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258. Charge Transfer as a Molecular Probe in Systems of Biological Interest

VI[1]): Interactions between Lysozyme and the Methyl 2-acetamido-6-O-(N-methyl-isonicotinylium)-2-deoxy-β-D-glucopyranoside Ion

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(28. VIII. 72)

Summary. The synthesis of methyl 2-acetamido-6-O-(N-methyl-isonicotinylium)-2-deoxy-β-D-glucopyranoside ion (**2**; iodide and chloride) is reported. Association with hen-egg-white lysozyme causes chemical shift changes for its acetamido and glycosidic methyl groups comparable to those observed for the monosaccharide lysozyme inhibitor methyl 2-acetamido-3-deoxy-β-D-glucopyranoside. The binding modes of the two compounds to the enzyme in solution therefore appear to be analogous. Furthermore, a charge transfer interaction of the pyridinium : indole type is observed spectrophotometrically, indicating that the **2**/lysozyme complex in solution is similar to that of the monosaccharide (and polysaccharide) inhibitor in crystals (proximity of the ligand O^6 to the enzyme Trp^{62}).

Introduction. – The current interests of one of us (*R.S.*) are centered around the process of biological recognition at the molecular level [2]. We are studying hormone/potential receptor and inhibitor (substrate)/enzyme interactions with fluorescent [3], NMR. [4], photo-affinity [5], radioactive [6], and charge-transfer (CT.) [7] probes.

Recent CT. investigations have indicated that N(1)-methyl-nicotinamide ion forms a molecular complex with Trp^{62} of hen-egg-white lysozyme in solution. An association constant of K = 3.2 l/mole was determined from spectrophotometric titration experiments [8]. According to X-ray crystallographic studies [9], mono- and polysaccharide inhibitors of the N-acetyl-glucosamine (NAG) and N-acetyl-muramic

[1]) Elektronen-Donator-Acceptor-Komplexe bei Polypeptiden. For paper V see [1].
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acid (NAM) type interact with the indole side chain of Trp^{62} through their appropriate C(6) oxygen (hydrogen bond?). Furthermore, the N-acetyl methyl of the NAG group associated with this site appears to be buried in a small hydrophobic region of the enzyme. This manifests itself in the difference-*Fourier* map and in NMR. chemical shift changes of the acetyl protons (if this sugar residue is present as methyl glycoside, the O(1) methyl protons are also characteristically shielded) [10].

Studies with 3-dimensional molecular models suggested that a NAG molecule carrying a N-methyl-isonicotinylium ion as electron acceptor on O(6) could be bound to the enzyme through its sugar moiety according to the crystallographically developed scheme and, at the same time, give rise to a CT. interaction with Trp^{62}. The present investigation with methyl 2-acetamido-6-O-(N-methyl-isonicotinylium)-2-deoxy-β-D-glucopyranoside ion **2**, indicates that this is actually the case. The N(2)-acetyl and O(1)-methyl groups are 'normally' associated with lysozyme (NMR.), and a strong CT. interaction between the electron acceptor pyridinium system and the electron donor indole side chain of a tryptophan residue (Trp^{62}) occurs. Complexation of the ligand appears to take place predominantly via the sugar moiety whereas the O(6) substituent retains a considerable amount of (rotational) freedom. This is substantiated by the corresponding (apparent) complexation constants measured for the N-acetyl group by NMR. ($K = 55.1\ Mol^{-1}$) and for the N-methyl-nicotinylium moiety spectrophotometrically ($K = 19.3\ Mol^{-1}$). Whereas the monosaccharide association remains almost unchanged after substitution with the CT. acceptor, the latter constant is enhanced about 6-fold over that observed for the N(1)-methyl-nicotinamide ion/lysozyme Trp^{62} complex [1] [8]. It is therefore reasonable to assume that CT. interaction and NMR. shielding are produced simultaneously with one and the same ligand molecule. We take this as further evidence for chemically identical association of the NAG type inhibitors in the crystalline and dissolved phases of lysozyme.

Experimental. NMR. spectra were determined on *Varian* instruments (T-60; XL-100). Chemical shift measurements on the **2**/lysozyme complex were made at 100 MHz and 20°, using a sweep width of 100 Hz with acetone as internal reference and the solvent D_2O deuterium as lock signal. UV. spectra were recorded on a *Beckman* Acta V recording spectrophotometer at 20° in teflon-stoppered cells of 1 cm pathlength.

Methyl 2-acetamido-6-O-isonicotinyl-2-deoxy-β-D-glucopyranoside (**1**). To a solution of 0.47 g (2 mMol) methyl 2-acetamido-2-deoxy-β-D-glucopyranoside (prepared according to [11]) in 5 ml dry pyridine, a solution of 0.5 g (2.2 mMol) isonicotinic acid anhydride (*Fluka*) in 10 ml dry pyridine was added dropwise at 0° over a period of 5 h. After further 15 h at 20°, the solvent was removed *in vacuo*, and the residue extracted with methanol (10 ml). The insoluble nicotinic acid was filtered off, and the filtrate evaporated *in vacuo*. The residue was washed with ether to remove residual pyridine.

NMR. inspection in the solvents CD_3OD, D_2O/DCl, and C_5D_5N revealed the presence of 4 different compounds: a) unreacted educt, b) **1** (main component): its N-acetyl signal coincided with that of the educt in all solvents, but its glycosidic OCH_3 signal appeared upfield relative to educt in CD_3OD and D_2O/DCl, and downfield in C_5D_5N. c) **1a** (a minor component): its N-acetyl signal appeared upfield (0.1 ppm) relative to the others; the glycosidic OCH_3 signal was not detected separately. **1a** is probably a product bearing the isonicotinyl group on C(3)—O (close to N-acetyl). d) **1b** (a minor component): signal integration suggested the presence of two isonicotinyl groups, its N-acetyl signal coincided with that of educt and **1** in all solvents; its OCH_3 signal coincided with that of educt, but could be seen separately in C_5D_5N.

Two crystallizations from isopropyl alcohol removed both educt and **1a** (m.p. 236–238°, dec.), but about 25% of **1b** remained. Recrystallization from acetonitrile yielded a product containing about 50% **1b**: from the mother liquor, essentially pure **1** (with less than 5% **1b**) was obtained by crystallization from isopropyl alcohol. M.p. 238–239° (dec.). IR. in KBr discs: O—C=O at 1730, N—C=O at 1640 cm^{-1}.

Structural proof for **1** was obtained from NMR. The upfield shift of the OCH_3 signal (in CD_3OD and D_2O/DCl) relative to educt indicates that the isonicotinyl group can shield the OCH_3 group. Model studies show that this is in accord with the C(6)—O position of the substituent group. Furthermore, a downfield shift of the C(6)—H_2 signal is observed on protonation of the isonicotinyl group ($CD_3OD \rightarrow D_2O/DCl$), which is further evidence for C(6)—O substitution.

Methyl 2-acetamido-6-O-(N-methyl-isonicotinylium)-2-deoxy-β-D-glucopyranoside chloride (**2**). 170 mg **1** and 89 mg methyl iodide were dissolved in 4 ml dimethylformamide; after 15 h at 20°, **1** was separated as an oil by adding ether. Repeated crystallization from methanol/ether yielded 200 mg slightly hydroscopic, orange product, identified by NMR. (Fig. 1).

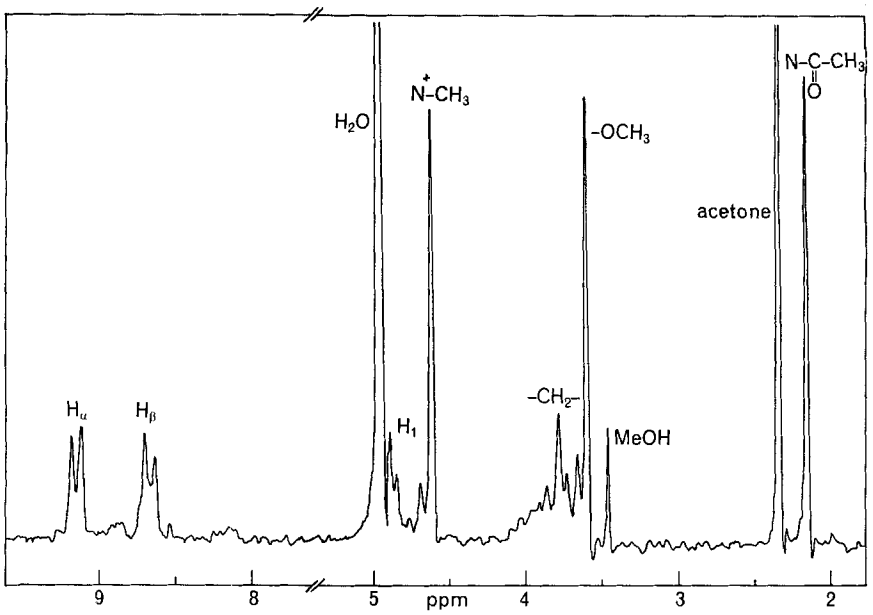


Fig. 1. *NMR. spectrum of* **2**, I^- (100 MHz, D_2O, reference internal acetone)

Samples of the iodide (53.8 mg) were dissolved in H_2O and filtered over a small column of anion exchanger (*Dowex* 21-k) in the Cl^--form. The eluate was lyophilized and 41 mg of **2**-chloride obtained as a hygroscopic, colourless product.

For *spectrophotometric titrations*, a cuvet was filled with 1.45 ml of a 5×10^{-3} M hen-egg-white lysozyme (*Sigma Chem. Comp.*, Grade 1, lot no. 110-8150) solution. To this, a solution of **2** (Cl^-) in 0.5 ml of the same lysozyme solution was added in small portions.

Results. – *NMR. measurements.* Association of **2** (I^-) with lysozyme was studied by the method of *Raftery* [10]. Lysozyme was titrated with **2** (I^-), and chemical shifts of various signals from **2** were measured relative to acetone as internal reference (Table 1). *Raftery* has shown that the shift of the N-acetyl signal (which can be

measured most precisely since it is close to the reference signal) can be used to estimate the association constant of the lysozyme inhibitor/complex. The expression used by *Raftery* is (1):

$$X_0 = P_0 \frac{\Delta_0}{\Delta} - \frac{1}{K} \tag{1}$$

wherein X_0 and P_0 are the analytical concentrations of ligand and protein, Δ and Δ_0 are the chemical shifts of the incompletely and completely complexed relative to the uncomplexed ligand. K is the association constant.

By plotting X_0 *versus* $^1/\Delta$ at constant P_0, both Δ_0 and K may be determined. This method has the disadvantage that plotting of $^1/\Delta$ values gives unequal statistical weight to the errors in determination of shifts at low and high Δ values. Expression (1) was therefore arranged to (2):

$$\Delta \cdot X_0 = -\frac{\Delta}{K} + P_0 \cdot \Delta_0 \tag{2}$$

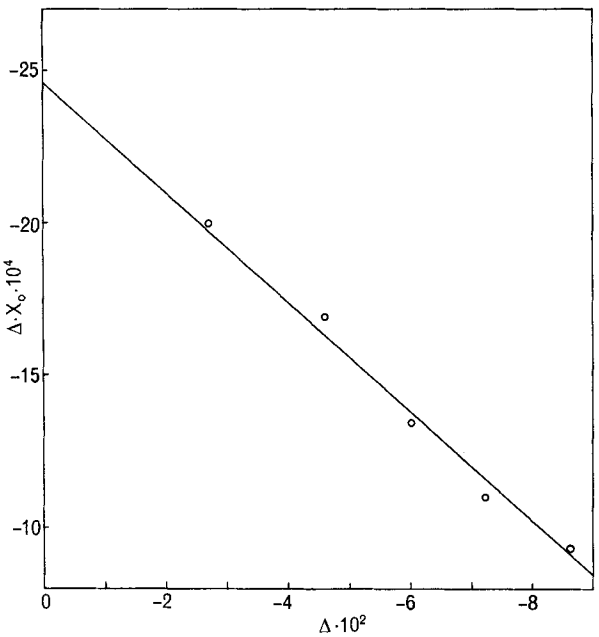


Fig. 2. *NMR. titration of lysozyme with* **2**, I^-. Plot of N-acetyl chemical shift data of Table 1 according to eq. (2)

By plotting $\Delta \cdot X_0$ *versus* Δ the following parameters were derived from least squares analysis (Fig. 2):

$$K = 55.1\ \text{Mol}^{-1};\ \Delta_0\ (COCH_3) = -0.49\ \text{ppm}$$

$$\text{correlation coefficient} = 0.993$$

(A plot according to *Raftery* gave essentially the same results).

The Δ_0 values of the other signals (Table 1) were derived by plotting their observed δ values *versus* those of the N-acetyl group (Fig. 3). Least squares analysis of these plots gave:

$$\Delta_0\,(OCH_3) = +0.17 \text{ ppm}; \Delta_0\,(H_\alpha) = -0.13 \text{ ppm}.$$

No significant shift was observed for the $N\text{–}CH_3$ signal.

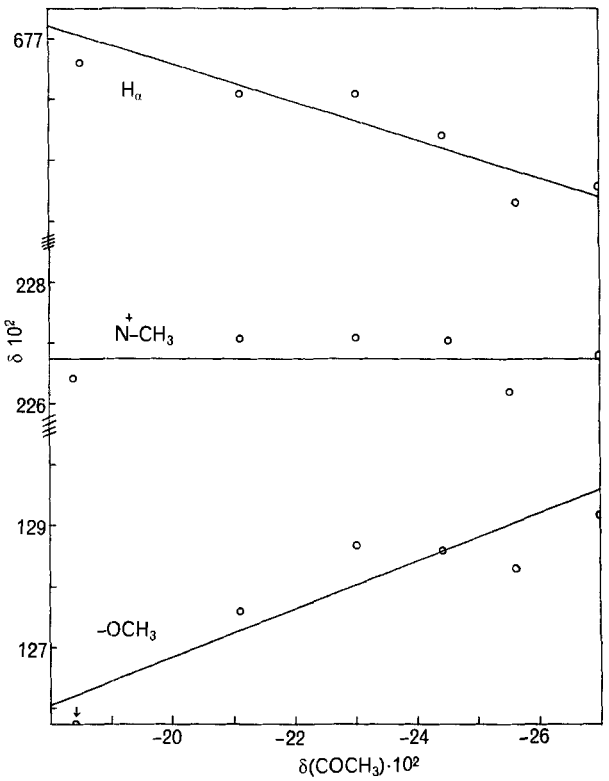


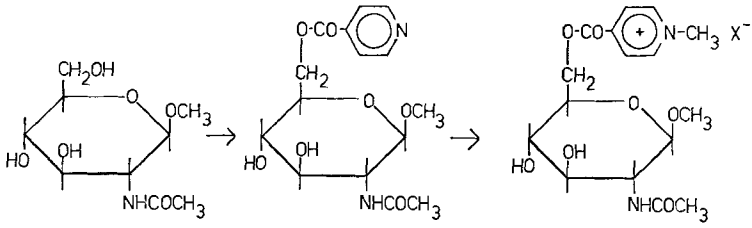
Fig. 3. *Determination of* $\Delta_0(OCH_3)$ *and* $\Delta_0(H_\alpha)$ *from the data of Table 1*

Spectrophotometric measurements. Since the weak CT. interaction of the iodide ion in **2** (I^-) disturbs spectrophotometric measurements, we used the chloride, **2** (Cl^-). Titration of 5×10^{-3} M aqueous lysozyme solution with **2** (Cl^-) gave a yellow colour, the intensity of which was monitored at 370 and 400 nm, according to the spectral characteristics of N(1)-methyl-isonicotinium amide/indole (tryptophan) complexes [1]. Results see Table 2.

The data were analyzed by a method analogous to the well-known *Scatchard* plot, but slightly modified to account for the fact that the condition $X_0 \gg P_0$ does not hold for all measurements. It can be shown [12] that for $X_0 \simeq P_0$ a modified expression (3) can be used:

$$\frac{A}{P_0X_0} = -K\frac{A(P_0 + X_0)}{P_0X_0} + K\varepsilon \qquad (3)$$

Synthetic scheme



1 **2** (X = I or Cl)

Table 1. *Chemical shift data on solutions of* **2** (I^-) *and lysozyme at 20° in* D_2O, lysozyme serving as its own buffer (pH = 4.95). All shifts, δ, relative to acetone; upfield shifts are indicated as negative (lower resonance frequency at constant magnetic field). Analytical concentrations: X_0 = [**2**]; P_0 = [lysozyme]. H_α is the hydrogen on C(2) and C(6) of the pyridinium ring

Concentration (M × 10^3)		Signal (δ in ppm)			
P_0	X_0	O ‖ C–CH_3	OCH_3	NCH_3	H^α
0	38	−0.184	+1.254	+2.264	+6.776
5	10.8	−0.270	+1.292	+2.268	+6.756
5	15.3	−0.256	+1.283	+2.262	+6.753
5	22.4	−0.244	+1.286	+2.271	+6.764
5	36.8	−0.230	+1.287	+2.271	+6.771
5	72.0	−0.211	+1.276	+2.271	+6.771

Table 2. *Absorption* ($A_{1\,cm}$) *of solutions containing a constant lysozyme concentration* ($P_0 = 5 \times 10^{-3}$ M) *and varying* **2** (Cl^-) *concentrations* (X_0) *in water at 20°*

X_0 (M × 10^{-3})	λ = 370 nm	λ = 400 nm
0	0.057	0.039
8.8	0.217	0.174
14.0	0.295	0.239
19.2	0.395	0.294
26.5	0.434	0.363
32.8	0.495	0.413
39.2	0.540	0.447
47.2	0.603	0.498

Least squares analysis of plots A/P_0X_0 *versus* $A(P_0 + X_0)/P_0X_0$ gave the following parameters (Fig. 4):

at 370 nm: K = 19.4 Mol^{-1}, ε = 238 (corr. coeff. 0.997)

at 400 nm: K = 19.2 Mol^{-1}, ε = 202 (corr. coeff. 0.998)

In Fig. 5, the absorption spectrum of the most concentrated titration solution is compared with the spectrum resulting from the interaction of **2** (Cl^-) with L-tryptophan methylester hydrochloride.

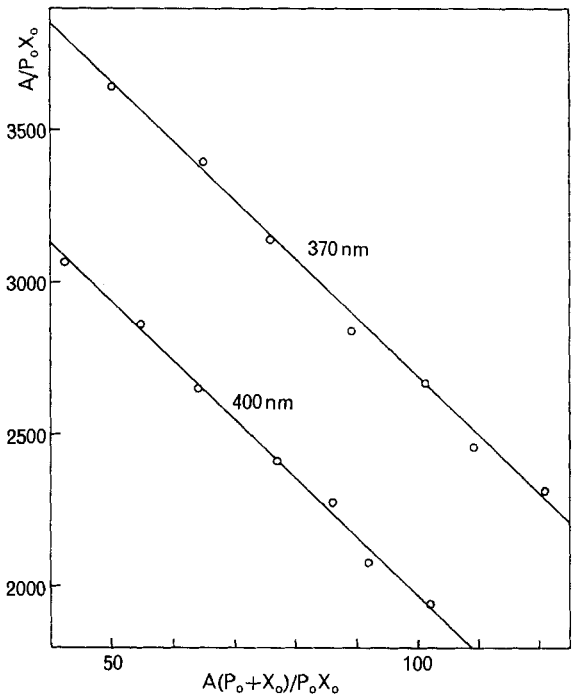


Fig. 4. *CT. titration of lysozyme with* **2**, Cl^-. Plot of absorption data of Table 2 according to eq. (3)

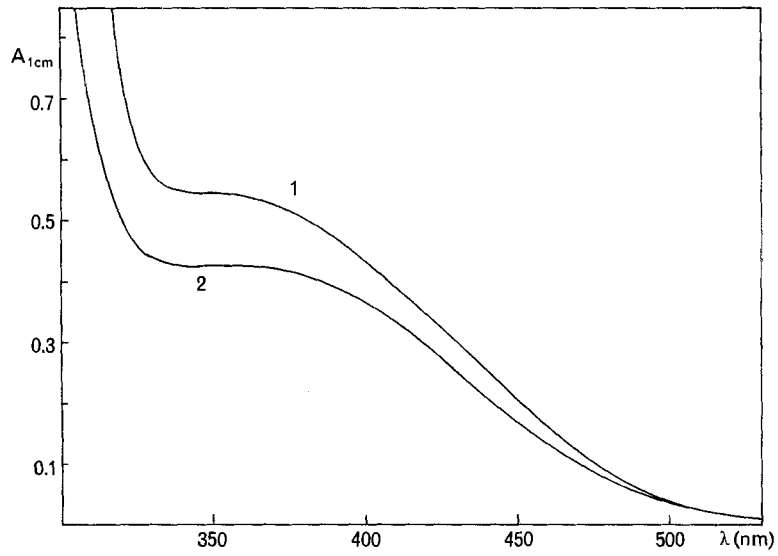


Fig. 5. *Long wavelength absorption spectra in* H_2O *at* pH 4.95. 47.2×10^{-3} M solutions of **2**, Cl^- with (1) 5×10^{-3} M lysozyme and (2) 5×10^{-3} M tryptophan methyl ester hydrochloride

Discussion. – In Table 3, the parameters determined by NMR. for the **2** (I^-): lysozyme complex are compared with those reported by *Raftery* [10] for the methyl 2-acetamido-2-deoxy-β-D-glucopyranoside: lysozyme complex under comparable conditions. Since the American authors have shown that the Δ_0 values are highly sensitive towards the mode of inhibitor/lysozyme binding, the remarkable correspondence between these parameters of the two complexes suggests analogous intermolecular contacts. The rather close similarity of the K values (NMR.) supports the view that the binding of **2** (I^-) to lysozyme is largely determined by association of its saccharide portion, and that complexation of the acceptor part plays a minor role. This was expected, because association constants (CT.) of pyridinium ions with lysozyme are small (about 3 Mol^{-1} [8]).

Table 3. *Parameters for complex formation of A)* **2** *(I^-)/lysozyme, and B) methyl 2-acetamido-2-deoxy-glucopyranoside/lysozyme* [**10**] *in D_2O at 20°* as derived from NMR. measurements

Complex	K(Mol^{-1})	$\Delta_0(COCH_3)$	$\Delta_0(OCH_3)$	$\Delta_0(H_\alpha)$	$\Delta_0(NCH_3)$
A	55.1	−0.49	+0.17	−0.13	0
B	44*)	−0.54 ± 0.04	+0.17 ± 0.03	–	–

*) Derived from the graph of log K *versus* 1/T in [10].

The data from the spectrophotometric titration of lysozyme with **2** (λ_{max} = 350 ± 5 nm, ε_{max} = 240 ± 20, K = 19.3 ± 0.2 Mol^{-1}) imply a CT. (electron donor/electron acceptor) interaction between the N-methyl-isonicotinylium group and a tryptophan residue (probably Trp^{62}) [1] [8]. The low ε value and the hypsochromic shift of the maximum relative to the intermolecular complex **2**: HCl, Trp-OMe (Fig. 5) suggest non-optimal complex geometry, *cf.* [13] [14]. Studies with molecular

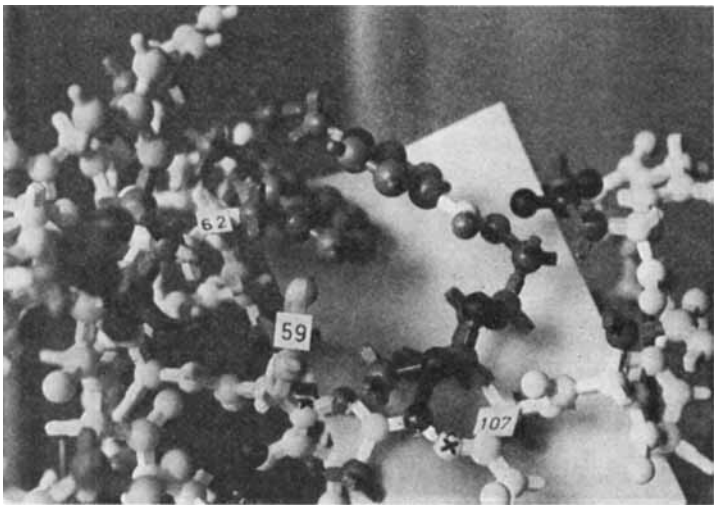


Fig. 6. *Model representation of the* **2** *ion lying in the lysozyme recognition site for NAG* (moiety NAG-*C* according to *Phillips* [9]). Acetyl amide group hydrogen bonded to Asn^{59} NH^{α} (x) and Ala^{107} CO (xx). N-Methylisonicotinium group in possible CT. interaction position with Trp^{62} indole. *Labquip* model (18, Rosehill Park Estate, Reading, UK)

models show that the distance between the N-methyl-isonicotinylium group of **2** and Trp^{62} varies strongly with rotation of the C(5)–C(6) and C(6)–O bonds; a closest contact of about 3–3.5 Å can be achieved (Fig. 6). The experimental ε_{max} might be a weighted average of ε_{max} values of different rotamers existing in a dynamic equilibrium, thus corresponding to the situation in simpler, intramolecular CT. complexes, *p.e. cyclo*-(6-carbamoyl-4-azonia)-phenylalanyl-tryptophyl chloride, *cyclo*-(9-carbamoyl-7-azonia)-trishomo-phenylalanyl chloride, and other, related L–L and L–D-diketopiperazines [14]. A rather large average distance between the electron donor and acceptor aromatic systems is also indicated by the comparatively small upfield shift ($\Delta_0 = -0.13$ ppm) of H_α in the complexed state. A shift of similar magnitude has been observed in [2,7-Orn(Pht)]-Gramicidin S and related, flexible *intramolecular* complexes [15], whereas *intermolecular* complexation of pyridinium ions with tryptophan derivatives leads to upfield shifts of 0.5–0.6 ppm for the pyridinium protons [14].

Although the association constant determined spectrophotometrically is definitely smaller than that determined by NMR. (for the N-acetyl-glucosamine moiety), it is still much larger than that of simple pyridinium/indole and pyridinium/lysozyme CT. complexes [8]. We believe that this is due to the fact that the N-methyl-isonicotinylium group of **2** is being held near the surface of the enzyme mainly by the association forces between lysozyme and the N-acetyl-glucosamine group of **2**. The reduction of the apparent K-value from 55.1 to 19.3 Mol^{-1} may be explained by the use of different assay procedures [16]. In fact, both of our values lie well within the range (15–65 Mol^{-1}) reported for N-acetylglucosamine : lysozyme binding as determined by various methods [10] [17].

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259. Pseudoasymmetrie in der organischen Chemie

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Herrn Prof. Dr. *A. Wettstein* zum 65. Geburtstag gewidmet

(21. VIII. 72)

Summary. The geometrical foundations of 'pseudoasymmetry' and several other related concepts of organic stereochemistry such as 'prochirality' and 'propseudoasymmetry' in two- and three-dimensional space have been explored. As a consequence some modifications of the *R,S*-system for specification of molecular chirality and stereoisomerism are proposed.

Mit dem Konzept des «asymmetrischen Kohlenstoffatoms» wollte *van't Hoff* zweierlei erreichen: anhand der Konstitutionsformel feststellen, ob eine Verbindung optisch aktiv sein kann und aus der Zahl der asymmetrischen Kohlenstoffatome die Zahl der möglichen Stereoisomeren ableiten [vgl. 1].

Die Wichtigkeit des *van't Hoff*'schen Konzeptes liegt nicht nur darin, dass man mit seiner Hilfe einen wesentlichen Teil (aber nicht das Gesamtgebiet!) der stereochemischen Statik behandeln kann, sondern dass es sich in verschiedener Hinsicht verallgemeinern lässt und dass es dadurch wegweisend für die Behandlung des gesamten Gebietes ist. In dieser Abhandlung wollen wir uns mit einem speziellen Problem auf diesem Gebiet, mit dem des «pseudoasymmetrischen Atoms» und mit der «Pseudoasymmetrie» im allgemeinen beschäftigen.

In der ersten Auflage seines Buches über die Lagerung der Atome im Raume [2] hat *van't Hoff* festgestellt, dass Verbindungen $C(R_1R_2R_3)C(R_4R_5)C(R_1R_2R_3)$ (Typus I) mit zwei konstitutionell gleichen, aber spiegelbildlichen asymmetrischen Kohlenstoffatomen «nicht in strengem Sinne symmetrisch sind». Erst *E. Fischer* hat auf Grund von Modellbetrachtungen die Zahl der möglichen Stereoisomeren für Verbindungen von diesem Typus richtig abgeleitet[1]).

[1]) Wir verweisen auf die Schilderung in seiner Autobiographie [3], wie er zusammen mit *A. von Baeyer* bei einem gemeinsamen Aufenthalt in Bordighera erfolglos versucht hat, das Problem zu lösen.