Binding and Catalysis with a Metal-induced Ternary Complex of an Ethylenediamine-substituted Cyclodextrin[1]

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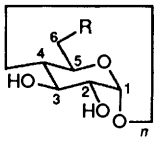
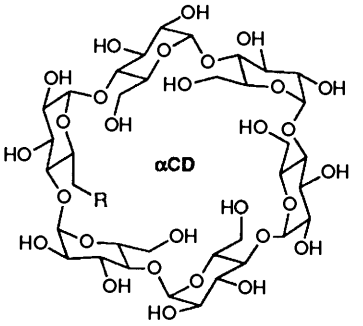
The binary complex ($CDen_2Cu$) from 6-(2-aminoethyl)amino-6-deoxy-β-cyclodextrin (CDen) and Cu^{2+} binds methyl orange (MO) about twice as efficiently as CDen alone, whereas brilliant yellow (BY), owing to the extended shape of this substrate, shows an approximately sevenfold increase in K. Deacylation of *p*-nitrophenyl benzoate (PNPB) shows, with an ethylenediamine model compound, the expected rate enhancement, which is retarded upon addition of sufficient Cu^{2+} to block the N lone pairs. In sharp contrast, deacylation of PNPB is accelerated by $CDen_2Cu$, whereas the 'shorter' *p*-nitrophenyl acetate (PNPA), being less suited to formation of a ternary inclusion complex, again exhibits a rate decrease. Catalytic rate constants k_c and Michaelis–Menten constants K_D are obtained from Lineweaver–Burk or Eadie plots; equilibrium constants for MO and BY have been studied at different wavelengths. The problems associated with the evaluation of the multiple variables in such equilibria are illustrated.

The ability of cyclodextrins to form binary complexes by inclusion of lipophilic guest molecules within their cavity[2] has already led to many reports on their use of enzyme-analogue catalysts,[3] in particular for acyl transfer and related reactions.[4] A further step towards mimicking enzyme functions can be attained by formation of ternary complexes, either with two substrates within the cavity,[5] or with one substrate inside, and a co-substrate, or an activating centre such as a metal ion outside the cavity.[6] The binding capacity can be substantially varied by coupling two cyclodextrins together, which has been done so far largely with the aid of *covalent* bonds between the cyclo-amyloses; the resulting CD dimers[6d,7] can exhibit binding constants exceeding 2×10^6 dm^3 mol^{-1}.[7c]

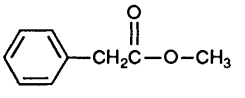
Our recent finding of strong allosteric binding of lipophilic substrates upon metal complexation[8] prompted us to look for a similar heterotopic cooperativity with CDs bearing ethylenediamine (CDen) as a transition-metal binding unit. Addition



αCD $n = 6$
βCD $n = 7$



CD (R=OH)
CDen (mono R=$NHCH_2CH_2NH_2$)



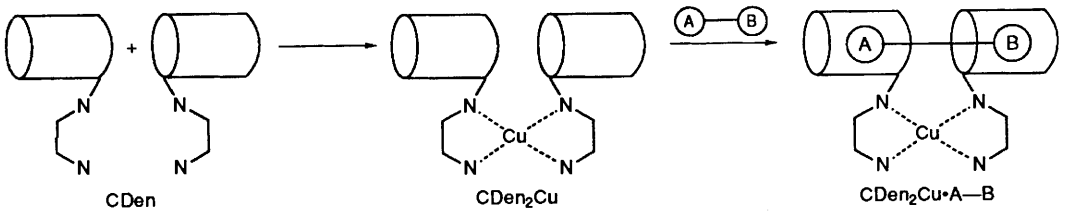
PAM

of, *e.g.* Cu^{2+} ions can be expected to lead to dimers which then should bind suitable substrates (A–B) more strongly than single CDs (Scheme 1). The presence of a metal ion close to a suitable function within the substrate A–B may furthermore catalyse reactions at this centre in such a ternary metalloenzyme-analogue complex. Such a system has in fact already been devised by Matsui *et al.*[6d] who observed, for furoin oxidations, up to 4.7-fold rate enhancements by β-$CDen_2Cu$. We wanted to explore the ternary complex principle (Scheme 1) both with respect to binding and to catalysis, using substrates, which, due to their 'longer' or 'shorter' shape are expected to show larger or smaller effects.

Results and Discussion

Binding Studies.—As a 'longer' substrate which could simultaneously fill both cavities of a ternary CDenCu complex we selected the azo-dye brilliant yellow (BY), which, to our knowledge, has not previously been studied with CDs. Methyl orange (MO), as a 'normal' substrate, has been measured several times with β-CD itself, however with quite variable equilibrium constants [in ($K \times 10^3$)] units: 2.6,[9d] 2.8,[9e] 3.0,[7c] 3.8,[9c] 4.5[9a]]. As we have shown recently[10] such variations are quite common, and are largely the result of additional complexes, such as 1:2 with K_2, or of 1:1 complexes with different conformations. These complications require at least measurements at several different wavelengths and the use of evaluation procedures which can handle several complexes simultaneously.

Although excellent computer curve fitting was usually obtained with the applied procedures[9] only the four variables to be determined for 1:1 and 1:2 complexes of CD and CDen (K_1, K_2, extinction coefficients E_1 and E_2) showed satisfactory convergence and relatively little dependence on the UV wavelength chosen. Table 1 contains a selection of best K values from measurements at the lowest and the highest wavelength at which the extinction still changed sufficiently during the UV titrations. Similar K values to those from variations of all four variables (procedure *d* in Table 1) were obtained by first calculating K_1 at lower host concentrations, and then K_2 by varying the host at higher concentrations, keeping the first-determined K_1 constant in the curve fitting (procedures *b* and *c* in Table 1). The constants thus obtained for MO with βCD agree well with the only available literature evaluation of K_1 *and* K_2 as does K_1 for CD (Table 1). The remaining wavelength dependence, particularly of the small K_2 values (Table 1), could, in principle, only be removed by taking into account further equilibria, which was considered to be impractical in view of the large number of variables. This holds even more for the K evaluation with the $CDen_xCu$ complexes, which contain CDen, CDenCu, and $CDen_2Cu$ in variable concentrations, which in the presence of the guest compounds

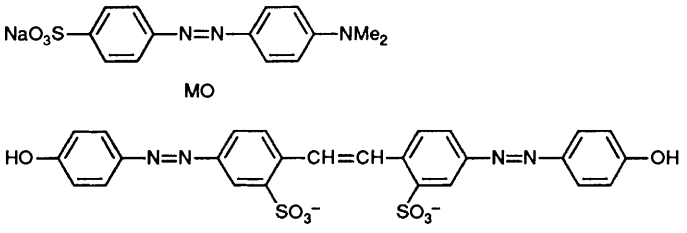


Scheme 1 The concept for formation of a metal-induced ternary complex

Table 1 Complexation constants K^a with methyl orange (MO) and brilliant yellow (BY)

System			$K_{av}/10^3$	$K/10^3$ 490 mm	$K/10^3$ 530 nm
MO + CD	1:1	K_1[b]	3.1	3.15	3.12
		[ref. 7(*c*):	3.0	—	—]
	1:2	K_2[c]	0.6	0.3	0.6
		[ref. 7(*c*):	0.6	—	—]
MO + CDen	1:1	K_1[b]	2.2	2.1	2.3
	1:1	K_1[d]	2.4	2.5	2.6
	1:2	K_2[d]	0.005	0.003	0.006
MO + $CDen_2Cu$	1:1	K_1[e]	3.2	2.9	3.4
	1:1	K_1[f]	7.7	6.8	8.4
	1:1	K_1[d]	4.6	5.2	4.8
	1:2	K_2[d]	0.01	0.005	0.015
MO + α-CD	1:1	K_1[b]	8.8	8.3	9.0
		[ref. 9(*b*)	7.84	—	—]
BY + CD	1:1	K_1	2.1	2.1 (470)	2.0 (550)
	1:2	K_2[c]	0.001	0.0006 (470)	0.002 (550)
BY + CDen	1:1	K_1[e]	1.8	1.7 (460)	2.1 (490)[g]
		K_2[c,h]	0.5	0.0006 (460)	0.002 (490)
BY + $CDen_2Cu$	1:1	K_1[e]	7.6	7.1 (440)	7.4 (510)
		K_1[f]	16	15.6 (440)	16.3 (510)
	1:2	K_2[c,h]	0.01	0.02 (470)	0.002 (510)[g]

[a] K in $dm^3\ mol^{-1}$ for binary (K_1) complexes, in $dm^6\ mol^{-2}$ for ternary (K_2) complexes. Measurements at pH 10.0 (0.05 mol dm^{-3} carbonate buffer) at (25.0 + 0.1) °C; evaluation of K based on extinction changes at usually 10 different wavelengths (490 and 530 are representative values only); see the text. The K_{av} values are rounded corresponding to the single K values obtained from best-fit procedures. [b] From fitting to a single 1:1 complex at low concentration of CD: MO (5.52–2.94) × 10^{-5} mol dm^{-3} and CD (0–1.41) × 10^{-3} mol dm^{-3}; MO (6.17–3.27) × 10^{-5} mol dm^{-3} and CDen (0–2.4) × 10^{-3} mol dm^{-3}; MO (6.17–2.98) × 10^{-5} mol dm^{-3} and α-CD (0–6.3) × 10^{-4} mol dm^{-3}; BY (1.51–0.71) × 10^{-5} mol dm^{-3} and CD (0–8.0) × 10^{-3}mol dm^{-3}; BY (1.51–0.76) × 10^{-6} mol dm^{-3} and CDen (0–0.002) mol dm^{-3}. [c] From fitting to 1:1 + 1:2 complexes with K_1 from *b*. Measurements at high concentrations of CD: MO (5.52–3.03) × 10^{-5} mol dm^{-3} and CD (0–6.79) × 10^{-3} mol dm^{-3}; MO (5.75–2.88) × 10^{-5} mol dm^{-3} and CDen (0–9.98) × 10^{-3} mol dm^{-3}; BY (1.51–0.71) × 10^{-5} mol dm^{-3} and CD (0–8.0) × 10^{-3} mol dm^{-3}; BY (1.51–0.72) × 10^{-5} mol dm^{-3} and CDen (0–0.01) mol dm^{-3}. [d] From repeated fitting to 1:1 + 1:2 complexes until change of K was minimized. [e] From 1:1 fitting assuming $[CDen_nCu] = [CDen]_{total}$. [f] From 1:1 fitting assuming $[CDen_2Cu] = \frac{1}{2}[CDen]_{total}$. [g] Range limited because of small extinction changes above 500 nm. [h] Tentative values, see the text.



MO
with CDen: $K_1 = 2.2 \times 10^3$ $K_2 \approx 5$
$CDen_2Cu$: $K_1 \approx 4.6 \times 10^3$ $K_2 \approx 10$

BY
with CDen: $K_1 = 1.8 \times 10^3$ $K_2 \approx 1$
$CDen_2Cu$: $K_1 \approx 7.6 \times 10^3$ $K_2 \approx 10$

Scheme 2 Significant complexation constants (from Table 1)

cannot be calculated with sufficient accuracy, particularly in view of only preliminary[6d] Cu complexation constants available. Therefore the ternary complexation constants were evaluated by assuming either CDenCu or $CDen_2Cu$ to be equal to the total CDen concentration (procedures *e*, *f* in Table 1); consequently the resulting K_1 values differed by a factor of 2, which still allowed us to draw conclusions with respect to the significant differences between binding of MO and BY (Scheme 2): the metal-induced dimerization of CDen units leads as expected to a considerably smaller K_1 increase for MO as compared with the longer BY.

Kinetic Results.—For the convenience of automatic measurements *p*-nitrophenol esters were chosen as substrates, in the form of the acetate (PNPA), as a 'shorter' guest, and the benzoate (PNPB) as a 'longer' guest compound. In a ternary complex (Scheme 1) the proximity of a metal ion, such as Cu^{2+}, to an ester function can lead to catalysis of acyl transfer, be it by Lewis acid carbonyl activation or by water activation *via* metal hydroxide.[10] This opens up the possibility of a *switchable catalyst* in which both stabilization of the ground state (ternary complex binding) visible in the Michaelis–Menten K_D constants, as well as of the transition state (visible in the k_{cat} of saturation kinetics) is brought about by transition-metal complexation.

Table 2 Deacylation/hydrolysis kinetics[a]

Entry		$k_{cat}/10^{-2}$ s^{-1} E	$k_{cat}/10^{-2}$ s^{-1} LB	$K_D/10^{-3}$ dm^3 mol^{-1} E	$K_D/10^{-3}$ dm^3 mol^{-1} LB	ψ(%) E	ψ(%) LB
	PNPA						
1	CDen	44.2	45.3	14.1	14.5	2.7	0.02
2	CDenCu	11.8	12.9	8.2	9.2	21	0.25
3	$CDen_2Cu$[b]	21.6	21.9	4.16	4.25	0.74	0.04
4	CD	6.8	6.9	6.8	7.0	0.45	0.00
5	Prop-en	k_2 = 2.13 dm^3 mol^{-1} s^{-1}		ψ = 0.17%			
6	Prop-en_2Cu[c]	k_2 = 0.72		ψ = 4.1%			
	PNPB						
7	CDen	3.7	3.8	2.53	2.61	0.45	0.02
8	CDenCu[d]	7.44	7.55	6.51	6.62	0.12	0.00
9	$CDen_2Cu$	5.5[e]	5.9[e]	1.35	1.55	13	2.2
10	CD	0.49	0.49	1.95	2.00	0.39	0.06
11	Prop-en	k_2 = 0.54 dm^3 mol^{-1} s^{-1}		ψ = 0.17%			
12	Prop-en_2Cu[c]	k_2 = 0.16		ψ = 3.6%			

[a] Measured at pH 10.7 (0.04 mol dm^{-3} Na_2CO_3 + 0.01 mol dm^{-3} $NaHCO_3$ buffer) at (25 + 0.1) °C. Catalytic rate constants k_{cat} and Michaelis–Menten constants K_D obtained from Eadie (E) or Lineweaver–Burk (LB) linearizations, usually from 7 pseudo-first-order rates at concentrations between 0.5 and 4.0 × 10^{-3} mol dm^{-3} for CDen and $CDen_2Cu$, and 0.5 and 5.0 × 10^{-3} mol dm^{-3} for CD. Correlation quality ψ [%] of the E or LB plots; linear coefficients $r \geq 0.99$ (except Eadie plot entry 2 (r = 0.928) and entry 9 (r = 0.954). Second-order rate constants k_2 (linear dependence of k_{obs} on C) observed with Prop-en ($H_3CCH_2CH_2$–NH–CH_2CH_2–NH_2) and its Cu complexes (the latter showing some non-linearity by rate decrease owing to the presence of more free amine at low concentrations; k_2 evaluated from initial slope). [b] Evaluated with four k_{obs} values (three points at lower concentrations omitted), assuming $[CDen_nCu] = \frac{1}{2}[CDen]_{total}$. [c] Assuming $[Prop\text{-}en_2Cu] = [Prop\text{-}en]_{total}$. [d] As *b*, but with $[CDen_nCu] = [CDen]_{total}$ = 0.5–2.0 × 10^{-3} mol dm^{-3}. [e] Evaluated from 5 k_{obs} values; assuming $[CDen_2Cu] = \frac{1}{2}[CDen]_{total}$.

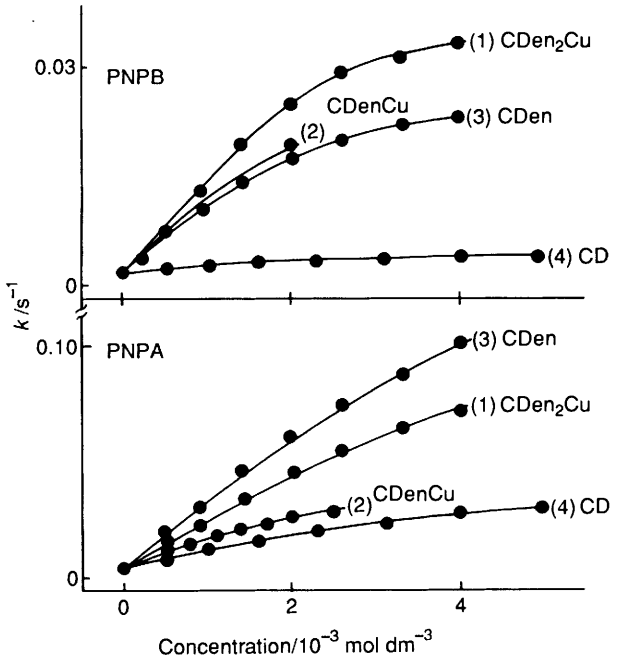
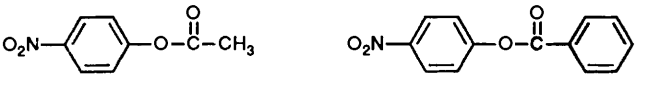


Fig. 1 Plots of observed pseudo-first-order rate constants (k) *vs.* molar concentrations (C) of catalysts; for conditions see footnotes to Table 2. The concentration scale for measurements with $CDen_2Cu$ is expanded by a factor of two; the curve with CDenCu is limited by the low solubility of this complex.

The photometrically measured liberation of *p*-nitrophenol from the esters always showed clean (pseudo-) first-order kinetics; the observed rate constants k_{obs} were followed at different concentrations of catalysts (or co-substrates) C and showed typical saturation kinetics (Fig. 1) with the exception of the diamines Prop–en and its copper complex Prop-en_2Cu. These were studied as model compounds in view of the similarly available nitrogen atoms in CDen to which the acyl group can transfer owing to its higher nucleophilicity. Prop-en reacts with both esters in a clean second-order reaction, which is slowed



PNPA PNPB

	PNPA k_c/k_o	PNPA $K_o \times 10^3$	PNPA k_c/K_o	PNPB k_c/k_o	PNPB $K_D \times 10^3$	PNPB k_c/K_D
CDen	79	14	31	19	2.5	15
CDenCu	21	8.5	14	39	6.5	11
$CDen_2Cu$	39	7	52	29	1.5	41
k_{anCu}/k_{cn}	0.34 (reverse!)			0.30 (Cu blocks N Lp's)		
Max. obs. rate increase (corrected)	≈ 1.6°			≈ 6.0°		

Scheme 3 Selection of catalytic constants (from Table 2)

down by a factor of *ca.* 3 upon addition of Cu^{2+} owing to blocking of the N lone pairs (Table 2). Similar behaviour is observed with PNPA, whereas, in contrast, addition of Cu^{2+} to CDen leads to *rate acceleration* (Table 2, Scheme 3), indicating that this more space-filling substrate can indeed form a productive ternary complex as envisaged in Scheme 1. If we correct for the negative effect of Cu^{2+} on the usual reactivity of ethylenediamine (factor of 3, see above), the maximum observed rate constant increase is *ca.* 6 for PNPB, but only *ca.* 1.6 for PNPA.

The extraction of the enzyme-analogue Michaelis–Menten K_D and k_{cat} constants from the observed saturation kinetics[11] is hampered, similarly to the binding analysis with the azo dyes, by too many variables for the catalysis by the copper complexes. Whereas the CDen-catalysed reaction showed clean linearity both with Eadie (E) and with Lineweaver–Burk (LB) plots, it was usually necessary to omit some k_{obs} values measured at higher $CDen_nCu$ concentrations, in particular for the Eadie treatment. As in the binding analyses, the $CDen_nCu$ concentrations were set equal to the total CDen concentrations. As a result the K_D and k_c constants thus obtained are only tentative (Table 2), but represent rather a *lower* limit for the performance of these catalysts with PNPB, as the efficiency of the copper-free CDen present in the solution is lower than that of $CDen_nCu$.

Table 3 Deacylation/hydrolysis kinetics with an unactivated ester (phenylacetic acid methyl ester)[a]

		[C]/10^{-4} mol dm^{-3}	k_{obs}/10^{-6} s^{-1}	(k_{obs}/[C]) × 100
1	CDen	0.98	2.31	2.4
2	Prop-en	0.98	2.39	2.4
3	Prop-en + Cu	20.2	6.31	0.43
		14.7		
4	Prop-en + Cu	0.98	3.34	3.4
5	CDen × Cu	0.98	4.51	4.6
6	CDen × Cu	9.8	15.0	1.5
		0.98	3.15	3.2
7	CDen + Cu	0.49		
8	(Prop-en)(en)Co^{3+} [b]	1.6	2.4	0.23
9	(CDen)(en)Co^{3+} [c]	3.93	2.63	0.67
10	no catalyst	—	2.43	—

[a] Measured at pH = 7.0 (0.1 mol dm^{-3} NaCl; 2% CH_3OH; [substrate] = 0.010 mol dm^{-3}) at (60.0 + 0.1) °C; reactions followed up to, usually, 2–5% conversion (pseudo-first-order assumed); [C] = cosubstrate or catalyst. [b] From Prop-en + Co^{3+}(en)$(NH_3)(NO_2)_3$ (J. I. Bailar Jr. and J. B. Work, *J. Am. Chem. Soc.*, 1946, **68**, 232). [c] Similar to *b* but with CDen (W. E. Cooley, C. F. Liu and J. C. Bailar Jr., *J. Am. Chem. Soc.*, 1959, **81**, 4189).

The calculated Michaelis–Menten constants (Table 2) show that the better performance with PNP**B** is largely due to the lower K_D values, as envisaged in the concept of metal-induced ternary complex stabilization.

Non-activated esters in contrast with *p*-nitrophenyl esters, have been shown to undergo catalysis by some copper complexes *more* efficiently.[10] Stimulated by this we have also measured hydrolysis rates of phenylacetic acid methyl ester (PAM), which, however, showed only very small accelerations with CDen, the Prop-en model compounds and the corresponding copper complexes, as did alternative cobalt(II) (Co^{2+}) complexes (Table 3). This is in line with the very special Cu^{2+} co-ordination found to be necessary[10] for a high activity with non-activated esters.

Conclusions

Both the binding and the kinetic studies validate the concept of formation of a metal-induced ternary complex with appropriately shaped substrates. The copper(II)-induced dimerization of two cyclodextrin units leads to particularly strong inclusion of a long azo dye substrate, as well as to higher K_D values in the Michaelis–Menten kinetics, whereas the catalytic rate constants k_{cat} are less affected. The relatively small magnitude of both the thermodynamic and the kinetic effects must be the consequence of a ternary complex geometry which is far from being ideal. Any misalignment between the rather rigid metal complex and the substrate is at the expense of additional strain energy. As with other synthetic ternary complexes[5c] only a few of the many complex conformations will be productive, whereas nature has gone to the expense of optimizing the geometries in corresponding enzyme–substrate systems.

Experimental

Binding constants were evaluated under the conditions given in Table 1 by UV spectroscopic titrations at, usually, *ca.* 10 different wavelengths (range, see Table 1), as described earlier for 1:1 complexes[12] and for 1:1 + 1:2 complexes;[9] for details see footnotes to Table 1.

Kinetic measurements were performed for PNPA and PNPB reactions (Table 2) by following the extinction at λ = 400 nm (Kontron Uvikon 860; appearance of *p*-nitrophenolate) with automatic data registration and processing using microcomputer programs for non-linear regression; the reactions showed linear first-order kinetics over several half-lives. The much slower PAM ester reaction (Table 3) was measured usually only up to 5% conversion with an automatic pH-stat technique (Metrohm E 373 with accessories) using 0.01 mol dm^{-3} NaOH as titrant.

6-(2-Aminoethyl)amino-6-deoxy-β-cyclodextrin (CDen) was obtained similarly to the literature[6d,13] from the corresponding tosylate[13a] δ_H([$^2H_6$]DMSO) 7.76, 7.74 (d, Ar-H_1 2 H), 7.45, 7.43 (d, Ar-H, 2 H), 4.84 (s, CH_3, 3 H) (lit.,[6d] δ 7.44 and 4.8); δ_C ([$^2H_6$]DMSO) 144.6, 133.0, 129.7, 127.4, 101.8 (C-1), 81.5 (C-4); 72.9, 72.3, 71.9 (C-2, C-3, C-5); 59.8 (C-6); 21.0 (CH_3).

The CDen[6d] from the tosylate reaction with excess ethylenediamine showed, after chromatography, no impurity by NMR spectroscopy $\delta_H(D_2O)$ 4.96 (s, H-1, 7 H), 3.73–3.85 (m, H-6, H-3, H-5, 28 H), 3.47–3.55 (m, H-2, H-4, 14 H), 2.57–2.69 (m, NCH_2, 4 H); $\delta_C(D_2O)$ 101.1 (C-1), 80.5 (C-4), 71.3, 71.4, 72.5 (C-2, C-3, C-5), 59.7 (C-6), 48.4 (CNH–), 39.1 (CNH_2); and smaller signals at δ 100.9, 82.9, 69.6, 49.5.

Acknowledgements

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