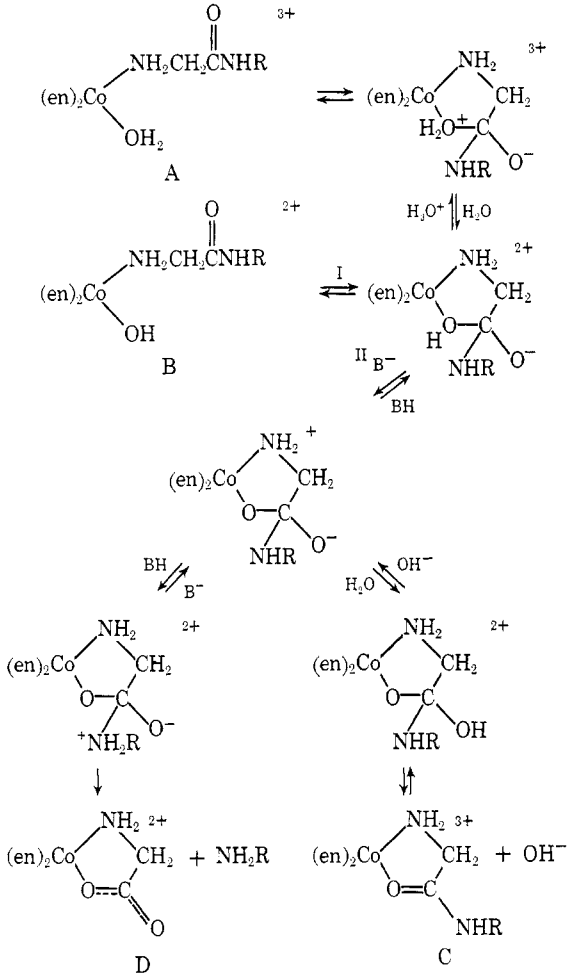
Scheme I



hydroxide ion can be a potent nucleophile for a carbonyl substrate even though the metal significantly reduces their basicity (*~10⁹ for OH⁻*).

The interrelation of the intramolecular hydrolysis of *cis*-$[Co(en)_2OH(glyNHR)]^{2+}$ and the intermolecular hydrolysis of $[Co(en)_2(glyNHR)]^{3+}$ by OH^- [2] is supported by the fact that the former reaction produces $[Co(en)_2(glyNHR)]^{3+}$ as well as the hydrolyzed product. A common intermediate, or set of intermediates, appears to be required. The observation of a similar Co(III) aminocarbinol intermediate which divides to chelated ester and chelated amide in the aminolysis of an amino acid ester[9] supports this claim. Amine loss follows the order $NH_3 > NH_2CH_2CO_2^- > NH_2CH_2CO_2C_3H_7$ (Table I), the order of decreasing basicity, and supports the contention that the amine leaving group is protonated. The same product ratio is found with both the aquo and hydroxo reactants in the absence of added buffer (Table I, pH 4 and 8) which supports the involvement of a single common intermediate leading to products. Also, for the hydrolysis of *cis*-$[Co(en)_2OH(glyglyOC_3H_7)]^{2+}$ in 0.1 *M* phosphate buffer at pH 7.4, 87% of $[Co(en)_2glyO]^{2+}$ is formed, compared with 45% at the same pH in the absence of buffer. This is consistent with general acid catalysis for the loss of amine and its relative absence for loss of OH. These observations are accommodated in the mechanism shown in Scheme I.

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It is proposed that the rate determining step for the intramolecular hydrolysis occurs in the proton abstraction step, II. This may be concerted accompanying I, but, since most of the bases used have pK_a's outside the range spanned by the substrate hydroxo ($pK_a \sim 20$ est) and the immediate addition product ($pK_a \sim 6$ est), we contend that a stepwise process will be preferred by all but very strong bases.[10] For bases of $pK_a > 6$ proton abstraction II becomes diffusion controlled, $k = 10^9$–10^{10}[B] sec^{-1}, with every contact leading to deprotonation. Thus, HPO_4^{2-}, PO_4^{3-}, and OH^- are equally effective ($k_{obsd}/[B] \simeq 0.1\ M^{-1}\ sec^{-1}$, Brønsted $\beta = 0$) whereas for maleate, succinate, acetate, tartrate, and furoate the second-order rate constant decreases linearly with decreasing pK_a, $\beta = 0.75$. Reprotonation by BH is unfavorable and the chelated amide C hydrolyzes to D with no B being formed. This latter reaction is not general base or acid catalyzed consistent with intermolecular attack of OH^- being rate determining.

We are at present extending these mechanistic aspects and are continuing our study of the source of the large activation.

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Stereochemistry of Oxidative Addition of Alkyl Halides to Palladium(0) Complexes

Sir:

The stereochemistry of oxidative addition[1] of alkyl halides to the transition metals of group VIII can provide information as to which of the many possible mechanisms is operative. The addition of alkyl halides to d^8 iridium complexes has been reported to proceed with retention,[2] inversion,[3] and racemization.[4,5] The racemization was proposed to proceed *via* a free-radical mechanism at the asymmetric carbon center. The kinetics of this reaction are consistent with nucleophilic displacement by iridium on carbon.[6] Similar oxidative additions of alkyl halides to d^8 cobalt have been reported to occur with inversion of configuration at carbon.[7] In the oxidative addition of silicon compounds to d^8 and d^{10} platinum,[8–10] d^8 iridium,[10] and cobalt,[10] however, retention of configuration at silicon was exclusively observed.

Oxidative addition reactions[11] of certain alkyl and

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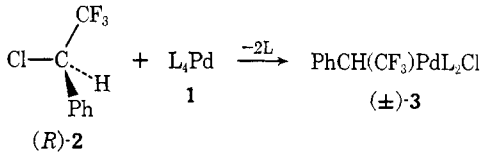
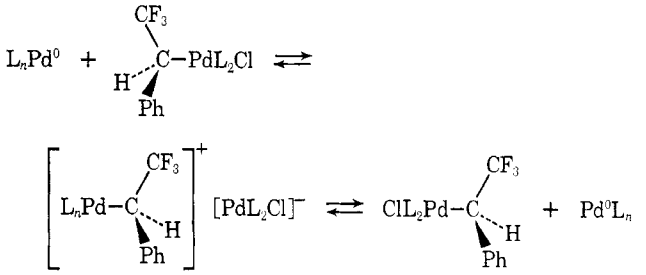
acyl halides with the d^{10} complex tetrakis(triphenylphosphine)palladium(0) (**1**) proceed rapidly under mild conditions to give *trans*-haloalkyl- or *trans*-haloacyl(triphenylphosphine)palladium(II) complexes. In a preliminary study[12] on the stereochemical details of oxidative addition of alkyl halides to palladium(0), chiral 1-phenyl-2,2,2-trifluoroethyl chloride (**2**)[13] was found to add to **1** affording a stable complex, **3**, which exhibited little or no optical rotation.



$L = PPh_3$

Although a reversible σ–π rearrangement[14] or a free-radical process[15] could account for the observed racemization, an alternative explanation may be that in solution an exchange reaction takes place *via* nucleophilic displacement by a palladium(0) species at the asymmetric carbon bound to palladium(II) in **3**. A

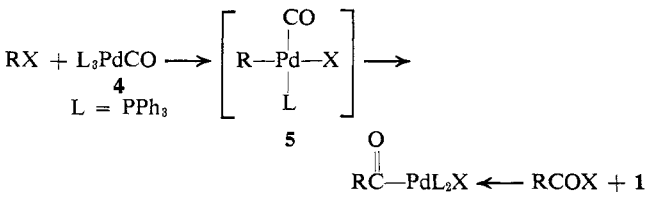


$L = PPh_3$

$n = 2$–4

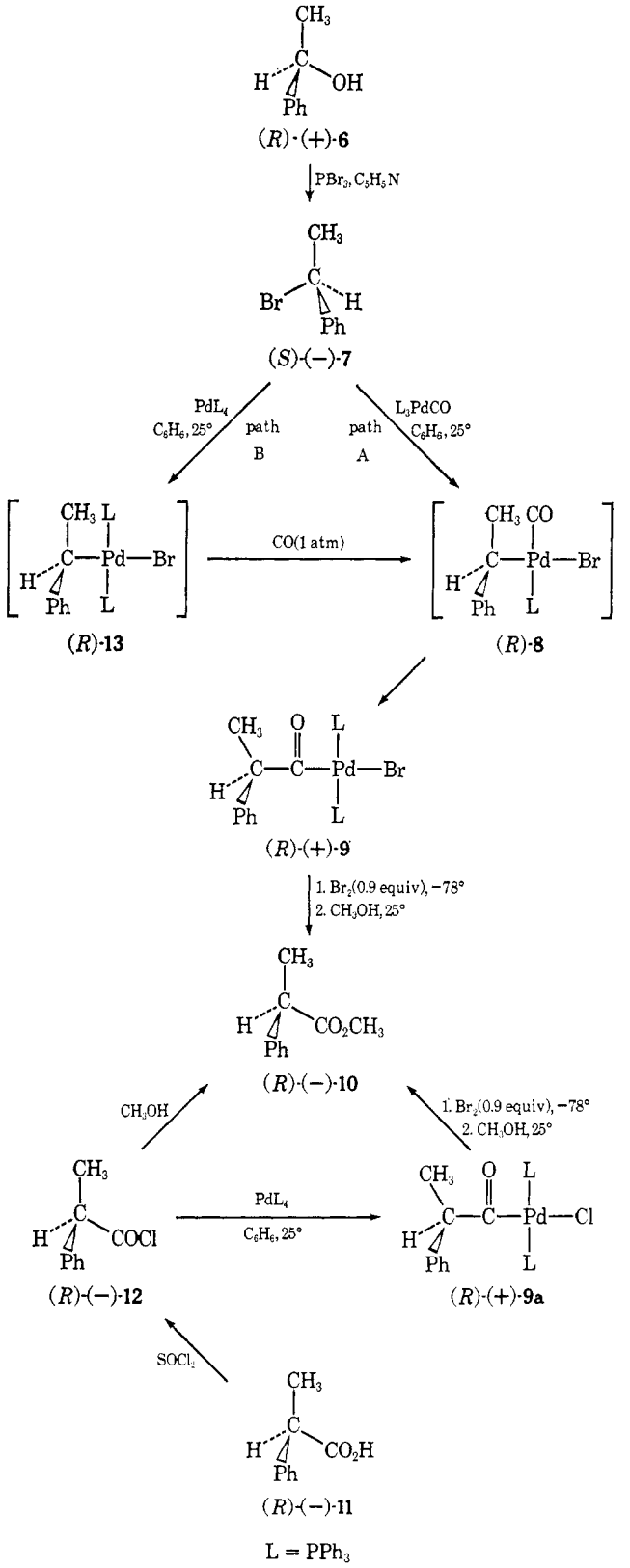
rapid carbon monoxide "insertion" into the palladium–carbon σ bond in **3**, however, could possibly prevent racemization.

Carbonyltris(triphenylphosphine)palladium(0)[16–19] (**4**) also undergoes oxidative addition reactions with a variety of organic halides to afford acylpalladium complexes which can alternatively be prepared by the oxidative addition of acyl halides to **1**.



It has been postulated[18] that this reaction proceeds initially by ligand dissociation to leave a coordinatively unsaturated species which then allows facile oxidative addition of the alkyl halide, generating intermediate **5**. A subsequent *intramolecular* carbon monoxide "insertion" affords the stable acylpalladium complex. If ligand migration occurs faster than β elimination,[20] then it would be likely that alkyl halides containing β-hydrogens could add to complex

Scheme I[a]



$L = PPh_3$

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Table I

Compound	Configuration	Observed specific rotation	Rotation of pure compound	% Optical purity
6	*R*(+)	$[\alpha]^{27}D$ +42.53 ± 0.02° (neat) $[\alpha]^{27}D$ +53.3 ± 0.8° ($CHCl_3$)	$[\alpha]^{27}D$ + 43.43° (neat)[a] $[\alpha]^{27}D$ +54.4° ($CHCl_3$)	98.0
7 (for path A)	*S*(−)	$[\alpha]^{25}D$ −90.8 ± 0.7° ($CHCl_3$)	$[\alpha]^{27}D$ −125.1° (neat)[b] $[\alpha]^{27}D$ −111.5° ($CHCl_3$)[c]	81.4
9 (path A) (78.4% yield)	*R*(+)	$[\alpha]^{27}D$ +32 ± 2° ($CHCl_3$)		
10 (from **9**) (path A)	*R*(−)	$[\alpha]^{27}D$ −59.6 ± 1.1° ($CHCl_3$)	$[\alpha]^{26}D$ −88.20° ($CHCl_3$)[d,e]	67.6
11	*R*(−)	$[\alpha]^{25}D$ −69.8 ± 0.5° ($CHCl_3$) $[\alpha]^{25}D$ −93.8 ± 0.2° (neat)	$[\alpha]^{25}D$ −75.8° ($CHCl_3$)[f] $[\alpha]^{25}D$ −101.9° (neat)	92.1
12	*R*(−)	$[\alpha]^{25}D$ −72.6 ± 0.3° ($CHCl_3$) $[\alpha]^{26.5}D$ −68.5 ± 0.4° ($CHCl_3$)		
9a	*R*(+)	$[\alpha]^{26.5}D$ +62.1 ± 0.8° ($CHCl_3$)		
10 (from **12**)	*R*(−)	$[\alpha]^{25}D$ −79.0 ± 0.7° ($CHCl_3$)	$[\alpha]^{26}D$ −88.20° ($CHCl_3$)	89.6
10 (from **9a**)	*R*(−)	$[\alpha]^{25}D$ −75.2 ± 1.0° ($CHCl_3$)	$[\alpha]^{26}D$ −88.20° ($CHCl_3$)	85.3
7 (for path B)	*S*(−)	$[\alpha]^{26}D$ −75.8 ± 0.3° ($CHCl_3$)	$[\alpha]^{27}D$ −111.5° ($CHCl_3$)	68.0
9 (path B) (92.0% yield	*R*(+)	$[\alpha]^{27}D$ +36 ± 1° ($CHCl_3$)		
10 (from **9**) (path B)	*R*(−)	$[\alpha]^{27}D$ −55.3 ± 0.7° ($CHCl_3$)	$[\alpha]^{26}D$ −88.20° ($CHCl_3$)	62.7

[a] Calculated using the value of $[\alpha]^{25}D$ 43.45 ± 0.10° (neat)[22] and assuming a linear relationship of $d[\alpha]^tD/dt = 0.012°/°C$. R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911); **105**, 1115 (1914). [b] Calculated from the value of 170°,[24] allowing for the density of **7** (d^{27} = 1.3584).[22] [c] Calculated based on the observation that a synthetic sample of optically active (*S*)-**7** gave $[\alpha]^{27}D$ = −78.7 ± 0.2° ($CHCl_3$) and $[\alpha]^{27}D$ −88.2 ± 0.1° (neat). [d] Determined by chiral nmr shift reagent method.[36-40] Enantiomeric ratios were calculated from peak areas of the methyl doublets. Area approximation was carried out comparatively by peak height and peak area measurements. Both methods agreed within 1%. [e] Values previously reported for optically pure **10** are as follows: $[\alpha]^{29}D$ 96.3° (neat)[27]; $[\alpha]^{27}D$ 109.2° (C_6H_6), $[\alpha]^{20}D$ 99.8° (ethanol), $[\alpha]^{23}D$ 98.8° (ethanol), $[\alpha]^{20}D$ 105.5° (neat)[28]; $[\alpha]^{21}D$ 99.4° (neat)[29]; $[M]^{25}D$ 170° (methanol) or $[\alpha]^{25}D$ 103.7° (methanol).[34] [f] The highest reported values for the pure acid are $[\alpha]^{25}D$ 76.3 ($CHCl_3$)[32] and $[\alpha]^{25}D$ 75.3° ($CHCl_3$).[31] 75.8° is the average of these values.

4 to afford acylpalladium complexes. Unfortunately **2** does not undergo facile oxidative addition to **4**.

Optically active (*R*)-(+)-α-phenethyl alcohol (**6**)[21,22] was converted to its (*S*)-(−)-bromide **7**[23-25] which underwent oxidative addition to **4** to afford a dextrorotatory[26] acylpalladium complex **9** (ir ($CHCl_3$) 1670 (C=O), (Nujol) 283 cm^{-1} (Pd–Br, trans to acyl)) (Scheme I). Complex **9** was then subjected to a bromine cleavage–methanolysis sequence to yield the known (*R*)-(−)-methyl α-phenylpropionate (**10**).[26,27-29]

The chloro analog **9a** of complex **9** was independently synthesized from optically active β-phenylpropionic acid (**11**)[30-34] *via* the corresponding acid chloride **12**.[32] Since the reaction of **12** with **1** does not involve the chiral center, complex **9a** then unequivocally has the *R* configuration. In addition, since carbon monoxide "inserts" into the palladium–carbon σ bond with 100% retention of configuration at carbon,[35] the oxidative addition step (**7** → **8**) must therefore involve *an inversion of configuration at carbon*. The absolute optical purity of **10** (Table I) was determined by nmr analysis using a chiral chemical shift reagent,[36-40] Eu(tfac)$_3$ (tfac = 3-trifluoroacetyl-*d*-camphorato anion). Assuming no loss of optical purity in the **12** → **10** conversion, the extent of racemization during the **11** → **12** transformation was therefore only 2.7% (compare **10** *vs.* **12**, Table I). The acyl complex **9a** (obtained from **12**) therefore was 89.6% optically pure, since the reaction **12** → **9a** does not involve the chiral center. Consequently, a net loss of optical activity of 4.8% in the **9a** → **10** step was realized. Allowing 4.8% racemization for the conversion of **9** to **10**, an optical purity of 71.0% can be assigned to **9**. The **7** → **8** → **9** transformation must encompass a net loss of optical activity from 81.4 to 71.0%. Since the carbon monoxide "insertion" step (**8** → **9**) is 100% stereospecific (*vide supra*), the conversion of **7** → **8** must be approximately 90% stereospecific.

Interestingly, the reaction (path B) between (*S*)-(−)-**7**[25] and **1** in a carbon monoxide atmosphere also led to the formation of the dextrorotatory acyl complex **9**, which was then degraded to the ester (*R*)-(−)-**10**. This reaction proceeds *via* the initial oxidative addition of **7** to **1** affording the alkylpalladium complex **13**, which undergoes carbon monoxide "insertion" to afford **9**. The "insertion" in this case occurs much more rapidly than β elimination. Again, since the "insertion" step occurs with 100% retention of configuration, the addition of **7** to **1** must take place with

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inversion of configuration. Allowing a 4.8% racemization for the chemical degradation of complex **9**, the stereospecificity of the oxidation step (**7** → **9**) was determined to be approximately 95% (compare the last three entries in Table I).

Inversion of configuration at the chiral carbon during the oxidative addition of **7** to either **1** or **4** suggests an SN2-type mechanism in which palladium(0) serves as a nucleophile. In the reaction of **7** and **4**, an alternative mechanism involving direct nucleophilic attack by the carbonyl group seems unlikely since metal carbonyls are known to be reactive toward bases.[41] Finally, invocation of a three- or four-centered mechanism which also allows pseudorotation to give configurational inversion is considered improbable on steric grounds.

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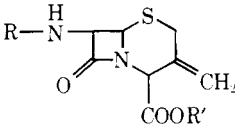
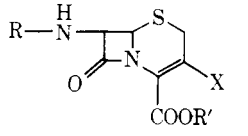
Chemistry of Cephalosporin Antibiotics. XXIX.[1] 3-Halo- and 3-Methoxy-3-cephems

Sir:

We have recently reported on the preparation of 3-methylenecephams[2] (**1a**) from cephalosporanic acids. Esters of 3-methylenecephams are isomerized to 3-methyl-3-cephems (**2a**), intermediates in syntheses[3] of cephalexin (**2b**, R = $C_6H_5CH(NH_2)CO$, R′ = H). Further exploration of the chemistry of 3-methylenecephams has led to the preparation of a new series of potent antibiotics having in common an electronegative heteroatom substitutent directly attached to the 3-position of the 3-cephem ring system.



1a, b



2a–c, X = CH_3 **5a, b**, X = Br
3a, b, X = OH **6a–c**, X = OCH_3
4a–c, X = Cl **7a**, X = CH_2OCOCH_3

The key step in the preparation of these new antibiotics is a low temperature ozonolysis of the 3-exomethylene function in esters of 3-methylenecephams to produce a 3-"oxo"-cephalosporin.[4] Thus, *p*-nitrobenzyl 7-amino-3-methylenecepham-4-carboxylate hydrochloride (**1b**, R = H·HCl, R′ = *p*-NB) with ozone in CH_3OH at −80°, followed by addition of sulfur dioxide, afforded a 75% yield of a crystalline (from acetone) 3-"oxo"-nucleus ester hydrochloride, mp 150–180° dec. The free amino ester (crystalline from EtOAc) was characterized as *p*-nitrobenzyl 7-amino-3-hydroxy-3-cephem-4-carboxylate (**3a**, R = H, R′ = *p*-NB) by elemental analysis and the following data. Uv spectrum (pH 7 phosphate buffer) showed λ_{max} 278 nm (ϵ 13,700) consistent with 3-cephem unsaturation or enol form of the 3-"oxo" derivative. In further support of an enol–keto equilibrium, this uv maximum reversibly decreased in intensity at low pH. The nmr spectrum (DMSO-d_6) showed signals at τ 6.22 (ABq, 2 H, C2–H_2) as well as all other signals expected for the proposed 3-hydroxy-3-cephem structure. Electrometric titration (66% aqueous DMF) showed pK_a values of 4.0 and 6.3, consistent with amino and enolic hydroxyl groups.

Acylation of the 3-hydroxy nucleus ester hydrochloride (**3a**) with thiophene-2-acetyl chloride in aqueous acetone solution containing excess $NaHCO_3$ gave *p*-nitrobenzyl 7-(thiophene-2-acetamido)-3-hydroxy-3-cephem-4-carboxylate (**3b**, R = thiophen-2-ylacetyl, R′ = *p*-NB) in nearly quantitative yield. The uv spectrum of **3b** (CH_3CN) showed λ_{max} 238 and 268 nm (ϵ 16,850 and 14,750, respectively). The nmr spectrum ($CDCl_3$) showed signals at τ 6.60 (s, 2 H, C2–H_2), 6.13 (s, 2 H, α-CH_2), 4.96 (d, 1 H, C6–H), 4.62 (d, 2 H, ester–CH_2), 4.46 (q, 1 H, C7–H), and 3.1–1.7 (m, 8 H, aromatic H and C7–NH). The pK_a of the 3-enolic OH was found to be 5.9 by titration (66% aqueous DMF).

Compound **3b**, with freshly distilled $SOCl_2$ in dry DMF at room temperature, gave *p*-nitrobenzyl 7-(thiophene-2-acetamido)-3-chloro-3-cephem-4-carboxylate (**4a**, R = thiophen-2-ylacetyl, R′ = *p*-NB) in 61% yield, mp 164–166°, crystallized from EtOAc–ether. Similarly, compound **3b** reacted with PBr_3 in DMF to give the corresponding 3-bromo-3-cephem derivative (**5a**, R = thiophen-2-ylacetyl, R′ = *p*-NB).

On treatment with PCl_5 and dry pyridine in CH_2Cl_2 at room temperature, compound **4a** undergoes imino-chloride formation at C7-amide and subsequent side-chain cleavage.[5] The resulting 3-chloro nucleus ester (**4c**, R = H·HCl, R′ = *p*-NB) crystallized as a hydrochloride directly from the reaction mixture in 49% yield, mp 168° dec. Compound **4c** with a variety of acid chlorides or mixed anhydrides gave a series of 3-chloro-3-cephem derivatives.[6]

The 3-hydroxy nucleus ester hydrochloride (**3a**) reacted with diazomethane[4] at room temperature in THF solution containing 1 mol of triethylamine. In this

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