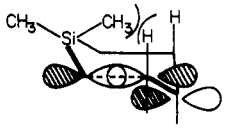
difference among the radicals is the low value of k_c^5 for α-U·.[15] Otherwise, the radicals are, by and large, comparable to the parent 5-hexen-1-yl radical. The low k_c^5 value for α-U· explains the unusual regioselectivity in its cyclization. It is diminished exo cyclization and not enhanced endo cyclization which is responsible. Explanation of the diminished exo cyclization must be somewhat speculative, because the factors involved in exo vs. *endo* cyclization are complex. Certainly a stereoelectronic rationale involving better orbital overlap for exo cyclization seems to be important.[16] Examination of molecular models (FMO) indicated that such overlap appeared to be more difficult in α-U· then in γ-U·. However, overlap for endo cyclization in α-U· appeared from the models to be equally effective as that for exo cyclization in γ-U·. Such stereoelectronic equivalence should make k_c^6 for α-U· comparable to R_c^5 for γ-U·. This is not the case, possibly because axial repulsion is developed in the endo cyclization of α-U· as shown.



Other factors might be mentioned, as well. Because one molecular orbital view of radical addition to a double bond ascribes cationic character to the radical,[17] it is possible that polar effects are also involved. The presence of silicon α to cationic centers is apparently destablizing, contrary to expectations.[18] If such an effect were operating in the present case, however, it would add to the difficulty of *any* cyclization of α-U·, a result in contrast to its "normal" k_c^6 value. Furthermore, the possibility that α-silyl radicals (such as α-U·) are stabilized relative to related carbon radicals,[6] which in turn would decrease their cyclization propensity, does not appear to be substantiated. Such stabilization could conceivably result in reversibility of the cyclizations of α-U·, especially via R_c^5 where the cyclized radical R· is primary. But the "normal" value of k_c^6 and the response of total rearrangement to dilution of TBTH, as exemplified by the constancy of the *r* value for α-U·, indicates that reversibility is not involved.[19] Nevertheless, reversibility in the cyclization of α-U· via k_c^5 would indeed lower both its *r* and *S* values relative to γ-U·, as observed. This possibility will be directly checked in future work.

At present the results are best explained, although not entirely satisfactorily, in terms of a stereoelectronic factor coupled with steric effects. Nonetheless, α-U· appears to be the first 5-hexen-1-yl-type radical bearing neither substituents on the vinyl group nor known radical stabilizing groups at the radical center which shows such decreased exo cyclization. This unusual result adds to others noted[20] for α-silyl radicals and makes one suspect that some deeper explanation for their behavior exists.

Lastly, comparison of the *r* values for TBTH vs. TBTD reduction allows the determination of k_H/k_D values for α- and γ-U·, 1.5 and 1.7, respectively. These values (which may be the same, considering experimental error) are somewhat lower than that reported for all-carbon cases (~3).[3] The interpretation of this difference as well as a better understanding of α-silyl radical cyclization (and other rearrangements) must await the results of further studies presently under way.[21]

Acknowledgment. I thank the Loyola University Research Committee and the Dow-Corning Copr. for grants in support of this work.

(14) Obviously the individual values of k_c^5 and k_c^6 (but *not* their ratio) depend upon the value used for k_H. The value chosen is taken from: Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 2* 1980, 1083. It represents the preferred value over a close range. Different values of k_H for α-U· and γ-U· would obviously affect the *r* values and possibly show comparable cyclization reactivities for the two systems. But the *S* values would remain as a glaring difference.

(15) A better comparison would involve α-±· vs. 2,2-dimethyl-5-hexen-1-yl radical and γ-U· vs. 4,4-dimethyl-5-hexen-1-yl radical. No published data on the latter have appeared, although the 2,2-dimethyl analogue has been reported to cyclize exclusively vis k_c^5 and about 10 times more rapidly at 80 °C than the parent (Beckwith, A. L. J.; Lawrence, T. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1535). Both observations only magnify the anomaly of α-U·.

(16) This view has been developed largely by A. L. J. Beckwith. Cf. ref 1 and references therein. For a recent theoretical treatment of this subject using MINDO/3-UHF calculations, see: Bischof, P. *Helv. Chim. Acta* **1980**, *63*, 1434.

(17) Fujimoto, H.; Yamabe, S.; Minato, T.; Fukui, K. *J. Am. Chem. Soc.* **1972**, *94*, 9205. Other (contrary) views are held. Cf. ref 1.

(18) Eaborn, C. "Organosilicon Compounds"; Butterworths: London, 1960; pp 431–434.

(19) For a situation involving reversibility and the thereby revised mathematical approach to obtain a constant *r* value, see: Wilt, J. W., Chwang, W. K., Dockus, C. F.; Tomiuk, N. M. *J. Am. Chem. Soc.* **1978**, *100*, 5534.

(20) For example, absence of 1,2-aryl shift: Wilt, J. W.; Kolewe, O.; Kraemer, J. F. *J. Am. Chem. Soc.* **1969**, *91*, 2624. Ease of formation from α-chlorosilanes.[6]

(21) Among other efforts, attempts to synthesize a chloride precursor to a β-U· analogue of α-±· have recently succeeded. Investigation of its cyclization, and, as mentioned in the text, studies on the possible reversibility of the cyclization of α-U· are in progress and will be reported subsequently. Another aim, the study of the unencumbered 1-sila analogue of the 5-hexen-1-yl radical, would appear to be quite difficult owing to the probable instability of its precursors. Such radicals substituted at silicon with phenyl, chloro, isopropyl, and methyl groups have been cyclized, though in low yield. Sakurai, H. *Free Radicals* **1973**, *2*, 793.

Silica-Bound Rhodium Hydride Catalysts for Arene Hydrogenation

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We have recently described the synthesis of a family of silica-bound rhodium hydride complexes including [Si]-ORh(allyl)H (**1**).[1] In contrast to conventional nonsoluble heterogeneous catalysts, these complexes can be characterized on the molecular level, and aspects of their chemistry can be elucidated readily as for their soluble counterparts. For example, the stoichiometric ligation of olefins or phosphine ligands to **1** could be explained by employing coordination number arguments for the Rh(III) center, which suggested the metal could behave as a formally four-coordinate species. We have observed that **1** is an efficient catalyst for olefin hydrogenation and have described a sequence, on the molecular level, which accounts for this catalytic behavior. Similar logic suggested that substrates requiring more than one site on a metal (for example, an arene) could be coordinated to **1**; activation of H_2 by the resulting species would provide a pathway for the catalytic hydrogenation of the substrate. Indeed, we found that **1** does catalyze arene hydrogenation under mild conditions.[3] In the course of these studies we have also discovered an unusual exchange process which takes place under the hydrogenation reaction conditions.

Hydrogenation of benzene catalyzed by **1** proceeded smoothly (to give cyclohexane) with essentially no decrease in rate even after >3000 turnovers. Naphthalene hydrogenation, however, took quite a different course; under the reaction conditions (500-psi H_2; 22 °C) the initial rate of hydrogenation (60 turnovers/h) was not maintained; rather, hydrogenation activity slowly decreased over ca. 300 turnovers and eventually approached a new, *constant* rate (7.7 turnovers/h). In this time period propane (0.7 equiv) was evolved.[4] Alkaline hydrolysis (1 M MeO^-/MeOH) of the

(1) Ward, M. D.; Schwartz, J. *J. Mol. Catal.* **1981**, *11*, 397. **1** was prepared by the sequence

$$[Si]\text{-}OH + Rh(allyl)_3{}^2 \rightarrow [Si]ORh(allyl)_2 \xrightarrow[1\ atm]{H_2} \mathbf{1}$$

(2) Powell, J.; Shaw, B. L. *Chem. Commun.* **1966**, 323.

(3) Catalytic hydrogenations were performed in a modified Parr minireactor equipped with a glass liner and nylon stirrer in order to preclude contact of the reaction mixture with the autoclave stainless steel surface. For conditions see Table I.

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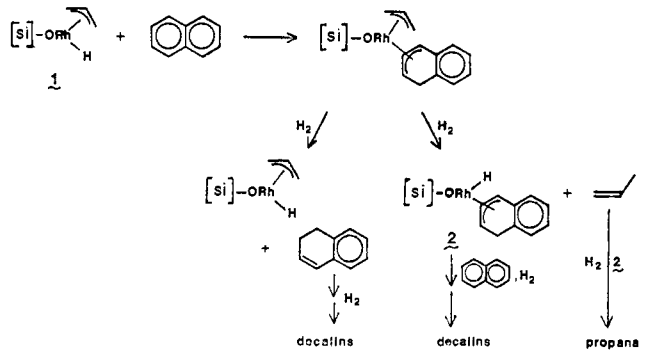
Scheme I



resulting catalyst species gave a mixture of decalins, tetralin, and naphthalene (0.3 equiv). These results suggest that the process responsible for the change in catalyst activity involved an *exchange* of the allyl ligand in **1** for one derived from the naphthalene substrate as shown in Scheme I, in contrast to a recent report that *loss* of the allylic group of η^3-$C_3H_5Co[P(OCH_3)_3]_3$ precedes formation of the cobalt hydride species catalytically active for arene hydrogenation.[7] In this scheme a silica-supported rhodium allyl naphthyl complex (**4**) is generated which reacts with H_2 to generate either propylene or reduced naphthalene species analogous to the preparation of **1** from [Si]-ORh(allyl)$_2$ and H_2.[1] This process suggests that catalyst **2** effects naphthalene hydrogenation by a similar route; that is, by reaction with the substrate to generate a dinaphthyl intermediate which then undergoes hydrogenation. The decrease in hydrogenation rate as the catalyst is converted from **1** to **2** is attributed to increased steric hindrance in the ligand environment of the rhodium center associated with the latter. Infrared analysis of **2** revealed the presence of rhodium hydride bands similar to **1**[5] (ν_{Rh-H} = 2000, 1845 cm^{-1}). A similar observation was made for the hydrogenation of 1,4,6,7-tetramethylnaphthalene under the same conditions (initial rate = 7.1 turnovers/h; "final rate" = 2.8 turnovers/h) to yield **3**, a methylated analogue of **2**. To verify that arene unit incorporation and not random decomposition was responsible for the decrease in activity of **1**, the relative catalytic hydrogenation activity of **1**–**3** was determined toward a given olefin, 2,3-dimethyl-2-butene. (These experiments were performed after **2** and **3** had exhibited a constant rate in hydrogenation of naphthalene and 1,4,6,7-tetramethylnaphthalene, respectively.) Indeed, the relative rates for hydrogenation of this substrate decreased in the order **1** > **2** > **3** as expected for increasing steric bulk of the allyl ligand present on rhodium (for **1**, 10 turnovers/min; for **2**, 3 turnovers/min; for **3**, 0.6 turnovers/min, all under the same conditions[6]). Exchange of the substrate with the alkyl ligand in hydrogenation experiments with mononuclear arenes did not occur; propane was not evolved during hydrogenation of such substrates, and infrared spectra of the catalysts before and after utilization were identical. Furthermore, the rate of catalytic hydrogenation of 2,3-dimethyl-2-butene measured for the catalyst recovered from benzene hydrogenation experiments was identical with that measured for **1**. Presumably the maintenance of some resonance stabilization in species such as **2** facilitates ligand exchange; apparently partially reduced monocyclic species are reduced to the cycloalkane more rapidly than is the bicyclic allylic unit.

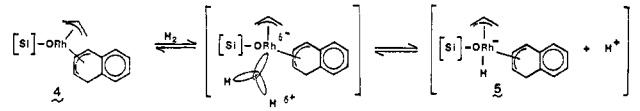
Relative rates for hydrogenation of a series of arenes are shown in Table I. The decrease in initial rate in the order benzene > naphthalene > anthracene > 1,4,6,7-tetramethylnaphthalene

Table I. Hydrogenation of Polynuclear Aromatics[a]

substrate	rate[b]
benzene	410
anisole	266
aniline	11
fluorobenzene	168
naphthalene	60
1,4,6,7-tetramethylnaphthalene	10
anthracene	39
phenanthrene	<0.1

[a] Reaction conditions: complex 1, 80 mg, 0.03 mmol; aromatic substrate, 14 mmol; solvent, 20 mL; hydrogen, 500 psi; 22 °C. [b] Initial rate is given as turnovers/h; products identified by GC/MS techniques and comparison with authentic samples.

Scheme II



correlates with the steric bulk of the substrate. For hydrogenation of bi- and trinuclear aromatics, a marked selectivity is observed,[8] although this is not so pronounced as it is for a recently reported catalyst.[9] For example, naphthalene is reduced almost exclusively to tetralin, which is then hydrogenated to both *cis*- and *trans*-decalin.[10] Anthracene hydrogenation occurred initially by preferential reduction of the external ring; 9,10-dihydroanthracene was never detected in these experiments.

According to Scheme II hydrogenation of the organometallic intermediate **4** proceeds via heterolytic activation of H_2.[11] This type of activation has been noted in the reaction between $RhCl_6^{3-}$ and $RuCl_6^{3-}$ with H_2[12] which was found to proceed most readily in basic solvents.[12a,13] Heterolytic activation of H_2 has also been postulated to occur in soluble transition-metal–alkyl complexes[14] (which leads to metal hydride and alkane) as it has been for rhodium–alkyl complexes derived from **1** and an olefin.[1] As noted for inorganic Rh and Ru species, the heterolytic activation of H_2 should be facilitated by the stabilization of the released proton by an electron pair: for the metal alkyl this pair could be the M–C bonding one (leading to M–C cleavage); for silica-bound complexes a lone pair of a basic oxygen atom of the support could suffice (as has been observed in the reaction between ZnO and H_2 in which Zn–H and new O–H species have been observed).[15] Subsequent attack of the proton on the rhodium–carbon bond of intermediate **5** would complete the catalytic cycle. The observation that **1** effects catalytic H–D exchange between a 50:50 H_2–D_2 mixture to produce a nearly statistical 1.2:2:1 H_2–HD–D_2 mixture concomitant with the appearance of pronounced infrared absorbance in the O–D region suggests the presence of "free" proton.

It has been suggested that η^4 coordination of an arene is necessary for activation of that substrate toward hydrogenation.[7,16]

(4) The presence of propane was verified by GC/MS and determined quantitatively by a calibrated PV trap and GC analysis with *n*-butane standard.

(5) Rhodium hydride absorbances for **1** were observed at 2010 and 1800 cm^{-1}.

(6) Olefin hydrogenation experiments were performed on a constant-pressure mercury buret system. Rates were determined by monitoring the uptake of H_2. Conditions were as follows: complex **1**, **2**, **3** (30 mg, 0.01 mmol Rh): 2,3-dimethyl-2-butene (2.00 mmol); hexane (15 mL); H_2 (1 atm); 22 °C.

(7) Bleeke, J. R.; Muetterties, E. L. *J. Am. Chem. Soc.* **1981**, *103*, 556.

(8) At 80% naphthalene conversion; tetralin–decalin = 15:1. At 45% anthracene conversion; tetrahydroanthracene–1,2,3,4,5,6,7,8-octahydroanthracene–1,2,3,4,9,10,11,12-octahydroanthracene–perhydroanthracene = 6.4:6.5:1.5:1.

(9) Grey, R. A.; Pez, G. P.; Wallo, A. *J. Am. Chem. Soc.* **1980**, *102*, 5948.

(10) The observation of *trans*-decalin requires the presence of free $\Delta^{1,9}$-octalin. We have observed this compound in minor amounts (<2%) as an intermediate in naphthalene hydrogenation.

(11) It is intriguing that the silica-bound rhodium allyl hydride complexes **1**–**3** are fairly resistant to hydrolysis under acidic conditions; a basic medium is required to cleave the allyl ligand from the metal. This implies that a buildup of negative charge on rhodium facilitates attack on the rhodium–carbon bond by proton. Similarly, attack of the newly formed proton on the anionic intermediate **5** should proceed readily.

(12) (a) James, B. R.; Rempel, G. L. *Can. J. Chem.* **1966**, *44*, 233. (b) Halpern, J.; James, B. R. *Can. J. Chem.* **1966**, *44*, 671.

(13) Hui, B.; James, B. R. *Chem. Commun.* **1969**, 198.

(14) Gell, K. I.; Schwartz, J. *J. Am. Chem. Soc.* **1978**, *100*, 3246.

(15) Kokes, R. J.; Dent, A. L.; Chang, C. C.; Dixon, L. T. *J. Am. Chem. Soc.* **1972**, *94*, 4429.

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)-$(PMe_3)_2H$,[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.

Acknowledgment. We acknowledge support for this research provided by the National Science Foundation (Grant CHE-79-00996).

(16) Stuhl, L. S.; DuBois, M. R.; Hirsekorn, F. J.; Bleeke, J. R.; Stevens, A. E.; Muetterties, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 2405.

(17) PMe_3–**1**, rate (turnovers/h): 0.0, 60 (initial rate); 0.125, 30; 0.25, 16; 0.50, 5.0; 0.75, 1.5.

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_γ–C–Lys15I) based on X-ray results of this EI complex.[4a-c]

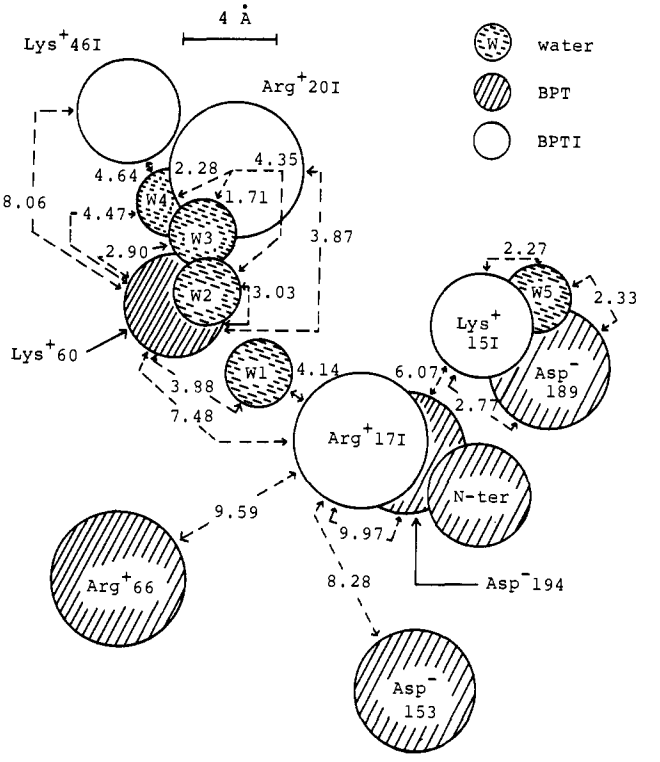

Figure 1. Schematic map depicting contact between ionic amino acid residues and water molecules in BPT–BPTI complex. Distances are given in Å and van der Waals radii of ionic groups (NH_3^+, CO_2^-, NH—C-(NH_2)=NH_2^+) are represented by the size of the circle.

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

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

(1) Green, T. R.; Ryan, C. A. *Plant Physiol.* **1972**, *51*, 19.

(2) Nolan, J. C.; Ridge, S.; Oronsky, A. L.; Slakey, L. L.; Kerwar, S. S. *Biochem. Biophys. Res. Commun.* **1978**, *83*, 1183.

(3) Nuerath, T.; Walsh, K. A. "Regulatory Proteolytic Enzymes and Their Inhibitors"; Magnusson, S., et al., Eds.; Pergamon Press: Elmsford, NY, 1977.

(4) (a) Huber, R.; Kukla, D.; Bode, W.; Schwager, P.; Bartels, K.; Deisenhoten, J.; Steigeman, W. *J. Mol. Biol.* **1974**, *89*, 73. (b) Ruhlman, A.; Kukla, D.; Schwager, P.; Bartels, K.; Huber, R. *Ibid.* **1973**, *77*, 417. (c) Blow, D. M.; Wright, C. S.; Kukla, D.; Ruhlman, A.; Steigmann, W.; Huber, R. *Ibid.* **1972**, *69*, 137. (d) Huber, R.; Kukla, D.; Ruhlmann, A.; Epp, O.; Formak, H. *Naturwissenschaften* **1970**, *57*, 389. (e) Huber, R.; Bode, W. *Acc. Chem. Res.* **1978**, *11*, 114. (f) Blow, D. M. *Ibid.* **1976**, *9*, 145. (g) Vincent, J. R.; Ladzunski, M. *Biochemistry* **1972**, *11*, 2967. (h) Kunitz, M.; Northrop, J. H. *J. Gen. Physiol.* **1936**, *19*, 991.

(5) A chloride bridged cation–cation interaction or water bridged hydrogen bonding had been proposed, without any discussions on its quantitative significance, as one of the subunit interactions of deoxyhemoglobin. Perutz, M. F. *Br. Med. Bull.* **1976**, *32*, 195. *BioSystems* **1977**, *8*, 261.

(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^δ, −0.115; C^ϵ, 0.050; N^ζ, −0.320; H^δ, 0.100; H^ϵ, 0.120; H^ζ, 0.320. Arg^+: C^δ, 0.120; N^ϵ, −0.300; C^ζ, 0.580; N^η, −0.390; $N^{\eta 2}$, −0.39; H^ϵ, 0.230; $H^{\eta 1}$, 0.280; $H^{\eta 2}$, 0.280. Asp^-: C^α, −0.060; C^β, −0.170; C^γ, 0.500; $O^{\delta 1}$, −0.570; O^δ, −0.570; H^α, 0.024; H^β, −0.020.[8]

0002-7863/81/1503-5255$01.25/0