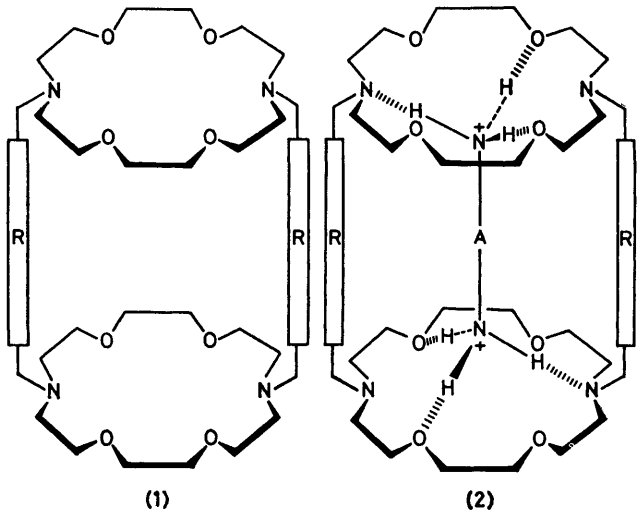
Dynamic Properties of Molecular Complexes and Receptor–Substrate Complementarity. Molecular Dynamics of Macrotricyclic Diammonium Cryptates

By JEAN-PIERRE KINTZINGER, FLORENCE KOTZYBA-HIBERT, JEAN-MARIE LEHN,* ALAIN PAGELOT, and KAZUHIKO SAIGO

(*Institut Le Bel, Université Louis Pasteur, 4 Rue Blaise Pascal, 67000 Strasbourg, France*)

Summary The correlation times of the diammonium cryptates of the macrotricyclic receptor molecules (**1a**—**d**) describe the molecular dynamics of these complexes and indicate that complementarity (steric fit) is reflected in dynamic coupling (dynamic fit) between receptor and substrate.

A MOLECULAR complex resulting from the binding of a substrate (σ) species to a receptor (ρ) molecule is defined not only by its classical features: structure, thermodynamic stability, and formation and dissociation kinetics, but also by its *dynamic cohesion*, *i.e.*, by the coupling between the molecular motions of the two (or more) entities of which it is composed.[1] Nuclear relaxation data provide an insight into local molecular motions, which may be divided into overall reorientations and internal segmental motions.[2] Extension of these methods to the investigation of molecular association[1,3,4] has shown that complexes of α-cyclodextrin present weak dynamic coupling between substrate and receptor.[1,4] The study of such dynamic coupling in molecular complexes may provide a means of testing *structural complementarity* between σ- and ρ-species, with strong or weak motional coupling depending on the degree of complementarity.[1]



This applies in particular to the recently described diammonium cryptates formed by several types of macrotricyclic[5,6] and macrotetracyclic[7] receptors, in which two macrocyclic subunits co-operate in substrate binding. In these inclusion complexes (**2**), $^{+}H_3N$–A–NH_3^{+} dications of various chain lengths are bound inside the polycyclic structure by interaction of each $-NH_3^{+}$ group with one of the two macrocyclic subunits of the ligand (**1**). Such cryptates have in particular been obtained with the macrotricycles (**1b**) and (**1c**), based on the [18]-N_2O_4 macrocyclic subunit.[6] We here extend these earlier studies to the new cryptands (**1a**) (m.p. 116 °C) and (**1d**) (m.p. 210 °C), obtained following the route published for (**1b**) and (**1c**),[6] and present results on the motional coupling in the diammonium cryptates of (**1a**—**d**). These receptor molecules provide a stepwise variation in cavity length by increasing the distance between the two macrocyclic binding sites.

The 250 MHz ^1H and 20·13 MHz ^{13}C n.m.r. spectra of compounds (**1a**—**d**) and of their diammonium cryptates with various substrate $\sigma = {}^{+}H_3N$–$[CH_2]_n$–NH_3^{+} dipicrates were measured. The nuclear relaxation times of all carbon atoms were determined, and the corresponding correlation times τ_c were calculated (Table). Relative segmental and intracomplex motions are described by the dynamic coupling coefficients[1] χ (Table).

(i) The free macrotricyles are approximately *isodynamic*; all carbon atoms have comparable correlation times, showing that their motions result from a similar combination of overall molecular reorientation and internal segmental motion. As expected, the molecules reorient more slowly as their size increases, τ_c (**1a**) < (**1b**) < (**1c**) < (**1d**).

(ii) As already observed,[6] complex formation with the ligands (**1a**—**d**), in which the aromatic residues form the walls of the internal cavity, produces *large upfield shifts* (up to 2·5 p.p.m.) for the CH_2 proton signals of the $^{+}H_3N$–$[CH_2]_n$–NH_3^{+} substrates (Figure). The shifts observed appear to be larger the better the fit between cavity size and substrate length. Indeed, molecular models show that the optimal substrates $^{+}H_3N$–$[CH_2]_n$–NH_3^{+} should have $n = 3$ for (**1a**), $n = 5$ for (**1b**), $n = 7$ for (**1c**), and $n = 10$ or 11 for (**1d**). Thus, the magnitude of the shifts is, at least to some extent, indicative of ρ–σ structural complementarity and chain-length selectivity of the tricyclic cryptands.

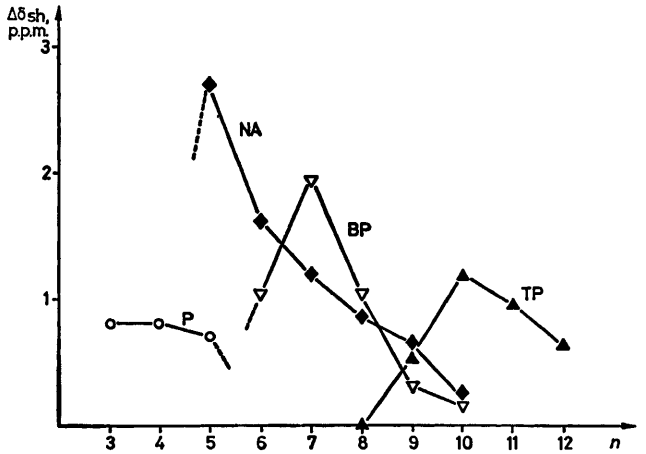


FIGURE. Largest upfield shift $\Delta\delta_{sh}$ observed for the substrates $^{+}H_3N$–$[CH_2]_n$–NH_3^{+} in the ^1H n.m.r. spectrum (250 MHz; 18 °C) of their complexes with a given receptor (**1a**) (P), (**1b**) (NA), (**1c**) (BP), and (**1d**) (TP), plotted against the chain length n. $\Delta\delta_{sh}$ is the chemical shift difference between the highest-field CH_2 signal in the complex and the reference value obtained for the same substrate when bound to two [18]–N_2O_4 macrocycles (see also Figure in ref. 6); for the longer substrates several CH_2 peaks may overlap; solvent $CDCl_3$–CD_3OD, 9:1. The dotted line indicates that the neighbouring substrate did not form a complex under the same conditions.

(iii) Complexation slows down the motions of the receptor by a factor of 2 or 3. The coefficient χ describing dynamic coupling between the motions of ρ and σ changes markedly from one ρ–σ pair to another. Restricting the analysis to the main features revealed by the τ_c and χ values, three types of behaviour (iv)—(vi) may be distinguished.

about the same [see for instance (**1b**) + σ (n = 7) and (**1d**) + σ (n = 12)].

(vi) Finally, in the case of the (**1c**) + σ (n = 9) and (**1d**) + σ (n = 8) complexes, the motions of ρ are significantly *slower*, whereas those of the substrate are *faster* than in the complexes with σ closer to optimal size. Also, in these

TABLE. Correlation times τ_c and dynamic coupling coefficients χ (in parentheses) obtained from C-13 relaxation times for the complexes of receptors (**1a**—**d**) with the diammonium substrates ^+H_3N–$[CH_2]_n$–NH_3^+.[a]

Receptor	Substrate	Receptor carbon atoms				Substrate carbon atoms					
	$^+NH_3$–$[CH_2]_n$–NH_3^+	CH_2Ar	CH_2N	CH_2O	Ar	CH_2 (1)	CH_2 (2)	CH_2 (3)	CH_2 (4)	CH_2 (5)	CH_2 (6)
(**1a**)	None	70	60	45	80						
	n = 3	110	110	95	120	105	105				
						(0·95)	(0·95)				
(**1b**)	None	75	60	50	85						
	n = 5	170	155	145	185	170	170	160			
						(1)	(1)	(0·94)			
	n = 6	175	160	145	175	135	125	120			
						(0·77)	(0·71)	(0·69)			
	n = 7	150	150	150	175	90	80	90	100		
						(0·60)	(0·53)	(0·60)	(0·67)		
(**1c**)	None	85	75	50	75						
	n = 7	170	170	145	145	155	135	150	140		
						(0·91)	(0·79)	(0·88)	(0·82)		
	n = 8	155	150	145	135	120	100	125	110		
						(0·77)	(0·65)	(0·81)	(0·71)		
	n = 9	230	230	210	205	90	110	95	70	80	
						(0·39)	(0·48)	(0·41)	(0·30)	(0·35)	
(**1d**)	None	140	100	90	105						
	n = 8	265	325	250	250	125	90	100	85		
						(0·47)	(0·34)	(0·38)	(0·32)		
	n = 9	200	200	200	145	155	90	85	105	105	
						(0·77)	(0·45)	(0·42)	(0·52)	(0·52)	
	n = 10	200	190	200	140	155	135	135	160	150	
						(0·77)	(0·67)	(0·67)	(0·80)	(0·75)	
	n = 11	200	200	190	140	160	100	90	90	90	110
						(0·80)	(0·50)	(0·45)	(0·45)	(0·45)	(0·55)
	n = 12	200	200	170	155	155	85	85	85	115	90
						(0·77)	(0·42)	(0·42)	(0·42)	(0·57)	(0·45)

[a] The ^{13}C relaxation n.m.r. spectra were recorded at 308 ± 2 K on a Bruker WP 80 SY spectrometer operating at a frequency of 20·13 MHz. The concentration of the solution was 0·05 M in 9 : 1 $CDCl_3$–CD_3OD. ^{13}C spin-lattice relaxation times T_1 were measured using the inversion recovery sequence (180, τ, 90, D) with $3T_1 \leqslant D \leqslant 5T_1$. The T_1 values were obtained by utilizing a 3-parameter non-linear least-squares fit (E. D. Becker, J. A. Ferretti, R. K. Gupta, and G. H. Weiss, *J. Magn. Reson.*, 1980, **37**, 381). The correlation times τ_c were calculated from the measured T_1 by the equation $T_1^{-1} = m\hbar^2\gamma_c^2\gamma_H^2\,\tau_c/r_{CH}^6 = m \times 2{\cdot}2 \times 10^{10}\,\tau_c$ where m is the number of protons bound to the carbon atom and r_{CH} the C–H bond length (1·085 Å); τ_c is given in picoseconds. The coupling coefficient $\chi = \tau_c(C_1)/\tau_c(ArCH_2N)$ at a given carbon atom C_1 is calculated with respect to the Ar CH_2N carbon atom taken arbitrarily as reference because it generally has the longest τ_c value. The substrates are dipicrate salts. The ^{13}C signals of the substrates are listed upfield from left to right; identification was often not clear: when signals overlap the same τ_c values are listed several times. An average value is listed for the relaxation times of the two OCH_2 carbons and for those of the aromatic carbons, since similar values were obtained within each type of signal. The correlation times of the picrate anions are much shorter (about 25—30 picoseconds) than those of the complex cations, indicating that cation–anion interaction does not lead to a dynamically tight ion pair.

(iv) The complementary ρ–σ pairs (**1a**) + σ (n = 3), (**1b**) + σ (n = 5), (**1c**) + σ (n = 7), and (**1d**) + σ (n = 10), display *strong dynamic coupling* (*isodynamic* ρ–σ *pair*). However, as the length of the optimal substrate chain increases, χ decreases [χ *ca.* 1 for (**1b**) + σ (n = 5), χ *ca.* 0·9—0·8 for (**1c**) + σ (n = 7), and χ *ca.* 0·8—0·7 for (**1d**) + σ (n = 10)], indicating that the chains of the bound substrate gain more internal flexibility as their length increases; one is tempted to relate this behaviour to the decrease in shelding observed for these species (Figure).

(v) When the substrate becomes either too short or too long χ decreases (<0·6), indicating a weakening of the cohesion of the complexes. The ρ–σ pair becomes *aniso-dynamic*; σ is less immobilized than in the case of the optimal pair, whereas the overall motions of ρ itself remain

cases weak or no shifts are observed for the ^1H n.m.r. signals of σ with respect to the reference. This might indicate that, when ligand and dication are ill fitting, complex species may form in which the substrate is bound, either internally or externally, by only one end group to a single macrocyclic unit of the ligand, leaving the other end free to participate in ion pairing and in the formation of larger molecular aggregates.

In conclusion, structural complementarity between ρ and σ in the present diammonium cryptates is reflected in the isodynamic character of the ρ–σ pair, leading to a '*dynamic fit*,' which results both from *steric fit* and from *dihapto-binding*, which maintains σ by anchoring its two end groups in the receptor. Thus, molecular dynamics studies provide important information about the nature of molecular

complexes and about ρ–σ complementarity. By extension, this applies also to cases where other data, such as chemical shift values, are not available.

We thank Dr. Christian Brevard and Bruker-Spectrospin S.A., Wissembourg, for extensive use of a WP 80 SY spectrometer.

(*Received, 1st May* 1981; *Com.* 522.)

[1] J. P. Behr and J. M. Lehn, *J. Am. Chem. Soc.*, 1976, **98**, 1743.
[2] J. R. Lyerla, Jr., and G. C. Levy, *Top. Carbon-13 Nucl. Magn. Reson. Spectrosc.*, 1974, **1**, 79; D. A. Wright, D. E. Axelson, and G. C. Levy, *ibid.*, 1979, **3**, 103 and references therein; Ch. Brevard, J. P. Kintzinger, and J. M. Lehn, *Tetrahedron*, 1972, **28**, 2429 and references therein; G. C. Levy, R. A. Komoroski, and J. A. Halstead, *J. Am. Chem. Soc.*, 1974, **96**, 5456; G. C. Levy and T. Terpstra, *Org. Magn. Reson.*, 1976, **8**, 658; W. F. Reynolds, P. Dais, A. Mar, and M. A. Winnick, *J. Chem. Soc., Chem. Commun.*, 1976, 757; R. Deslauriers and I. C. P. Smith, *Biopolymers*, 1977, **16**, 1245; G. C. Levy, M. P. Cordes, J. S. Lewis, and D. E. Axelson, *J. Am. Chem. Soc.*, 1977, **99**, 5492.
[3] Ch. Brevard and J. M. Lehn, *ibid.*, 1970, **92**, 4987.
[4] R. J. Bergeron and M. A. Channing, *J. Am. Chem. Soc.*, 1979, **101**, 2511.
[5] M. R. Johnson, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1979, 309; R. Mageswaran, S. Mageswaran, and I. O. Sutherland, *ibid.*, p. 722.
[6] F. Kotzyba-Hibert, J. M. Lehn, and P. Vierling, *Tetrahedron Lett.*, 1980, **21**, 941.
[7] F. Kotzyba-Hibert, J. M. Lehn, and K. Saigo, to be published.