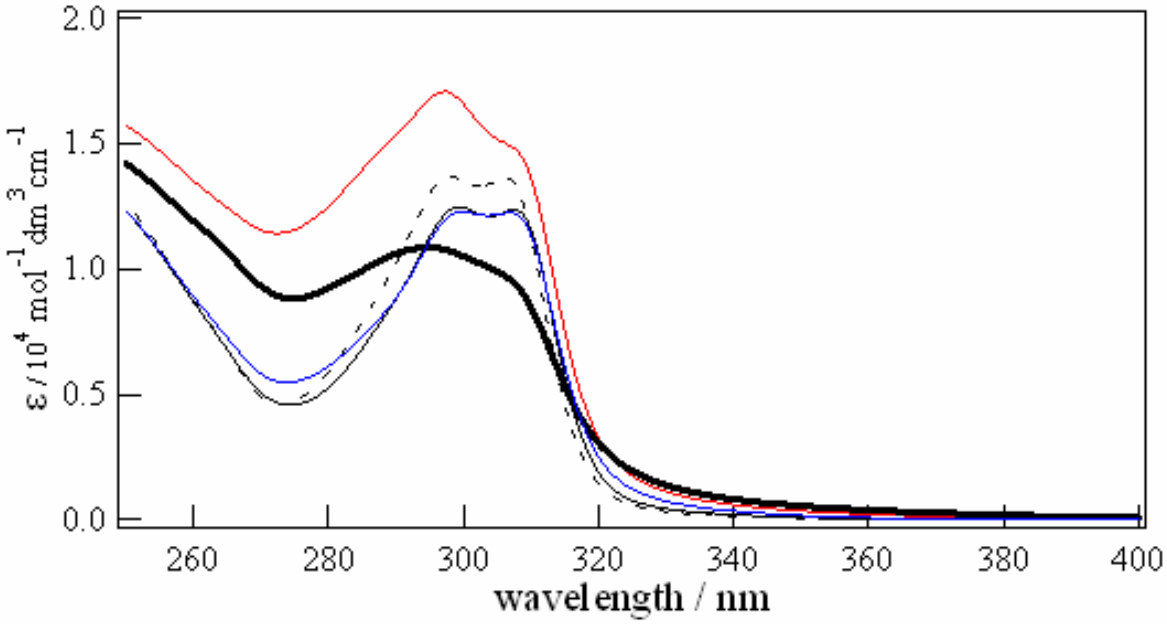
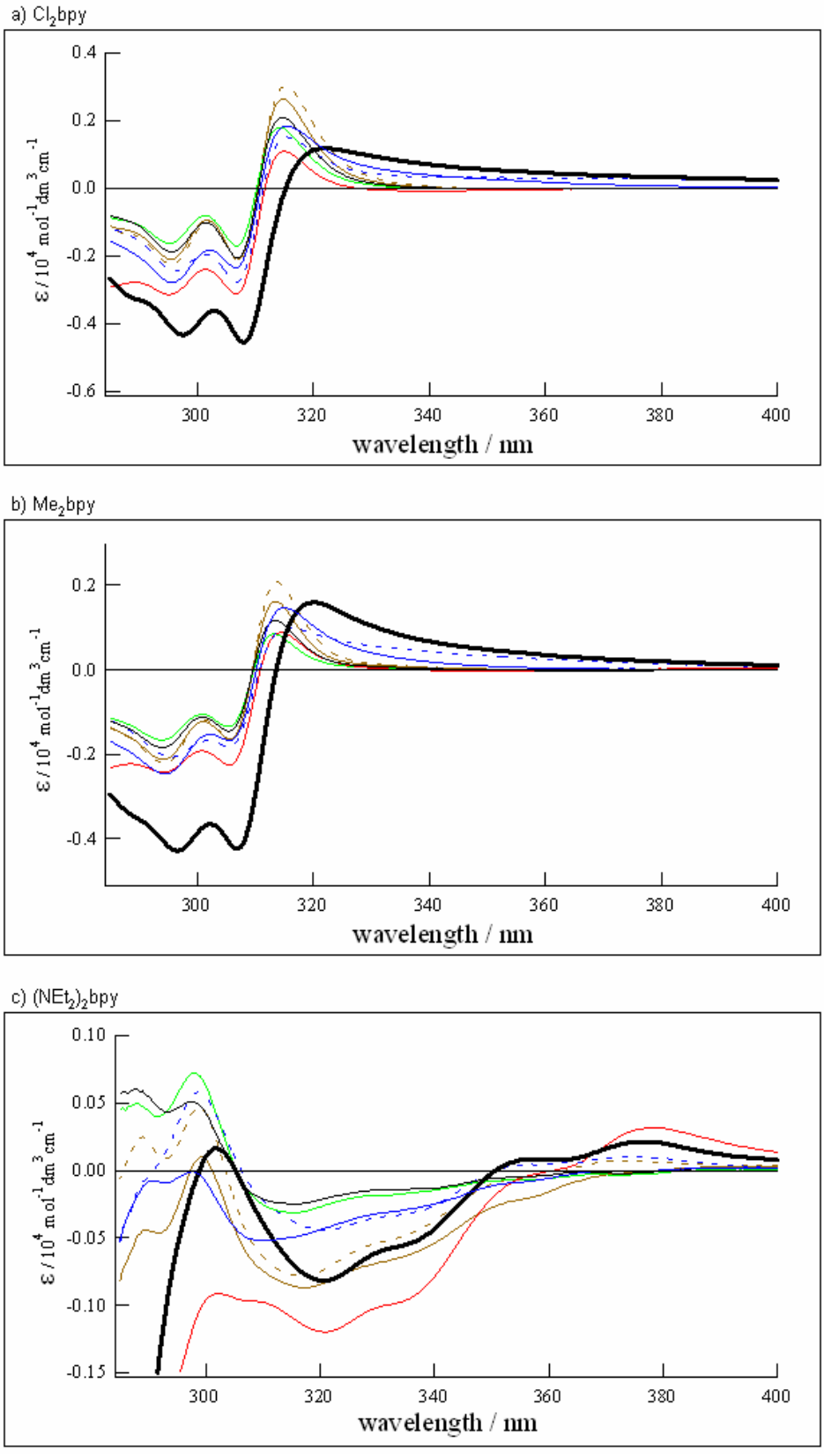


Fig. 1 T. Yajima et al.



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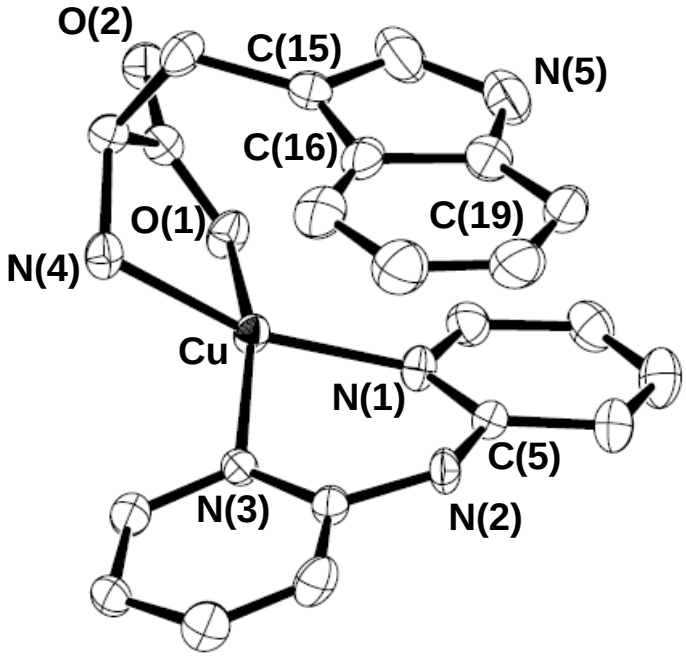

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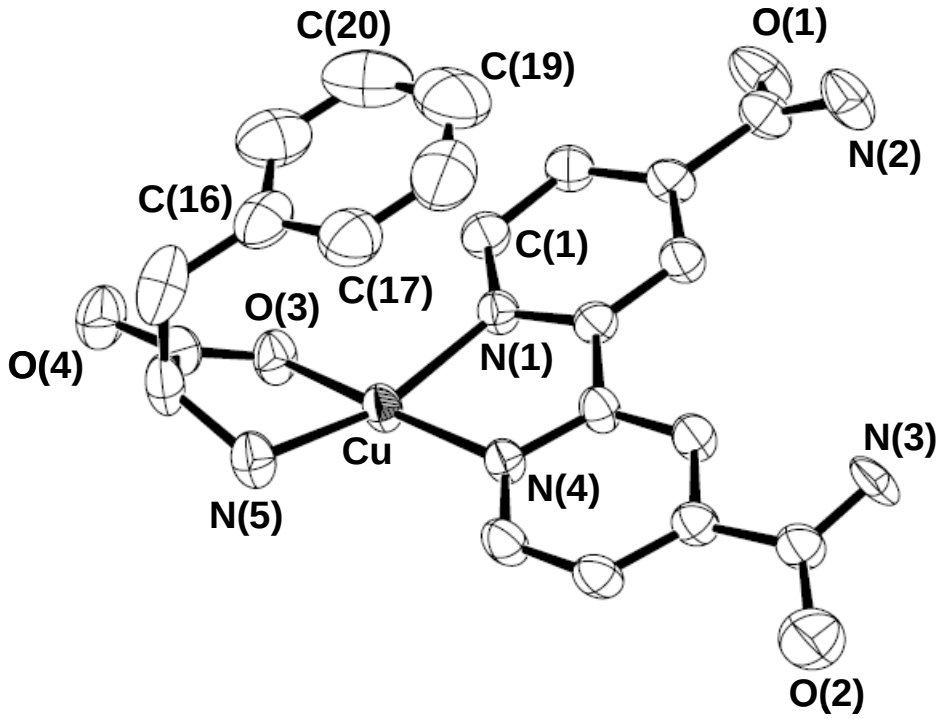

Fig. 4 T. Yajima et al.

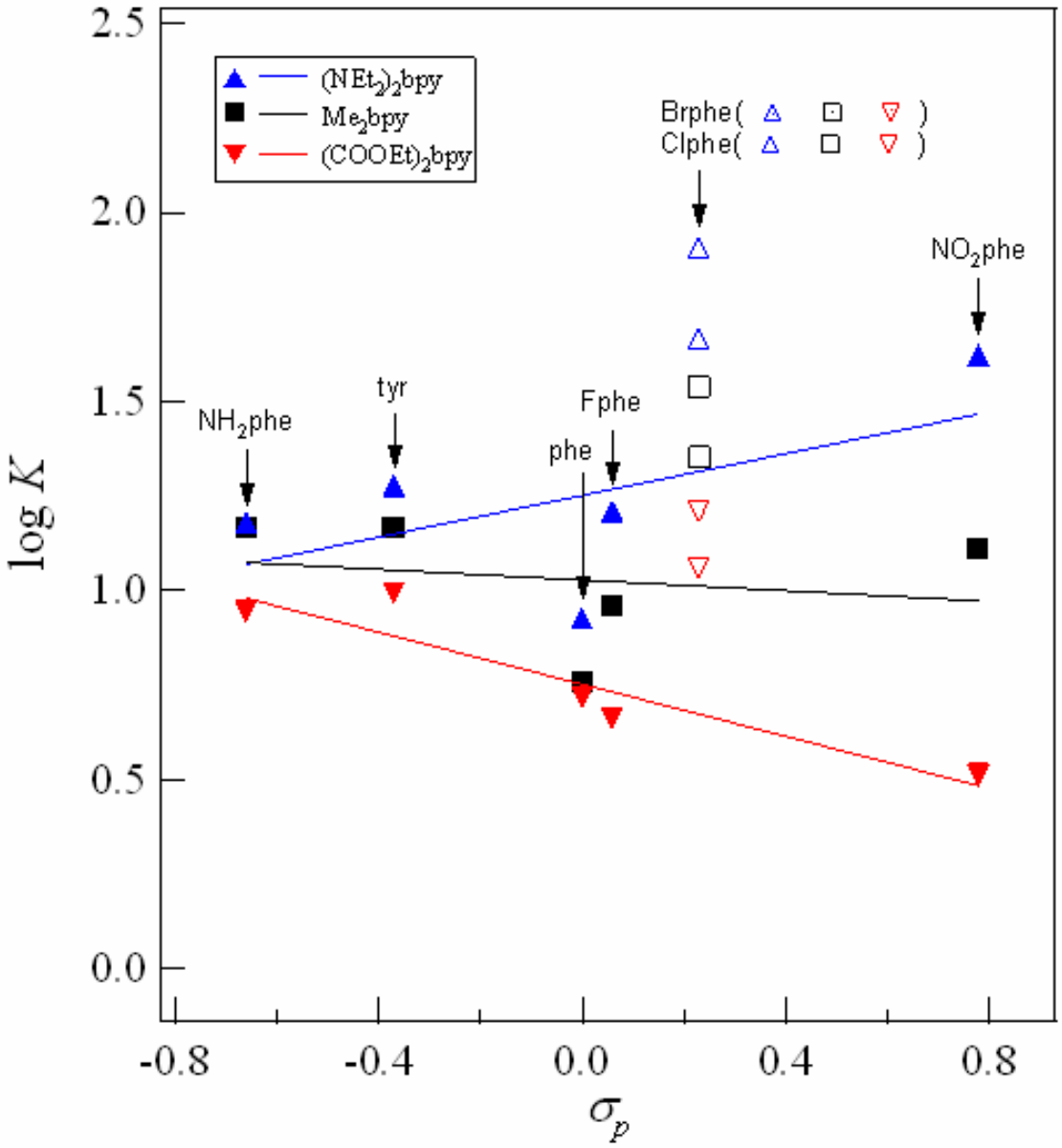

Fig. 5 T. Yajima et al.