Complex **1** is formally four-coordinate (omitting any weak ligation by μ-oxide units of silica); hence facile η^4 coordination of arene can be achieved. It is noteworthy then that [Si]-ORh(allyl)(PMe$_3$)$_2$H,[1] prepared from **1** and an excess of PMe$_3$, is totally inactive toward arene hydrogenation. Indeed, the addition of even *1* equiv of PMe$_3$ to **1** completely quenches hydrogenation of the aromatic substrate (the five-coordinate adduct [Si]-ORh(allyl)(PMe$_3$)H could not bind the arene in η^4 fashion). Increasing the PMe$_3$–**1** ratio from 0 to 1 caused a smooth decrease in the initial rate of naphthalene hydrogenation.[17] The observation of a nonzero rate at PMe$_3$–**1** ratios of less than 1.0 shows that the active species in arene hydrogenation is indeed **1** and not a trace impurity.

Anisole is hydrogenated at a slower rate than benzene, and aniline is reduced more slowly than all the arenes studied. We propose that this is due to the ability of these substrates to coordinate to rhodium competitively through their functional groups.[16]

The silica-bound rhodium hydrides described herein, while insoluble like typical "heterogeneous" catalysts, exhibit reactivity according to predictable patterns. Consequently, their reactivity can be understood on the "molecular level" in terms familiar to the study of "homogeneous" complexes, and the development of new "heterogeneous" species, such as those described herein, can proceed rationally. The introduction of new classes of "heterogeneous" catalysts, which have been designed to accomplish a given transformation, can now be anticipated.

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A Novel Mode of Protein–Protein Interaction. Water-Bridged Cation–Cation Interaction in Trypsin–Inhibitor Complex

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Very specific blocking of the active site of proteolytic enzyme by the inhibitor is commonly supposed to be of central significance to the regulatory control of zymogen activation[1,2] which is important in biological functions such as hormone production, blood clotting, or fertilization.[3] Basic bovine pancreatic trypsin inhibitor[4] (abbreviated as BPTI or I) is of particular importance among those proteinic inhibitors, since the association constant of BPTI with bovine pancreatic trypsin (abbreviated as BPT or E), $>10^{13}$ M^{-1} at neutral pH, is one of the highest values ever determined for protein–protein interaction.[4g] This extremely strong binding had been attributed to van der Waals interaction, hydrogen bonding, a very specific electrostatic interaction (Asp189E···Lys15I), and/or formation of a tetrahedral intermediate (Ser195E–O$_\gamma$–C–Lys15I) based on X-ray results of this EI complex.[4a–c]

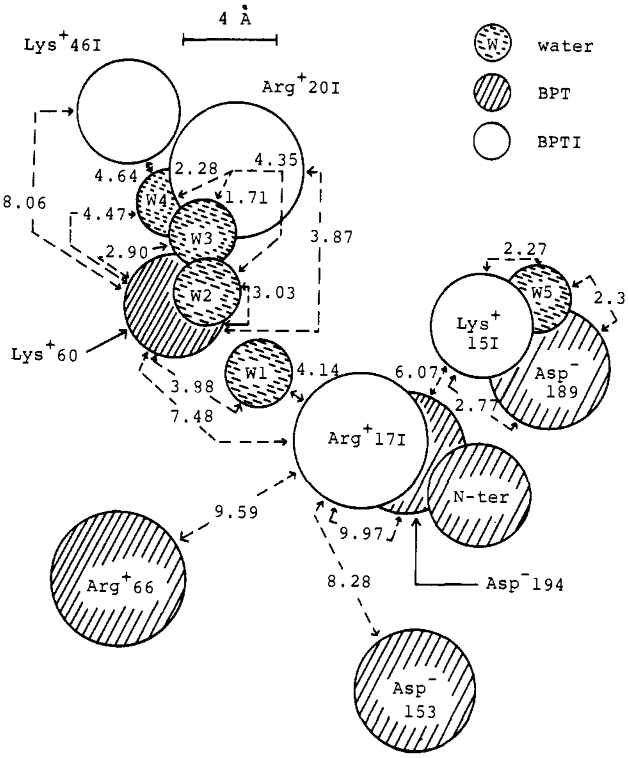

Figure 1. Schematic map depicting contact between ionic amino acid residues and water molecules in BPT–BPTI complex. Distances are given in Å and van der Waals radii of ionic groups (NH$_3^+$, CO$_2^-$, NH—C(NH$_2$)=NH$_2^+$) are represented by the size of the circle.

Now we wish to report that a new unique mode of interaction, water-bridged cation–cation interaction, is operating in the EI complex via electrostatic stabilization.

Figure 1 is a schematic map depicting contact of ionic amino acid residues, and their interionic distances (shorter than 10 Å), with water molecules existing within 5-Å distance from an ionic residue of E or I.

Cationic residue NH$_3^+$-Lys60E of trypsin is located in close proximity to *cationic* residue guanidinium$^+$-Arg20I (r = 3.87 Å) and also very close to *cationic* residues guanidinium$^+$-Arg17I (r = 7.48 Å) and NH$_3^+$-Lys46I (r = 8.06 Å) of the inhibitor (Figure 1). Such a situation of cationic contact is unusual, and if the simplest assumption of an ionic interaction[6] [estimated by eq 1, D = 2, q, partial charge; D, dielectric constant; r, distance; m, number of partial point charges on BPT under consideration (up to 3224); n, number of partial point charges on BPTI under consideration (up to 855)] is made, E_{el} summed over each cation

$$E_{\mathrm{el}} = \sum_{i=1}^{m} \sum_{j=1}^{n} \frac{332 q_i q_j}{D r_{ij}} \tag{1}$$

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(6) (a) D = 2 is suggested by H. A. Scheraga et al.[8] CNDO/2 partial charges were used.[8] (b) Other evaluations of D, $D = 6R - 7$ (3–7 Å) and D = 3 (below 3 Å): Schwarzenbach, G. *Z. Phys. Chem.* **1936**, *176*, 133. D = 1–4 (R = 6 Å); Scheraga, H. A. *Chem. Rev.* **1971**, *71*, 195. (c) The electrostatic interaction energy (E_{el}) for Lys60E···Arg17I, Lys60E···Arg20I, Lys60E···Lys46I, and Asp189E···Lys15I interaction amounted to +15.99, +26.26, +20.19, and −35.99 kcal mol^{-1}, respectively, when the following partial point charges were taken into the account. Lys$^+$C$^\delta$, −0.115; C$^\epsilon$, 0.050; N$^\zeta$, −0.320; H$^\delta$, 0.100; H$^\epsilon$, 0.120; H$^\zeta$, 0.320. Arg$^+$: C$^\delta$, 0.120; N$^\epsilon$, −0.300; C$^\zeta$, 0.580; N$^\eta$, −0.390; N$^{\eta2}$, −0.39; H$^\epsilon$, 0.230; H$^{\eta1}$, 0.280; H$^{\eta2}$, 0.280. Asp$^-$: C$^\alpha$, −0.060; C$^\beta$, −0.170; C$^\gamma$, 0.500; O$^{\delta1}$, −0.570; O$^\delta$, −0.570; H$^\alpha$, 0.024; H$^\beta$, −0.020.[8]

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Table I. Electrostatic Interaction Energies for Important Ion Pairs and Overall Nonbridged Electrostatic Energy of BPT–BPTI Complex

BPT (partial charge)[a]	BPTI (partial charge)[a]	r, Å	E_{el} (D = 2), kcal mol^{-1}	E_{el} (D_{eff}), kcal mol^{-1}
NH_3^+ (Lys60E)[b]	guanidinium$^+$ (Arg20I)		+14.80	+0.416[d]
H_1^{ζ} (+0.32)	N^{ϵ} (−0.30)	6.44	−2.47	−0.063 (78)
	C^{ζ} (+0.58)	5.63	+5.47	+0.140 (78)
	$N^{\eta 1}$ (−0.39)	6.38	−3.24	−0.083 (78)
	$N^{\eta 2}$ (−0.39)	4.29	−4.83	−0.124 (78)
	H^{ϵ} (+0.23)	7.40	+1.65	+0.042 (78)
	$H_1^{\eta 1}$ (+0.28)	7.37	+2.02	+0.052 (78)
	$H_2^{\eta 1}$ (+0.28)	6.11	+2.43	+0.062 (78)
	$H_1^{\eta 2}$ (+0.28)	3.87	+3.84	+0.151 (51)
	$H_2^{\eta 2}$ (+0.28)	3.90	+3.80	+0.098 (78)
N^{ζ} (−0.32)	N^{ϵ}	7.43	+2.14	+0.05 (78)
	C^{ζ}	6.58	−4.68	−0.120 (78)
	$N^{\eta 1}$	7.25	+2.86	+0.073 (78)
	$N^{\eta 2}$	5.24	+3.95	+0.101 (78)
	H^{ϵ}	8.38	−1.46	−0.037 (78)
	$H_1^{\eta 1}$	8.25	−1.80	−0.046 (78)
	$H_2^{\eta 1}$	6.90	−2.15	−0.055 (78)
	$H_1^{\eta 2}$	4.74	−3.14	−0.097 (65)
	$H_2^{\eta 2}$	4.90	−3.03	−0.078 (78)
	Other 18 Partial Charge Pairs			
NH_3^+ (Lys60E)	NH_3^+ (Lys46I)		+7.45	+0.092 [e]
NH_3^+ (Lys60E)	guanidinium$^+$ (Arg17I)		+8.80	+0.226 [f]
CO_2^- (Asp189E)	NH_3^+ (Lys15I)		−20.7	−2.185 [g]
all atoms[c]	all atoms[c]		+589.1	−38.7 [h]

[a] CNDO/2 partial charge.[8] [b] Partial charge on H_2^{ζ} or H_3^{ζ} is +0.32. [c] For other partial charges involving those on backbone atoms and side residue atoms, refer to ref 8. [d] $m = 4, n = 9$. [e] $m = 4, n = 4$. [f] $m = 4, n = 9$. [g] $m = 3, n = 4$. [h] $m = 3224, n = 855$.

Table II. Electrostatic Energy due to Counterion Bridge at W1, W2, or W4 Position[d]

BPT	BPTI	r, Å	D_{eff}	E_{el}^{bridge}, kcal mol^{-1}
OH^- (W1)[a]	guanidinium$^+$ (Arg20I)			−0.40[d]
	N^{ϵ}	5.20	8	−1.01
	C^{ζ}	5.56	14	1.41
	$N^{\eta 1}$	6.79	14	−2.55
	$N^{\eta 2}$	5.00	34	0.56
	H^{ϵ}	5.55	8	3.25
	$H_1^{\eta 1}$	7.36	25	−0.55
	$H_2^{\eta 1}$	7.28	70	−0.18
	$H_1^{\eta 2}$	5.64	31	−0.41
	$H_2^{\eta 2}$	4.14	14	−1.19
	guanidinium$^+$ (Aeg17I)			−10.89[d]
	NH_3^+ (Lys46I)			−0.20[e]
	all atom (BPTI)			−20.9[f]
all atom (BPT)	OH^- (W2)[b]			−15.0[g]
	OH^- (W4)[c]			−7.3[g]

[a] Counterion of Lys60E. [b] Counterion of Arg20I. [c] Counterion of Lys46I. [d] See Table I for partial point charges of guanidinium group. Point charge of −1 on the oxygen atom was used for OH^-. [d] $m = 1, n = 9$. [e] $m = 1, n = 4$. [f] $m = 1, n = 855$. [g] $m = 3224, n = 1$.

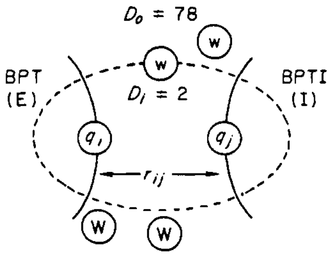
Table III. Intermolecular Electrostatic Interaction Energy between BPT–BPTI Calculated by Equation 1

		E_{el}, kcal mol^{-1}
total $E_{el}^{nonbridge}$	BPT···BPTI	−38.7[a]
total E_{el}^{bridge}	BPT·water···BPTI	−20.9[b]
	BPTI·water···BPT	−10.7[c]
total E_{el}^{water}	BPT·water···BPTI·water	+7.9[d]
	E_{el}^{total} =	−62.4

[a] $m = 3224, n = 855$. [b] $m = 13, n = 855$. [c] $m = 3224, n = 6$. [d] $m = 13, n = 6$.

pair amounts to +14.80 kcal mol^{-1} for NH_3^+(Lys60E)···guanidinium$^+$(Arg20I), +7.45 kcal mol^{-1} for NH_3^+(Lys60E)···NH_3^+(Lys46I), or +8.80 kcal mol^{-1} for NH_3^+(Lys60E)···)-guanidinium$^+$(Arg17I) (see Table I for CNDO/2 partial charges used), indicating that a serious destabilization should be accompanied by these cationic contacts. The sum of the above three destabilization energies, +31.05 kcal mol^{-1}, is much larger than the calculated stabilization energy of E_{el} = −20.7 kcal mol^{-1} (eq 1, D = 2) for the important ion pair interaction CO_2^-(Asp189E)···NH_3^+(Lys15I) of the normal BPT–BPTI cation–anion recognition! The above result of the serious electrostatic repulsion was unchanged, even when the E_{el} summation was taken over larger number of atoms, e.g., other atoms on amino acid side residue, having smaller partial charges[6c] or over all atoms of the complex, where the E_{el} value amounted to +589.1 kcal mol^{-1} (Table I).

However, very interestingly, four water molecules were found to intervene between those cations, viz., Lys60E···W1···Arg17I, Lys60E···W2, W3···Arg20I, Lys60E···W4···Arg20I, Lys46I (Figure 1), strongly suggesting that the electrostatic interaction occurs through water molecules or more plausibly hydroxide anion (as counterion bridge). Beside W1–W4, other water molecules in the neighborhood must be taken into consideration in the sense that they surely must have an effect on the local (effective) dielectric constant, D_{eff}. To develop these ideas, two approaches were followed. First, to evaluate D_{eff}, the Westheimer–Kirkwood theory[7] was extended to a from generally applicable to the protein–protein interaction involving water. Thus, the partial charges[8] q_i and q_j were placed at the focuses of a spheroid, the boundary face of which is defined by the nearest water molecule. Accordingly it



is assumed that the spheroid interior, which is completely devoid of water molecules, has the inner dielectric constant D_i = 2,

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whereas we assumed the outer dielectric constant to be $D_0 = 78$.[7,9] The latter (zero-order) approximation seems to be appropriate for those ion pairings depicted in Figure 1, where 22 other water molecules are present in the neighborhood.[10a,c] Then, the effective dielectric constant, D_{eff}, is given by the Westheimer–Kirkwood equation[7a] (eq 2) and the intermolecular electrostatic energies

$$\frac{1}{D_{\text{eff}}} = \frac{1}{D_{\text{i}}} + \left(\frac{1}{D_{\text{o}}} - \frac{1}{D_{\text{i}}}\right)\sum_{n=0}^{\infty} \frac{U_n}{[1 + (D_{\text{i}}/D_{\text{o}})]C_n} \tag{2}$$

calculated by using D_{eff} ($r_{ij} < 15$ Å, $|q| > 0.01$, eq 1, $D = D_{\text{eff}}$) are shown in the last column of Table I. To each ionic residue a given counterion, H_3O^+ or OH^- with point charge on the oxygen atom, was assigned in same place as the nearest water molecule.[10b]

Most of the repulsive interactions between (partial) charges of the same sign (espe Lys60E···Arg17I, 20I, Lys46I) were markedly reduced, e.g., from E_{el} ($D = 2$) = +14.80 kcal mol^{-1} to E_{el} (D_{eff}) = +0.416 kcal mol^{-1} for NH_3^+ (Lys60E)···guanidinium$^+$ (Arg20I) interaction, as expected by taking proximal water molecules into account (Table I).[11a] Thus, the overall electrostatic interaction without bridges became attractive ($E_{\text{el}}^{\text{nonbridge}}$ = −38.7 kcal mol^{-1})[11b] (Table I).

The electrostatic energy due to water (counterion) bridging ($E_{\text{el}}^{\text{bridge}}$) which is the sum of the following two interactions—counterions of BPT···BPTI, where m is the number of counterions of BPT (up to 13) and n is the number of partial point charges on BPTI under consideration (up to 855) and BPT···counterions of BPTI, where m is the number of partial point charges on BPT under consideration (up to 3224) and n is the number of counterions of BPTI (up to 6)—was calculated by using eq 1 ($D = D_{\text{eff}}$). Table II gives the calculated $E_{\text{el}}^{\text{bridge}}$ values obtained for the counterions W1, W2, and W4 when W3 and W5 are neutral water particles.[12] The overall $E_{\text{el}}^{\text{bridge}}$ value summed over all (partial) point charge pairs and $E_{\text{el}}^{\text{nonbridge}}$ are given in Table III together with a correction term, $E_{\text{el}}^{\text{water}}$, the electrostatic energy due to interactions between counterions of E and I.

It is evident that W1, W2, and W4 contribute significantly to the stabilization of the EI complex by behaving as OH^- (counteranion), as exemplified by the negative $E_{\text{el}}^{\text{bridge}}$ values of −20.9, −15.0, and −7.3 kcal mol^{-1} for the interactions OH^-(W1)···BPTI, BPT···OH^-(W2), BPT···OH^-(W4), respectively (Table II).

Most importantly, the overall electrostatic energy due to the water (counterion) bridging was found to be −31.6 kcal mol^{-1} (Table III). Evidently, overall $E_{\text{el}}^{\text{bridge}}$ is one of the most outstanding terms contributing to the electrostatic interaction ($E_{\text{el}}^{\text{total}}$ = −62.4 kcal mol^{-1}) in the EI complex (Table III).

In conclusion, the water bridged cation–cation interaction significantly stabilizes the BPT–BPTI complex, and also any repulsive electrostatic interaction is markedly reduced by water molecules in the proximity. These may be seen in protein–protein interactions in general.

Acknowledgment. We thank Dr. R. Huber and Dr. P. Schwager of Max-Planck Institute für Biochemie for the generous supplying of atomic coordinates of BPT and BPT–BPTI complex.

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(10) (a) The total number of water molecules (except W1–W5), which was found within 5-Å distance from any of 10 ionic residues (Figure 1) but not placed between E and I, was 22. (b) Within 5 Å from ionic residue. (c) Lys46I and Arg20I find very few number of atoms on the residue of E in their neighborhood, viz., W1–W4 are very close to the complex surface.

(11) (a) The result of significant reduction of repulsive interaction was unchanged, even when $D_0 = 70$ was assumed, as exemplified by E_{el} ($D = D_{\text{eff}}$) = −0.459 kcal mol^{-1} for NH_3^+(Lys60E)···guanidinium$^+$(Arg20I) interaction or overall $E_{\text{el}}^{\text{nonbridge}}$ ($D = D_{\text{eff}}$) = −39.6 kcal mol^{-1}. (b) Most of this remarkable EI complex stabilization comes from interactions of (intermolecular) ion pairs separated by <10 Å, since the $E_{\text{el}}^{\text{nonbridge}}$ value amounted to −35.9 kcal mol^{-1} when $r < 10$ Å was assumed.

(12) This counterion configuration was the optimized one which led to the largest calculated $E_{\text{el}}^{\text{bridge}}$ value for W1–W5, by varying the kind, +, neutral, or −, of counterions on those water positions.

Optically Detected Magnetic Resonance Evidence for Carcinogen–Nucleic Acid Interaction in the Tetrahydro-9,10-epoxybenzo[*e*]pyrene–DNA Adduct

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There is now strong evidence that the carcinogenic action of polycyclic aromatic hydrocarbons (PAH) is mediated via metabolically activated intermediates[1] and that the critical initiating step in carcinogenesis is the covalent binding of these intermediates to DNA.[2,3] Recent results have shown that the qualitative nature of the PAH–DNA binding site may be correlated with its carcinogenicity,[4] indicating that structural characterization of carcinogen–nucleic acid adducts may prove important in relating these complexes to subsequent events in carcinogenesis.

Here we use the technique of optically detected magnetic resonance (ODMR)[5] to probe the structure of the adduct of the tetrahydro-9,10-epoxy derivative of benzo[*e*]pyrene (BePE, Figure 1a)[6] with DNA. BePE, while not an in vivo metabolite of benzo[*e*]pyrene,[7,8] is a potent mutagen and tumorigen[7,9] and is assumed to initiate carcinogenesis by its direct binding to DNA.[7,9] Preliminary linear electric dichroism results have indicated that the pyrene chromophore in the BePE–DNA adduct is approximately parallel to the planes of the DNA bases,[10] raising the possibility that the chromophore may be intercalated in the nucleic acid. However, these results alone are only suggestive of intercalation and do not exclude a completely nonintercalated adduct in a base parallel conformation. In the present study, we obtain ODMR results indicating that the pyrene triplet chromophore in the BePE–DNA adduct exists in a heterogeneous environment intermediate between that expected for intercalation and complete solvent exposure.

The BePE–DNA in vitro adduct was prepared analogously to the benzo[*a*]pyrene adduct,[11] yielding ca. 2 adducts per 1000 nucleotides. All studies on the adduct were done in 1:1 (v/v) ethylene glycol–sodium cacodylate buffer. The epoxide was acid hydrolyzed into the corresponding H_4-9,10 diol (BePD) which was used to model environmental effects on the BePE–DNA adduct, as both possess nearly identically substituted chromphores and the BePD is conveniently stable and soluble in a variety of solvents.

We chose the two solvent environments for the BePD of dry pyridine and ethylene glycol–buffer, so as to model the extreme possibilities of complete adduct chromophore intercalation between nucleic acid bases and total solvent exposure, respectively. All glycol–buffer solutions were quickly immersed in liquid nitrogen

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