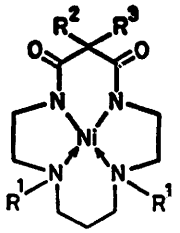
N- and *C*-Methylation of 5,7-Dioxo-1,4,8,11-tetra-azacyclotetradecanato-(2−)nickel(II)

By WILLY BACHMANN, STEFAN BÜRKI, and THOMAS A. KADEN
(*Institute of Inorganic Chemistry, University of Basel*, CH-4056 *Basel, Switzerland*)

Summary The reaction of the title complex with MeI in dimethyl sulphoxide–KOH gives a series of products methylated at the amino nitrogens and at the methylene group of the malonamide unit.

WAGNER and BAREFIELD[1] have shown that one can alkylate the Ni^{II} complexes of tetra-azamacrocycles in dimethyl sulphoxide (DMSO) using KOH or $MeSOCH_2^-$ Na^+ as a base and that one sometimes obtains isomers which are not directly accessible through the complexation of Ni^{II} and the corresponding alkylated macrocyclic ligand. For example, the per-methylation of the Ni^{II} complex of 1,4,8,11-tetra-azacyclotetradecane gives the *trans*-III (*R,S,S,R*)† isomer,[1] whereas the complexation of Ni^{II} with 1,4,8,11-tetramethyl-1,4,8,11-tetra-azacyclotetradecane produces the *trans*-I (*R,S,R,S*)† isomer.[2]

Following their procedure we dissolved the title complex (**1**)‡ in DMSO in which finely pulverised KOH was suspended and treated it with a tenfold excess of MeI for 60 min at room temperature, expecting to obtain one or both isomers of complex (**2**). However, after work-up, a thin-layer chromatogram (Alox Merck, $CHCl_3$–MeOH 100:15) indicated that at least four components were present in the reaction mixture. These were separated on a preparative scale on a Chromatotron§ using a 2 mm thick Alox-coated rotor and $CHCl_3$–MeOH 96:6 as eluant. The four pure



(**1**) $R^1 = R^2 = R^3 = H$
(**2**) $R^1 = Me$, $R^2 = R^3 = H$
(**3**) $R^1 = R^2 = Me$, $R^3 = H$
(**4**) $R^1 = R^2 = R^3 = Me$

† The nomenclature used was introduced by B. Bosnich, C. K. Poon, and M. L. Tobe, *Inorg. Chem.*, 1965, **4**, 1106.

‡ Complex (**1**) was prepared from $Ni(OH)_2$ and 5,7-dioxo-1,4,8,11-tetra-azacyclotetradecane: I. Tabushi, Y. Taniguchi, and H. Kato, *Tetrahedron Lett.*, 1977, 1049.

§ The Chromatotron (Harrison Research, Palo Alto, U.S.A.) is a preparative, centrifugally accelerated, radial thin-layer chromatograph, which usually gives a better separation than conventional column chromatography.

products were designated as F1 (15%), F2 (5%), F3 (24%), and F4 (30%) according to their elution sequence.

Compound F4 was shown by elemental analysis and its ^{1}H n.m.r. spectrum (CD_3OD) (δ 2·69, 6H, s, MeN) to be the expected complex (**2**). Its identity was also confirmed by preparing the free ligand through reductive methylation of 5,7-dioxo-1,4,8,11-tetra-azacyclotetradecane with HCO_2H–H_2CO and complexing it with Ni^{II}. The product was identical with F4.

The other components F1, F2, and F3 have more than two methyl groups per Ni^{II}. Besides *N*-methylation it is conceivable that in the presence of a strong base *C*-alkylation at the methylene group of the malonamide unit can take place. F1 was a tetramethyl derivative and its ^{1}H-n.m.r. spectrum (δ 2·65, 6H, s, MeN; 1·20, 3H, s, and 1·65, 3H, s, Me_2C) is compatible with structure (**4**). There are two possibilities to explain the nonequivalence of the two methyl groups R^2 and R^3. The malonamide moiety may be nonplanar, but this seems rather improbable because of the planarity of the deprotonated amide nitrogens and also because no deviation from planarity has been observed in the analogous open chain ligand *N*,*N*′-bis(2-aminoethyl)-malonamide.[3] Alternatively, if the ligand is planar two diastereoisomers will be possible: an *N-meso* form with the two methyl groups R^1 on the same side of the co-ordination plane, and an *N*-racemic form with one methyl group R^1 above and the other below the plane. In the *N*-racemic isomer the two methyl groups R^2 and R^3 are magnetically equivalent, whereas in the *N-meso* isomer they are not. A similar result was also found by Hay and Norman[4] who studied the ^{1}H n.m.r. spectrum of the Co^{III} complex of 5,7-dioxo-1,4,8,11-tetra-azacyclotetradecane. The two protons of the methylene group in the malonamide unit appear as an AB-spectrum, indicating that they are not equivalent.

F2 and F3 (obtained only in small amounts) are the Ni^{II} complexes (**3**). They differ in their R_f values (F2: 0·66 and F3: 0·44) and in their ^{1}H n.m.r. spectra (F2: δ 2·85, 6H, s, MeN and 1·40, 3H, d, MeC; F3: δ 2·64, 6H, s, MeN and 1·76, 3H, d, MeC) so they must be isomers. Following the same arguments as for F4 it is possible that they are the two diastereoisomers with the methyl group R^2 on either the same or the opposite side as the methyl groups R^1 in their *N-meso* configuration.

Our results show that it is possible, under strongly alkaline conditions, to methylate not only the co-ordinated amino nitrogens but also the methylene group of the malonamide unit in complex (**1**) without attacking and destroying the amide linkage. The metal ion is at the same time a protecting group for the amide bond and an activator for the *C*-alkylation.

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[1] F. Wagner and E. K. Barefield, *Inorg. Chem.*, 1976, **15**, 408.
[2] E. K. Barefield and F. Wagner, *Inorg. Chem.*, 1973, **12**, 2435; M. J. d'Aniello, M. T. Mocella, F. Wagner, E. K. Barefield, and I. C. Paul, *J. Am. Chem. Soc.*, 1975, **97**, 192; R. Buxtorf, W. Steinmann, and Th. A. Kaden, *Chimia*, 1974, **28**, 15; R. Buxtorf and Th. A. Kaden, *Helv. Chim. Acta*, 1974, **57**, 1035.
[3] H. A. O. Hill and K. A. Raspin, *J. Chem. Soc. A*, 1968, 3036.
[4] R. W. Hay and P. R. Norman, *Transition Met. Chem.*, 1980, **5**, 232.