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INFLUENCE OF STRUCTURE ON THE ISOMERIZATION OF DIALKYLAMINOALKYLBENZOTRIAZOLES

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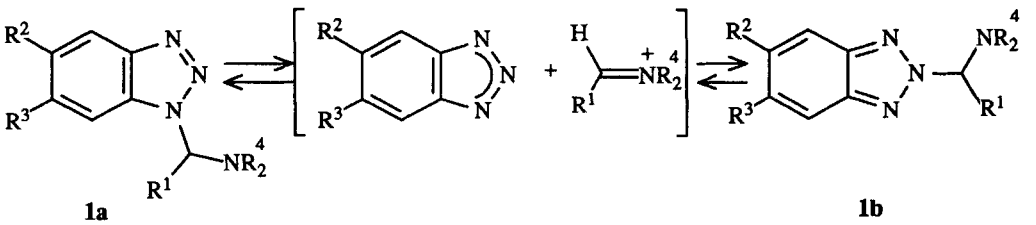
The N-1 to N-2 substituent isomerization in a series of 4-methyl and 4,7-dimethyl-*N*-(α-morpholinoalkyl)benzotriazoles and in 1,5-bis(morpholinomethyl)benzo[1,2-*d*:4,5-*d'*]bistriazole was studied and the influence of the structure on this process was evaluated.

INTRODUCTION

The spontaneous interconversion of benzotriazole adducts of type **1** (R^1 = H, aryl or alkyl) between forms **a** and **b** (Scheme 1) is well know.[1,2] The electronic and steric effects of the substituents R^1–R^4 and the effects of the solvent polarity on this isomerization have been studied extensively in our laboratory,[3] with results fully consistent with the proposed ionic intermolecular mechanism (Scheme 1).

In most of the cases studied, the 1-substituted benzotriazoles **1a** are the predominant components in the equilibrium mixtures. However, bulky R^1 and/or R^4 substituents and non-polar solvents favor the 2-isomers **1b**, and in extreme cases **1b** can become the lowest energy species.[3] With the specific objective of studying the effects of substitution in the benzene ring at the positions adjacent to the nitrogen atoms, we have now extended our studies to such Mannich adducts substituted in the 4 and in the 4,7-positions of the benzotriazole ring and to those from benzobistriazoles.



1a **1b**

Scheme 1

RESULTS AND DISCUSSION

Preparation and characterization of the adducts

The benzotriazole adducts **4–7**, **9** and **10** were prepared by a known method[1] from morpholine, the appropriate aldehyde and 4-methyl- (**2**), 4,7-dimethyl- (**3**) or 5,6-dimethylbenzotriazole (Schemes 2 and 3). Preparative details and elemental analyses for the products are presented in Table 1. The assignments of the ^{1}H NMR spectra (Table 2) and the ^{13}C NMR spectra (Table 3) are based on our previous work on similar adducts.[3]

4-Methylbenzotriazole (**2**), which has been described previously[4] but not adequately characterized, was prepared in two steps. Commercially available 2-methyl-6-nitroaniline was reduced to 2,3-diaminotoluene, which was then converted to **2** using the standard literature procedure for the preparation of a benzotriazole.[5] The synthesis of 4,7-dimethylbenzotriazole (**3**) was more laborious: 2,5-dimethylaniline was converted to 3,6-dimethylbenzene-1,2-diamine in four steps, using a method reported for similar compounds,[6] and then cyclized[7] to **3**.

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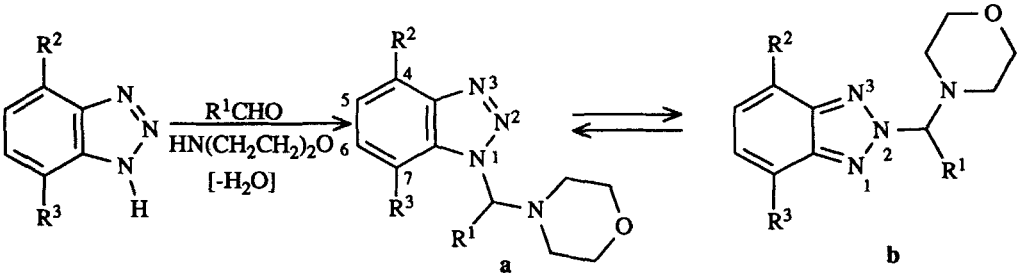


2 $R^2 = Me$, $R^3 = H$

3 $R^2 = R^3 = Me$

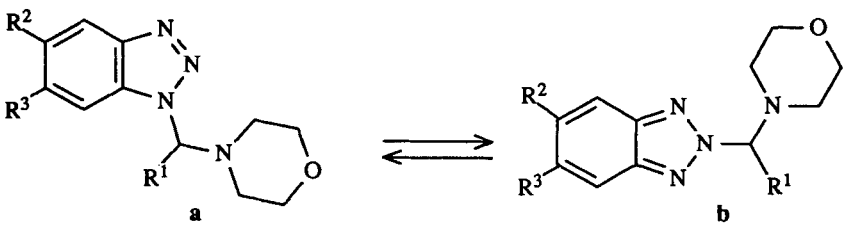
4 $R^1 = H$, $R^2 = Me$, $R^3 = H$

5 $R^1 = i\text{-Pr}$, $R^2 = Me$, $R^3 = H$

6 $R^1 = H$, $R^2 = Me$, $R^3 = Me$

7 $R^1 = i\text{-Pr}$, $R^2 = Me$, $R^3 = Me$

Scheme 2



8 $R^1 = R^2 = R^3 = H$

9 $R^1 = H$, $R^2 = R^3 = Me$

10 $R^1 = i\text{-Pr}$, $R^2 = R^3 = Me$

Scheme 3

Table 1. Preparation of compounds 4–7 and 9–11

Compound	R^1	R^2	R^3	M.p. (°C)	Yield (%)	Found (%)			Molecular formula	Required (%)		
						C	H	N		C	H	N
4	H	Me	H	Oil	93	M^+ 232·1310			$C_{12}H_{16}N_4O$	M^+ 232·1324		
5	*i*-Pr	Me	H	90–94	62	M^+ 274·1801			$C_{15}H_{22}N_4O$	M^+ 274·1793		
6	H	Me	Me	110–114	72	63·56	7·40	22·90	$C_{13}H_{18}N_4O$	63·39	7·37	22·75
7	*i*-Pr	Me	Me	84–90	36	66·15	8·39	19·66	$C_{16}H_{24}N_4O$	66·63	8·39	19·43
9	H	Me	Me	144–146	71	63·04	7·31	22·95	$C_{13}H_{18}N_4O$	63·39	7·37	22·75
10	*i*-Pr	Me	Me	120–124	72	66·29	8·42	19·54	$C_{16}H_{24}N_4O$	66·64	8·39	19·43
11	—	—	—	214–218	92	53·38	6·20	—	$C_{16}H_{22}N_8O_2$	53·62	6·19	—

Benzo[1,2-*d*:4,5-*d'*]bistriazole was prepared according to the literature method[8,9] and was reacted with morpholine and formaldehyde in methanol to afford adduct **11** in good yield. According to the ^1H and ^{13}C NMR spectra, **11** exists in solution as a mixture of the three interconverting 1,1'- (**11a**), 1,2'- (**11b**) and 1,3'- (**11c**) isomers (Scheme 4). The assignment of the spectra was made according to data previously published for the three individually characterized isomeric compounds 1,7-, 1,6- and 1,5-diaminobenzo[1,2-*d*:4,5-*d'*]bistriazole.[9]

Table 2. ^{1}H NMR spectra (300 MHz, $CDCl_3$, TMS) of adducts **4–7**, **9** and **10**

Compound	R^1	R^2	R^3	CH	Morpholine	Benzotriazole ring
1-Isomers:						
4	—	2·80[a]	—	5·40	3·69,[b] 2·75[b]	7·75–7·12[b]
5	3·05,[b] 1·23,[d] 0·63[d]	2·82[a]	—	4·95[c]	3·71,[b] 2·64[b]	7·72–7·11[c]
6	—	2·62[a]	2·62[a]	5·33[a]	3·70,[b] 2·74[b]	7·10[f]
7	—	—	—	—	—	—
9		2·43[a]	2·41[a]	5·35[c]	3·69,[b] 2·70[b]	7·79,[a] 7·34[a]
10	3·04,[b] 1·18,[d] 0·65[d]	2·43[a]	2·41[a]	4·95[c]	3·66,[b] 2·61[b]	7·81,[a] 7·29[a]
2-Isomers:						
4	—	2·78[a]	—	5·53	3·69, 2·65	7·75–7·12[b]
5	2·95,[b] 1·19,[d] 0·67[d]	2·68[a]	—	5·09[c]	3·71,[b] 2·59[b]	7·72–7·11[c]
6	—	2·62[a]	2·62[a]	5·54[a]	3·71,[b] 2·74[b]	7·03[a]
7	2·93,[b] 1·18,[d] 0·67[d]	2·62[a]	2·62[a]	5·09[c]	3·69,[c] 2·63[b]	7·01[a]
9	—	2·41[a]	2·41[a]	5·47[a]	3·69,[b] 2·63[b]	7·61[a]
10	2·87,[b] 1·22,[d] 0·62[d]	2·41[a]	2·41[a]	5·01[c]	3·66,[b] 2·61[b]	7·62[a]

[a] Singlet.
[b] Multiplet.
[c] d, J = 10 Hz.
[d] d, J = 7 Hz, Me.
[e] Four muptiplets.
[f] d, J = 6 Hz.

Table 3. ^{13}C NMR spectra (300 MHz, $CDCl_3$, TMS) of adducts **4–7**, **9** and **10**

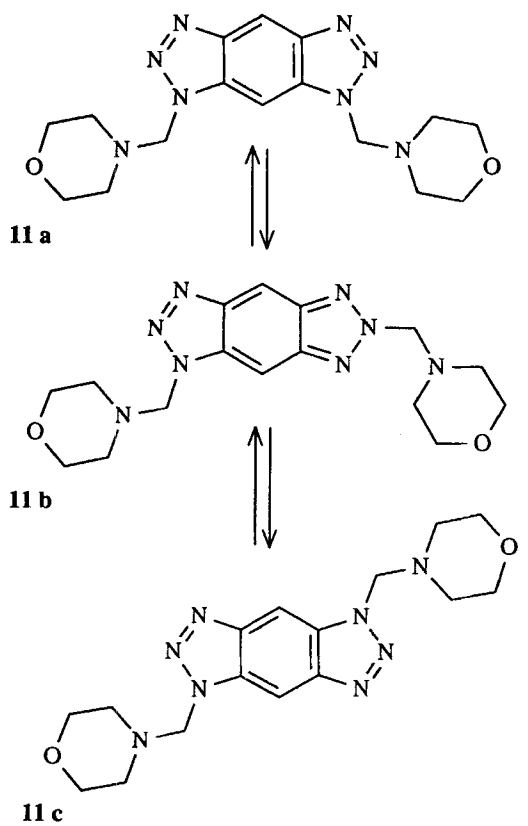
Compound	R^1	R^2	R^3	CH	Morpholine	Benzotriazole ring
1-Isomers:						
4	—	16·6	—	69·2	66·5, 50·4	146·0, 134·0,[a] 127·5, 126·6,[a] 123·7, 107·0
5	28·6, 19·2,[a] 19·1[a]	16·7	—	85·6	66·9, 49·0	144·0,[a,b] 134·3,[a] 127·2, 123·5, 107·0
6	—	16·9	16·9	70·4	66·6, 50·5	125·8, 123·9[b]
7	—	—	—	—	—	—
9	—	21·0	20·4	69·1	66·6, 50·5	145·1, 137·9, 133·7, 132·9, 119·0, 109·2
10	28·6, 19·3[a] 19·0[a]	21·0	20·2	85·3	66·9, 48·5	144·5, 137·5, 133·7, 133·4, 118·9, 109·1
2-Isomers:						
4	—	16·8	—	76·8	66·7, 50·0	144·0, 130·3,[a] 128·3,[b] 125·5,[a] 115·4[b]
5	28·5, 19·3,[a] 19·9[a]	17·2	—	92·3	67·0, 48·5	143·7,[a] 130·5,[a] 129·0, 126·2, 115·4[b]
6	—	17·0	17·0	76·8	66·8, 50·1	144·6, 128·7, 125·6
7	28·6, 19·3, 19·2	17·0	17·0	92·1	67·1, 48·5	143·9, 125·8, 125·1
9	—	20·1	20·1	—[c]	66·8, 50·1	143·7, 137·0, 116·7
10	28·5, 19·9,[a] 19·1[a]	20·8	20·8	92·0	66·8, 48·9	142·8, 136·5, 116·6

[a] Assignments between corresponding peaks of the two isomers are interchangable.
[b] Some quaternary C-atom signals not detected.
[c] Overlaps with $CDCl_3$ signals.

Calculation of equilibrium constant (K) and free energies (ΔG°) for the isomerization

The isomeric compositions of the compounds were measured by integrating the NC*H*(R^1)— proton signals in bromoform-*d* and toluene-d_8. Our previous experience for most *N*-(α-aminoalkyl)benzotriazoles is that they exist solely as the 1-isomer in the solid state, but that on dissolution in a solvent equilibrium is rapidly achieved between the 1- and the 2-isomers. Interestingly, we now find that for adducts **9** and **10** the formation of the 2-isomer is noticeably slow. To ensure that equilibrium had been established, the solutions were allowed to stand at ambient temperature for 10–48 h (or until the ^{1}H NMR integration ratios were constant) before final measurements were carried out. The resulting equilibrium constants and the corresponding ΔG° values are given in Table 4.

Our results demonstrate that the presence of a methyl group at the C-4 and/or C-7 positions strongly disfavors substitution on the adjacent nitrogen atoms(s). Thus, the ^{1}H and ^{13}C NMR spectra of the dimethyl derivative **7** in four different solvents ($CDCl_3$, $CDBr_3$, toluene-d_8 and CD_3CN) showed no 1-isomer **7a** (detection limit



11 a

11 b

11 c

Scheme 4

estimated as 2%), whereas for its less hindered analog **6** the equilibrium was strongly skewed in favor of **6b** (percentage ratio **6a** : **6b** = 7:86, i.e. ΔG° = 1·5 kcal mol^{-1} in $CDBr_3$; ratio 6:88, ΔG° = 1·5$_5$ kcal mol^{-1} in toluene-d_8) (the degeneracy of the 1- and 3-positions in the symmetrically substituted adducts is taken into account in these ratio values).

The 4-methyl derivative **4** now has three possible isomers with the 1- and 3-positions being different. The amount of the 2-isomer is 25% in $CDBr_3$ and 30% in toluene. From the results for **6** discussed above, we infer the amount of the 3*H*-isomer to be 7% in $CDBr_3$ and 6% in toluene-d_8, although no signals arising from this isomer were detected (presumably they overlapped with those of the 1-isomer, as observed[3] for similarly substituted adducts). In **4**, the relatively unhindered form **4a** predominates.

The magnitude of the steric interaction between the 4-(7-)methyl and the 1-morpholinomethyl group can be estimated by comparing the thermodynamic parameters of **6** and **9** in toluene-d_8 and in $CDBr_3$. Thus, the energy contribution of the 4-methyl and 7-methyl groups, ΔG°_{steric} should be the sum of the values of the individual ΔG° values calculated for **6** and **9**. Hence we predict that in $CDBr_3$ $\Delta G^\circ_{steric} = 1{\cdot}5 + 0{\cdot}3 = 1{\cdot}8$ kcal mol^{-1}, whereas in toluene-d_8 $\Delta G^\circ_{steric} = 1{\cdot}75$ kcal mol^{-1}.

The interaction between the 4-(7-)methyl and the 1-[morpholino(isopropyl)methyl] groups in **7** (no 1- or 3-isomers detected) can be estimated only indirectly. From the ΔG° value for **10** and the theoretical energy value[10] for an equilibrium too one-sided to measure by ^{1}H NMR (2·3 kcal mol^{-1} for 98% isomeric composition), it is at least $\Delta G^\circ_{steric} = 2{\cdot}3 - 0{\cdot}50 = 1{\cdot}8$ kcal mol^{-1} in

Table 4. Thermodynamic and kinetic[a] parameters

Compound	R^1	R^2	R^3	K[b]		ΔG°(kcal mol^{-1})[c]		T_c (°C)[d]	$\Delta G^\ddagger$ (kcal mol^{-1})[e] (CDBr$_3$)
				$CDBr_3$	Toluene-d_8	$CDBr_3$	Toluene-d_8		
4[f]	H	Me	H	2·72	2·15	−0·6	−0·4$_5$	138	20·8
5[f]	*i*-Pr	Me	H	0·65	0·35	+0·2$_5$	+0·6	110	19·5
6[f]	H	Me	Me	0·08	0·07	+1·5	+1·5$_5$	145	22·0
7[f]	*i*-Pr	Me	Me	—	—	—	—	—	—
8[g]	H	H	H	1·80	—	−0·3$_5$	—	86	18·3
9[g]	H	Me	Me	1·70	1·40	−0·3	−0·2	120	20·0
10[g]	*i*-Pr	Me	Me	0·40	0·25	+0·5	+0·8	115	20·2
11[h]				1·90[i]	—	−0·3$_5$	—	128	20·0
				15·30[j]	—	−1·6	—		

[a] Measured in $CDBr_3$.
[b] Measured at 22 °C; $K = P_1/P_2$ (P_i = population of the *i*-isomer).
[c] ±0·05; a negative ΔG° value indicates predominant 1-isomer.
[d] ±3; in $CDBr_3$.
[e] Indicates 2- to 1-isomer conversion; error = ±0·3 kcal mol^{-1}.
[f] Refers to Scheme 2.
[g] Refers to Scheme 3.
[h] Refers to Scheme 4.
[i] Refers to $K = [1,3']/[1'1']$.
[j] $K' = [1,3']/[1,2']$.

$CDBr_3$. A direct measurement cannot be made since only the **b** form of **7** can be detected.

For the benzobistriazole adduct, the 1,3′-isomer **11c** (two degenerate species) predominates in the mixture over the (possibly more hindered by buttressing) 1,1′-isomer **11a** (two degenerate species); the 1,2′-isomer **11b** (four degenerate species) is much less favored. The percentage ratio of the isomers **11a** (1,1′):**11b** (1,2′):**11c** (1,3′) is 33:4:63 in $CDBr_3$. This is an unexpected isomeric distribution, as based on the results for simple benzotriazoles[3] a considerably larger amount of **11b** would have been expected.

Variable-temperature ^{1}H NMR study: calculation of the energies of activation ($\Delta G^{\neq}$)

The temperatures at which the signals of the NCH_2N and $NCH(R^1)N$ protons due to forms **a** and **b** coalesced were measured in $CDBr_3$ and the approximate energies of activation calculated as reported before.[3] The values so obtained are given in Table 4 and they all refer to a 2- to 1-isomer conversion. Appropriate corrections were made for **5**–**6** and **10** for which ΔG° is positive. The values are considerably higher than those of the unsubstituted compound **8**.[3] This reflects the destabilizing effect of the electron-releasing methyl substituents on the intermediate benzotriazolate anion (Scheme 1). On the other hand, the steric effect of the methyl groups in **5**–**7** renders the 1-isomers thermodynamically less favored than the 2-isomers, and this adds to the apparent energy of activation for a 2- to 1-isomer conversion. Regarding the benzobistriazole adduct **11**, the isomerization should involve more than two ionic intermediates, and therefore the interconversion mechanism is less clear than that of the other adducts.

In summary, the substituent isomerization in *N*-(α-aminoalkyl)benzotriazoles is a general process; the relative amounts of the isomeric species in the solution are severely affected not only by increased solvent polarity (favoring the 1-isomer[3]) but also by ring-substituent steric interactions (favoring the 2-isomer).

EXPERIMENTAL

General. The ^{1}H and ^{13}C NMR spectra were carried out using a Varian VXR-300 spectrometer. Tetramethylsilane was the internal reference for ^{1}H NMR spectra whereas the $CDCl_3$ peak at 77·00 was used for the ^{13}C NMR spectra. Deuterated bromoform was purchased either from Aldrich or from Cambridge Isotopes and was allowed to stand over K_2CO_3 and 3Å molecular sieves for 2 days. VT-NMR spectra and coalescence temperatures were measured twice using 0·1 M solutions in $CDBr_3$ as reported before.[3] Energy of activation values that did not agree within 0·3 kcal mol^{-1} were rejected. 5,6-Dimethylbenzotriazole was purchased from Aldrich.

4(7)-Methylbenzotriazole **2**. 2-Methyl-6-nitroaniline (15·2 g, 0·1 mol) was reduced with concentrated HCl (50 ml) and granulated tin (25 g). The mixture was adjusted to a pH 10 and the product was extracted with diethyl ether. The crude *o*-diamine (obtained in 86% yield, m.p. 56–59 °C; lit.[11] m.p. 60 °C) was diazotized with $NaNO_2$ in glacial acetic acid according to the literature procedure for the synthesis of benzotriazole,[5] and the crude **2** was recrystallized from benzene (67%, m.p. 145–148 °C; lit.[12] m.p. 150 °C). ^{1}H NMR (DMSO-d_6): δ 2·6 (s, 3 H, CH_3), 7·2 (d, J = 7 Hz, 1 H), 7·3 (dd, J = 7, 8 Hz, 1 H), 7·7 (d, J = 8 Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ 16·8, 112·0, 124·7, 125·3, 125·2, 138·6, 139·1.

4,7-Dimethylbenzotriazole **3**. 2,5-Dimethylaniline was successively acetylated, nitrated and reduced to 3,6-dimethylbenzene-1,2-diamine according to a known procedure.[7] The diamine was then cyclized to **3** according to the procedure described for benzotriazole[5] (yield over five steps 13%; m.p. 278–280 °C; lit.[7] m.p. 276–278 °C). ^{1}H NMR (DMSO-d_6): δ 2·6 (s, 6 H), 7·1 (s, 2 H). ^{13}C NMR (DMSO-d_6): δ 16·6, 125·0 (broad).

Preparation of adducts **4**–**7**, **9** and **10**. Equimolar amounts (0·003 mol) of the appropriate substituted benzotriazole, the aldehyde and morpholine were stirred in methanol (15 ml) for 18 h. After evaporation of the solvent, the residue was purified differently in each case: **4** was obtained as an oil; **5** was also an oil which, on standing under vacuum at room temperature for 3 days, crystallized and was washed with cold diethyl ether and dried; **6** was a solid which was recrystallized from hexane; the crude solid **7** was dissolved in boiling hexane, the insoluble residue discarded, the solution decolorized with charcoal and the pure product finally obtained; **9** was recrystallized from diethyl ether; solid **10** (prepared in refluxing methanol) was washed with cold diethyl ether. The properties of the compounds are listed in Table 1.

Preparation of 1,5-(dimorpholinemethyl)benzo[1,2-d:4,5-d′]bistriazole **11**. 1,5-Dihydrobenzo[1,2-*d*:4,5-*d*′]bistriazole (1·6 g, 0·01 mol)[8,9] and morpholine (0·022 mol) in methanol (10 ml) were treated with paraformaldehyde (0·025 mol) and the mixture was refluxed for 24 h. After cooling to room temperature, the precipitate formed was collected and washed with methanol and dried (92%). The NMR spectra indicated a mixture of interconverting isomers: ^{1}H NMR ($CDCl_3$, 1,3′-isomer: δ 2·70 (m, NCH_2CH_2O), 3·71 (m, NCH_2CH_2O), 5·53 (s, NCH_2N), 8·28 (s, 2 H, ring); 1,1′-isomer: δ 2·70 (m, NCH_2CH_2O), 3·71 (m, NCH_2CH_2O), 5·47

(s, NCH_2N), 7·66 (d, J = 1 Hz, 1 H), 8·82 (d, J = 1 Hz, 1 H); 1,2′-isomer: δ 2·78 (m, NCH_2CH_2O), 3·71 (m, NCH_2CH_2O), 5·66 (s, NCH_2N), 8·04 (d, J = 1 Hz, 1 H), 8·70 (d, J = 1 Hz, 1 H). ^{13}C NMR ($CDCl_3$), 1,3′-isomer: δ 50·6, 66·6, 69·9 (NCH_2N), 98·2, 132·2, 146·4; 1,1′-isomer: δ 50·7, 66·6, 69·8, 87·0, 110·4, 134·1, 144·7; 1,2′-isomer: δ 50·1, 66·8, 78·3, 94·7, 107·9 (owing to the low concentration of this isomer in the mixture, the remaining quaternary carbon atoms were not observed).

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