Conformational Studies by Dynamic NMR. 37.[1] Monitoring the Stereomutations of Symmetric Amines by Means of a Chiral Auxiliary Agent

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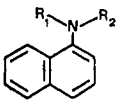
The chiral auxiliary agent (*R*)-*l*-2,2,2-trifluoro-1-(9-anthryl)ethanol was used to monitor the exchange between the enantiotopomers of symmetric amines lacking diastereotopic probes. The free energies of activation for stereomutations involving both C–N rotation and N-inversion processes were measured by line-shape simulation of the low-temperature NMR spectra. The effect of the chiral alcohol upon the barriers has also been evaluated, thus allowing one to compare these data with those of other amines where the stereomutations had been detected in achiral environments. The existence of steric deceleration for the exchange between enantiotopomers related by torsion and of steric acceleration for enantiotopomers related by N-inversion has been also verified. The highest N-inversion barrier observed in a simple noncyclic trialkyl amine (8.6 kcal mol^{-1} for Me_2NEt) could thus be measured.

Introduction

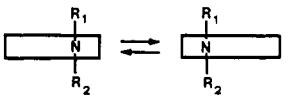
Hindered aromatic amines sometimes show conformational atropoisomerism owing to the restricted rotation about the Ar–N bond:[3,4] this effect can usually be observed by NMR when appropriate diastereotopic probes are present in the molecule. The barrier to N-inversion in aromatic amines is much too low to be detected by NMR,[5] unless the nitrogen atom is part of a three- or four-membered ring.[6,7] As a consequence the stereomutation occurring in open-chain hindered aromatic amines can be described as a torsion of the dynamic plane, containing the rapidly inverting nitrogen atom, with respect to the aromatic ring.[8] Recent examples of this process are offered by *N*,*N*-dialkyl-1-naphthylamines such as 1–3:



1: R_1 = Me, R_2 = *i*-Pr
2: R_1 = R_2 = *i*-Pr
3: R_1 = Me, R_2 = *t*-Bu
4: R_1 = R_2 = Me

When R_1 and R_2 are different (as for instance in **1**) the molecule yields a pair of enantiomeric conformers[9] as shown in Scheme I. If one of the R groups is a diastereotopic probe, the chirality is detectable by NMR, usually at low temperature, in that the geminal groups of the probe

Scheme I



(in **1** the pair of methyl groups of the isopropyl moiety) become anisochronous when the stereomutation is slow on the NMR time scale.[10,11] For such probes to display anisochronous groupings, however, it is not required that chiral conformers are actually created; it is sufficient that the plane bisecting the two geminal groups is not coincident with the plane of symmetry of the whole molecule.[10,11] Thus when R_1 = R_2 = *i*-Pr (**2**) the methyl groups are anisochronous at low temperature,[12] although **2**, contrary to **1**, does not give rise to chiral conformers. The line-shape analysis[13] yielding the enantiomerization barrier[9] in the case of **1** will thus measure, in **2**, a torsional barrier[12] corresponding to a process called enantiotopomerization.[14]

When R_1 is different from R_2, but neither of them is a diastereotopic probe (as for instance in **3**), the existence of enantiomeric conformers is not detectable by NMR.[9,15] If the measurement is however carried out in a chiral environment,[16] two different NMR spectra will be observed at low temperature,[9,17] owing to the existence of diastereomeric solvates, and the interconversion barrier can thus be measured. Finally when R_1 is equal to R_2 without being a diastereotopic probe (as in **4** where R_1 = R_2 = Me), their enantiotopic relationship is again undetectable in an

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Table I. Free Energies of Activation ($\Delta G^{\ddagger}$ in kcal mol^{-1}) Measured for the Enantiotopomerization of 4–8 in the Presence of Optically Pure Pirkle's Alcohol at the Temperatures Indicated. The Chemical Shift Difference ($\Delta\nu$ in Hz) for the Protons of Diastereotopic NMe Groups Are Also Given at the Temperature Reported in Parentheses

compd	motion	$\Delta G^{\ddagger}$(corrctd)[a]	$\Delta G^{\ddagger}$(measd)	temp, °C	solvent	$\Delta\nu$	spectrometer frequency, MHz
4	rotation	7.8	8.3 ± 0.2	−93	CD_2Cl_2/CHF_2Cl	140 (−120)	200
5	rotation		>14	−36	CD_2Cl_2	12.5 (−100)	200
6 (Me_2NEt)	inversion	8.6	10.4 ± 0.3	−74	toluene/CHF_2Cl	11.2 (−90)	300
7 ($Me_2NCHEtMe$)	inversion		7.8 ± 0.15[b]	−114	toluene/CHF_2Cl	31.0 (−125)	200
7	inversion	7.8	9.6 ± 0.3	−93	CHF_2Cl[c]	8.5 (−100)	200
8 ($Me_2NCH_2CHMe_2$)	inversion	8.5	10.3 ± 0.3	−89	CD_2Cl_2/CHF_2Cl	11.0 (−96)	200

[a] Values reduced by 0.5 or 1.8 kcal mol^{-1} to account for the effect of Pirkle's alcohol respectively on rotation or inversion. [b] In this case Pirkle's alcohol was not employed and the value was used to establish the correction for *N*-inversion (see text). [c] The lock was provided by some CD_3OD that also helped to keep the chiral alcohol in solution at low temperature.

achiral medium. When a chiral auxiliary agent is introduced the methyl groups will become anisochronous at low temperature since the whole molecule has, according to Scheme I, the symmetry required to monitor th presence of a chiral center, i.e., the molecule itself behaves as a diastereotopic probe.[4] What makes the case of **4** different from that of **1** or **3** is the fact that in the latter derivatives *all* the NMR signals should, in principle, be split in a chiral environment[9] whereas in **4** *only* the methyl groups are expected to display[18] a pair of lines.

The studies of dynamic processes where a whole molecule becomes a probe of its own motion, following the introduction of a proper chiral center, are not limited, in principle, to the case of torsional processes as that previously discussed.[18] Although never reported so far, the method should also work for other stereomutations having the same symmetry requirements such as, for instance, inversion at the nitrogen atom.[19,20]

In the present work we investigated the stereomutational barriers of symmetric amines lacking diastereotopic probes both in the case of rotation and N-inversion processes.

Results and Discussion

The 200-MHz room-temperature spectrum of **4** in the presence of an enantiomerically pure chiral auxiliary agent (Pirkle's alcohol,[21] (*R*)-*l*-2,2,2-trifluoro-1-(9-anthryl)ethanol: $ArCHCF_3OH$, with Ar = 9-anthryl) displays, as anticipated, a single signal for the two methyls that eventually split into a pair of lines below a coalescence temperature of −90 °C. The line-shape simulation provides a barrier for this dynamic process equal to 8.3 ± 0.2 kcal mol^{-1} (Table I). By taking into account the perturbation due to the presence of the Pirkle's alcohol (which is known[9] to increase the torsional barriers by 0.5 kcal mol^{-1} in this class of compounds) the enantiotopomerization of **4**, in the absence of a chiral agent, should thus have a free energy of activation equal to 7.8 kcal mol^{-1}. This value matches remarkably well with that predicted (7.3 kcal mol^{-1}, for the Ar–N torsional process in **4** on the basis of an empirical relationship,[9] thus confirming that the stereomutation is

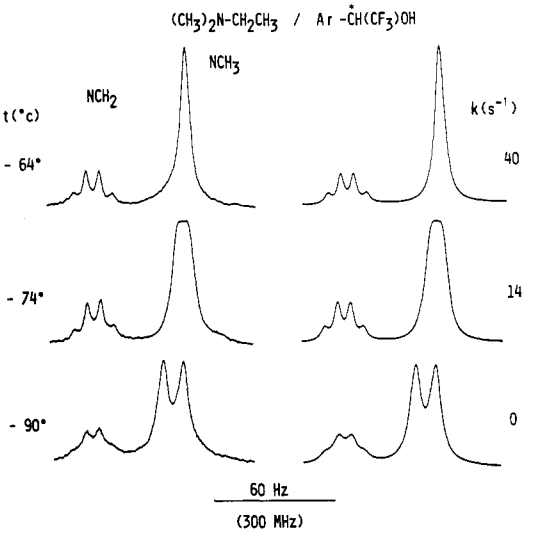
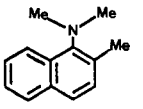


Figure 1. Experimental (left) and computer simulated (right) 300-MHz proton spectra of the NCH_2 and NCH_3 signals of *N*,*N*-dimethylethylamine (**6**) in the presence of enantiomerically pure Pirkle's alcohol (molar ratio 1:5) at three selected temperatures in toluene-d_8/CHF_2Cl (1:3 v/v) as solvent. The NMe_2 signal splits into two lines below −74 °C since the pyramidal nitrogen renders the whole amine a prochiral object.

due to rotation rather than to N-inversion. The latter motion, in fact, could be responsible in principle for the observed spectral behavior but additional evidence, favoring rotation, comes also from an analogous experiment carried out on *N*,*N*,2-trimethyl-1-naphthylamine (**5**)



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The steric effect due to the introduction of a methyl group in position 2 would greatly enhance a torsional barrier (steric deceleration) whereas it would not greatly modify, or possibly reduce, an N-inversion barrier (steric acceleration).[22-27] The 200-MHz spectrum of **5** in the presence of the same chiral auxiliary agent displays a single line for the methyl group in position 2 at any temperature

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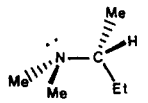
but a pair of lines for the *N*-methyl groups below −35 °C. The separation of these lines decreases on raising the temperature[9,16] (from 12.5 Hz at −100 °C to 0.7 Hz at −36 °C) so that the difference becomes eventually too small to unambiguously distinguish between the shape due to coalescence from that due to overlapping without exchange. Nonetheless, a lower limit could be established for the $\Delta G^{\ddagger}$ value, which must certainly be larger than 14 kcal mol^{-1}. This agrees with the expectation for rotation rather than for N-inversion.

On the other hand a suitable molecule where enantiotopomerization due to N-inversion, not otherwise detectable, could be observed by means of this technique is *N*,*N*-dimethylethylamine (**6**). At a temperature where the lifetime of the nitrogen in the pyramidal arrangement is sufficiently long, the whole molecule has the same symmetry of the diastereotopic isopropyl group: the introduction of a chiral auxiliary agent will thus make diastereotopic the two enantiotopic *N*-methyl groups. So far the simplest trialkylamine where N-inversion had been detected was *N*,*N*-diethylmethylamine that yielded the highest barrier reported in such a class of compounds (7.9 ± 0.4 kcal mol^{-1}).[20f] *N*,*N*-Dimethylethylamine (**6**), being less crowded, should give an even higher N-inversion barrier (steric deceleration).[22-27] As shown in Figure 1 the signal of the NMe_2 group, in the presence of the mentioned Pirkle's alcohol, splits into a pair of lines below a coalescence temperature of −74 °C. The barrier obtained from the line-shape simulation (10.4 ± 0.3 kcal mol^{-1}) seems however quite large for N-inversion, particularly when compared with that[20f] of $MeNEt_2$. Such a large value is in part attributable to the presence of Pirkle's alcohol. Drakenberg and Lehn[28] did show in fact that the large N-inversion barriers of cyclic aziridines measured in hydrocarbons (e.g., toluene) further increase by as much as 2 kcal mol^{-1} in an alcoholic environment (e.g., in methanol). In order to evaluate the effect of Pirkle's alcohol upon the N-inversion of amines like **6**, we devised a case (*N*,*N*-dimethyl-2-butylamine, **7**) where a chiral center is directly bonded to the Me_2N moiety. At low temperature the pyramidal dimethylamino group becomes a diastereotopic probe (much in the same way as the $CHMe_2$ group is such a kind of probe at any temperature) sensitive to the presence of the chiral center.



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Whereas N-inversion can be detected in **6** only in a chiral environment, the corresponding barrier could be measured in **7** both in the absence and in the presence of the chiral alcohol. The two $\Delta G^{\ddagger}$ values were found,[29] respectively, 7.8 and 9.6 kcal mol^{-1}, thus showing that the presence of an excess of alcohol increases the N-inversion barrier of these amines by 1.8 kcal mol^{-1}. The $\Delta G^{\ddagger}$ value of Me_2NEt (**6**) thus becomes, after the correction, 8.6 kcal mol^{-1} and it can be now compared with the values reported in the literature for other amines. This is one of the highest N-inversion barriers ever reported for a simple acyclic trialkylamine,[30] in that is even larger than that[20f] of Et_2NMe, as we had anticipated on the basis of the steric acceleration effect.[22-27] A barrier (10.3 ± 0.3 kcal mol^{-1}), essentially equal to that of **6**, has also been obtained for the analogous *N*,*N*-dimethylisobutylamine ($Me_2NCH_2CHMe_2$, **8**).

Conclusion

The chiral auxiliary agents can be satisfactorily employed to monitor enantiotopomerizations involving not only torsional processes, as previously demonstrated,[18] but also N-inversion. In the latter case the use of Pirkle's alcohol as a chiral auxiliary agent increases the barrier by about 1.8 kcal mol^{-1}. This effect can be helpful in that it makes the dynamic process amenable to NMR investigations at higher temperatures. The separation of the lines however decreases when the temperature is raised and care has to be taken in order not to misinterpret the nature of the line shape, for the two lines might overlap (as in **5**) before reaching the exchange region. Anyway a lower limit for the barrier can be at least established in these cases. The use of higher magnetic fields and, when soluble, of larger amounts of the chiral agent can be helpful to verify and, possibly, to overcome this inconvenience.

Experimental Section

Materials. The purity of the compounds employed was judged to be >95% by ^{1}H and ^{13}C NMR (see supplementary material).

***N*,*N*,2-Trimethyl-1-naphthylamine**[32] **(5).** 2-Methyl-1-naphthylamine (5 g, 35 mmol) and methyl iodide (2.1 mL, 35 mmol) were heated in toluene (40 mL) for 18 h at 100 °C (autoclave). After being cooled at room temperature, the system was treated with sodium hydroxide (20%), extracted with ether, and purified on a silica column (eluent petroleum ether/ether 100:1) to yield 0.8 g of **5**. In addition *N*,2-dimethyl-1-naphthylamine (1.6 g) was also recovered. Derivative **5** had the following: mass spectrum *m*/*e* 185.1201 ($^+$M) (calcd for $C_{13}H_{15}N$ 185.1204); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.45 (3 H, s, Me), 3.0 (6 H, s, Me_2N), 7.0–8.0 (5 H, m, Ar), 8.2 (1 H, m, H-8); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.7 (CH_3), 43.9 (NCH_3), 125.2 (CH), 125.6 (CH), 125.8 (CH), 126.3 (CH), 128.85 (CH), 130.9 (CH), 133.7 (C), 134.0 (C), 134.5 (C), 144.9 (C). These values parallel those reported in ref 32.

***N*,*N*-Dimethyl-1-naphthylamine**[32] **(4)** was obtained by reacting 1-naphthylamine in the same way. **4**: mass spectrum *m*/*e* 171 ($^+$M); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.85 (6 H, s, Me_2N), 7.0 (1 H, m, Ar), 7.2–7.6 (4 H, m, Ar), 7.8 (1 H, m, Ar), 8.25 (1 H, m, H-8); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 45.0 (NCH_3), 114.0 (CH), 123.0 (CH), 124.3 (CH), 125.2 (CH), 125.8 (CH), 128.4 (CH), 129.15 (C), 135.1 (C), 151.2 (C). These values parallel those reported in ref 32.

2-Methyl-1-naphthylamine[32] was prepared by reduction with H_2 (Pd as a catalyst) of 2-methyl-1-nitronaphthalene. The latter (mp 67–68 °C) was obtained by reacting 2-methylnaphthalene (28 g) with a 65% solution of nitric acid (25 g) for 6 h at 75 °C: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.4 (3 H, s, Me), 4.25 (2 H, s br, NH_2), 7.2–7.9 (6 H, m, Ar). The ^{13}C spectrum was consistent with that reported in ref 32.

***N*,*N*-Dimethyl-2-butylamine**[33] **(7).** 2-Butylamine (7 g, 100 mmol) was mixed with formic acid (19.6 mL) and with a 40% solution of formaldehyde (23 mL).[34] The temperature was slowly raised to 80 °C and the reaction was completed in 4 h. To the

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(29) The steric acceleration is again detectable in **7** with respect to **6**: in the same conditions the latter has in fact a larger barrier (10.4 vs 9.6 kcal mol^{-1}) since the ethyl, being a primary group, is smaller than the secondary 2-butyl group.

(30) A quite complex system having a trisubstituted amino moiety (i.e., hexakis(diethylamino)benzene) has been reported[31] to have, apparently, a $\Delta G^{\ddagger}$ = 10 kcal mol^{-1} for N-inversion. On the other hand the analogous 1,3,5-tris(diethylamino)-2,4,6-tris(dimethylamino)benzene has a much lower N-inversion barrier ($\Delta G^{\ddagger}$ = 8.2 kcal mol^{-1}).[31]

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cooled solution was added hydrocloric acid (35%, 10 mL), and subsequently the system was carefully treated with KOH (vigorous reaction) to give a liquid that after extraction with ether and elimination of the solvent yielded 3.8 g of 7: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.75–0.9 (6 H, m, 2 Me), 1.2 (1 H, m, HC*H*), 1.45 (1 H, m, *H*CH), 2.15 (6 H, s, Me_2N), 2.3 (1 H, m, CH); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 11.0 (CH_3), 13.2 (CH_3), 26.1 (CH_2), 40.7 (NCH_3), 60.8 (NCH).

***N,N*-Dimethylisobutylamine**[33] **(8)** was obtained with the same procedure as 7. 8: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (6 H, d, *Me*$_2$CH), 1.70 (1 H, m, CH), 1.97 (2 H, d, CH_2), 2.17 (6 H, s, Me_2N); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.4 (CH_3), 26.7 (CH), 46.5 (NCH_3), 69.2 (NCH_2).

NMR Spectra. The spectra were run on a Varian Gemini spectrometer operating at 200 MHz. The 300-MHz spectra of 7 were run on a Bruker CXP 300. The variable-temperature devices were calibrated with the standard methanol sample. For temperatures lower than the freezing point of methanol, a sample containing CH_3OH, CD_3OD, and CHF_2Cl was employed. The chemical shift differences between CH_3 and OH in this sample were measured, with the help of a thermistor, at 100 MHz down to −125 °C. The same sample was subsequently used in the 200- and 300-MHz spectrometers when required. The samples containing CHF_2Cl were prepared by sealing the NMR tubes connected to a vacuum line. The chemical shift differences of the diastereotopic NMe groups were found to depend upon the molar ratio of the Pirkle alcohol. As the chemical shift differences decrease on raising the temperature they were measured at various temperatures below the exchange region and the extrapolated values were employed for the line-shape simulation. The results turned out to be more reliable when relatively small $\Delta G^{\ddagger}$'s are involved: in fact in the case of 5, where the barrier is much larger, the shift difference becomes negligible before reaching the temperature where the exchange occurs. The advantage of using the highest available magnetic fields is clearly illustrated by the case of 6. At 200 MHz the chemical shift difference between the diastereotopic NMe groups was quite small (e.g. 7.5 Hz at −90 °C) so that the rate constant obtained by simulation at the coalescence (6 s^{-1} at −77 °C) was possibly affected by a large error. The value was indeed quite dependent upon the choice of the line width in absence of exchange (4.7 Hz at −77 °C). This parameter had been taken equal to that of the NCH_2 quartet[35] at the same temperature since they had been found to have equal values when the methyl signals did not undergo dynamic exchange (e.g., at −90 °C). The same sample examined at 300 MHz (Figure 1) yielded, at the coalescence, a larger rate constant (14 s^{-1} at −74 °C) that was therefore affected by a smaller uncertainity. It is gratifying however to realize that the $\Delta G^{\ddagger}$ values obtained at two different frequencies are essentially equal within the errors.

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Supplementary Material Available: Proton (200 MHz) and ^{13}C (50.3 MHz) NMR spectra in $CDCl_3$ for compounds 4, 5, 7, and 8 (8 pages). Ordering information is given on any current masthead page.

(35) In principle the geminal protons of the CH_2 group should display two different shifts owing to the presence of the chiral alcohol: the difference was probably too small in the examined sample to be detectable. The same happened for the CH_2 group in 8 where, on the contrary, the methyl groups of the diastereotopic isopropyl moiety display the expected chemical shift difference induced by the presence of the chiral alcohol.

Photochemistry of Stilbenes. 8. Eliminative Photocyclization of *o*-Methoxystilbenes[1]

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The synthetic value of the eliminative photocyclization of *o*-methoxystilbenes to give phenanthrenes with loss of the elements of methanol has been enhanced by the use of *tert*-butyl alcohol as the solvent and sulfuric acid as a catalyst. 2-Methoxy-5-X-stilbenes and 2-methoxy-3-X-stilbenes undergo this photoreaction to produce the corresponding 2-X-phenanthrenes and 4-X-phenanthrenes, respectively. This regioselective photochemical route to these particular types of substituted phenanthrenes represents an improvement synthetically over the well-known oxidative photocyclization method with meta-substituted stilbenes, from which approximately 1:1 mixtures of 2-substituted and 4-substituted phenanthrenes usually are obtained. An attempt to extend the scope of this eliminative photocyclization method to the synthesis of benz[*a*]anthracene by the ultraviolet irradiation of 3-methoxy-2-styrylnaphthalene was not successful, but this synthetic objective was achieved in an alternative way by the eliminative photocyclization of 5,6,7,8-tetrahydro-3-methoxy-2-styrylnaphthalene followed by oxidation of the resulting 8,9,10,11-tetrahydrobenz[*a*]anthracene with DDQ.

The photocyclization reaction exemplified by the conversion of *cis*-stilbene to phenanthrene through ultraviolet irradiation in solution in the presence of iodine and dissolved oxygen is a valuable synthetic method for the preparation of a wide variety of carbocyclic and heterocyclic systems.[2a] There is, however, an unfortunate limitation in the synthetic utility of this venerable photoreaction: simple meta-substituted stilbenes usually give approximately 1:1 mixtures of 2-substituted and 4-substituted phenanthrenes.[3] This presents practical difficulties for two reasons: not only is there an upper limit of about 50% on the yield of either phenanthrene isomer, but also the mixture of the two isomers often is very dif-

(1) (a) Part 7: Mallory, F. B.; Mallory, C. W.; Sen Loeb, S. E. *Tetrahedron Lett.* **1985**, *26*, 3773. (b) Taken from the Ph.D. Dissertation of M. J. Rudolph, Bryn Mawr College, 1988.

(2) (a) Mallory, F. B.; Mallory, C. W. *Org. React. N.Y.* **1984**, *30*, 1–456. (b) Reference 2a, page 34. (c) Reference 2a, page 48.

(3) Product ratios skewed in favor of the 2-substituted phenanthrene have been found, however, for stilbenes with certain strongly electron-withdrawing[4] or sterically demanding[5] meta substituents.

(4) (a) Gore, P. H.; Kamonah, F. S. *Synth. Commun.* **1979**, *9*, 377. (b) Kende, A. S.; Curran, D. P. *J. Am. Chem. Soc.* **1979**, *101*, 1857. (c) Joly, M.; Defay, N.; Martin, R. H.; Declerq, J. P.; Germain, G.; Soubrier-Payen, B.; Van Meerssche, M. *Helv. Chim. Acta* **1977**, *60*, 537.

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