Conformational Studies by Dynamic Nuclear Magnetic Resonance Spectroscopy. Part 27.[1] Kinetics and Mechanism of Annular Tautomerism in Isomeric Triazoles

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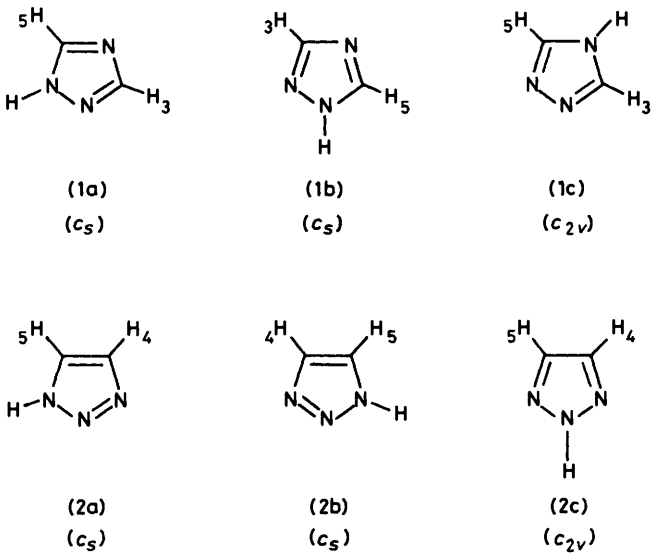
The rates for the prototropic shift of the NH hydrogen in the two isomeric triazoles [(1) = 1,2,4- and (2) = 1,2,3-triazole] have been measured at low temperature by ^{1}H n.m.r. (100 and 300 MHz). Only the less symmetric (c_s) of the two possible annular tautomers was found to be populated in the case of (1), whereas both (c_s and c_{2v}) were detected in (2). The relative proportions in the latter compound are dramatically dependent on temperature, concentration, and solvent. In either triazoles the kinetic process appears to be intramolecular and the mechanism corresponds to a 1,2 prototropic shift. The parameters of activation yielded similar $\Delta H^{\ddagger}$ (5.8 and 6.5 kcal mol^{-1}) and quite negative $\Delta S^{\ddagger}$ (−29 and −19 cal mol^{-1} K^{-1}) values, thus indicating a relatively low probability of attaining the ordered (three-membered) cyclic transition state.

Tautomerism in five-membered azaheterocyclic compounds has been extensively investigated owing to its importance in connection with molecules of biological interest [2,3] such as, for instance, histidine. Authoritative documentation on tautomerism in heterocyclic molecules [4] is now available, with extensive references updated to 1975. The technique most suited for studying this phenomenon is n.m.r., which has been widely used to investigate, particularly, tautomerism in five-membered di- and tri-azaheterocyclic compounds.

Direct evidence of the effects due to annular tautomerism has been obtained for 1,2-diazole (pyrazole): low-temperature n.m.r. measurements yielded spectra fitting c_s rather than c_{2v} symmetry. This behaviour was observed by both ^{1}H [5,6] and ^{13}C n.m.r. [6-8] in various solvents. Furthermore, the use of ^{13}C n.m.r., coupled with the m.a.s. technique, allowed the detection of annular tautomerism in the solid state [9] both in 1,2-diazole and in its 1,3 isomer (imidazole). In addition to the simple observation of tautomerism, kinetic data leading to the activation parameters were also obtained [8] for solutions of pyrazole in dimethyl sulphoxide (DMSO).

Annular tautomerism can also take place in azoles with three nitrogen atoms: 1,2,4- and 1,2,3-triazole. In 1,2,4-triazole (1) the autotropic shift can lead to two equivalent tautomers (1a and b) with c_s symmetry (*s*-tautomer); in principle, one can also expect a tautomer (1c) with c_{2v} symmetry (*v*-tautomer). Annular tautomerism might also occur in 1,2,3-triazole (2) where the equivalent tautomers (2a and b) have c_s symmetry (*s*-tautomer) and (2c) has c_{2v} symmetry (*v*-tautomer).

Direct evidence for annular tautomerism was obtained for (1) by means of low-temperature ^{1}H n.m.r.[10] The assignment of c_s symmetry [*i.e.* (1a) = (1b)] to the observed tautomer was made by comparison of the ^{1}H shifts with those of *N*-methyl derivatives: the *v*-tautomer (1c) was not observed.[10] Subsequent investigations [11] on the averaged ^{13}C shifts at room temperature were inconclusive with regard to the detection of annular tautomerism in both (1) and (2). On the other hand, an indirect indication of the existence of the phenomenon was obtained in the case of (2) from the determination of averaged H–^{13}C coupling constants.[12] To the more stable tautomer (60%) the structure with c_s symmetry [*i.e.* (2a) = (2b)] was assigned, the structure with c_{2v} symmetry (2c) accounting for the remaining 40%. A recent ^{15}N investigation [13] gave additional support to the existence of annular tautomerism in (2), although individual tautomers were not directly detected. The



structure with c_s symmetry [(2a) ≡ (2b)] was again assigned to the more stable species in $CDCl_3$ (66%) whereas in [$^2H_6$]-DMSO the structure with c_{2v} symmetry (2c) was believed to be more favoured (55%). In the same study the ^{15}N data of 1,2,4-triazole (1) were interpreted as indicative of the presence of *v*-tautomer (1c) in a non-negligible amount (3—8%). A previous ^{14}N investigation [14] had, however, reached quite different conclusions since (2c) was believed to be present in almost 100% (in methanol) and (1c) was quoted as having (in dioxane–methanol) a relative abundance of 40%.

Elguero *et al.* have pointed out,[4] however, that indirect methods of determining the relative population of tautomers when ' fixed ' derivatives are used to interpret an ' average ' property are often unreliable.

Our present understanding of tautomerism in triazoles is thus quite contradictory. Only for (1) and for a 3,5-derivative [15] was direct detection of tautomers obtained, whereas for (2) only indirect evidence is available. Furthermore there are no quantitative data concerning the rates of these tautomeric processes. As pointed out in ref. 4 the problem is still ' the most confused of all the simple cases of annular tautomerism '.

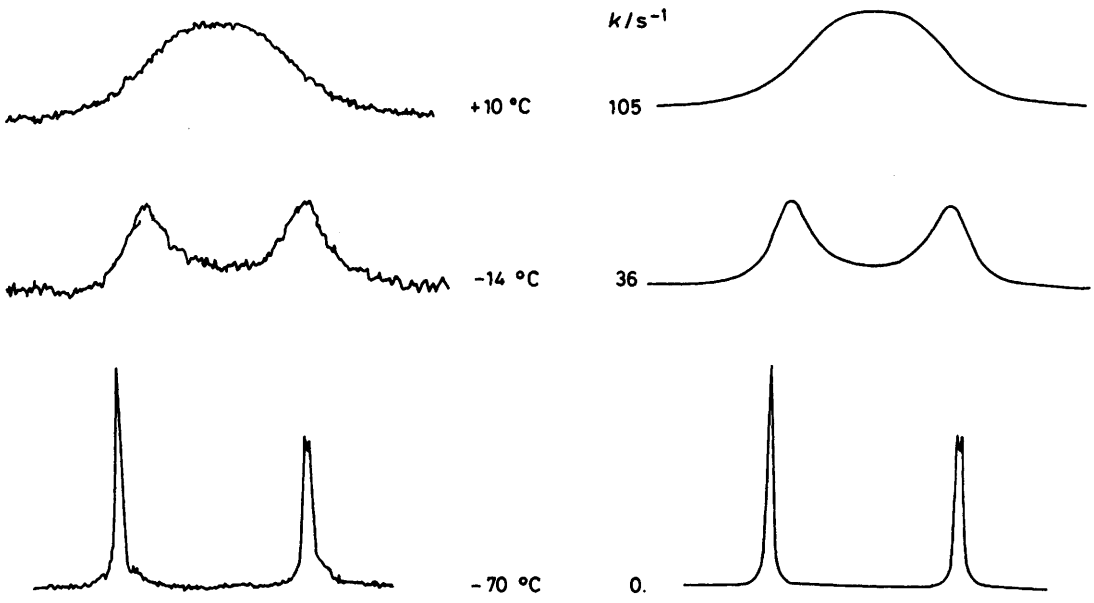


Figure 1. Experimental (left) and computer-simulated (right) 100 MHz spectrum of 1,2,4-triazole (1) in [$^2H_8$]THF (0.08M) as function of temperature

Table 1. Spectral parameters (chemical shifts in p.p.m., J in Hz) of 1,2,4-triazole (1) measured (100 MHz) at −70 °C in [$^2H_8$]THF (0.08M) and of 1,2,3-triazole (2) measured (300 MHz) at −98 °C in CD_2Cl_2 (0.05M)

Compound		s-Tautomer	v-Tautomer
1,2,4-Triazole (1)	H-3	8.63	
	H-5	8.07	
	NH	13.90	
	$J_{5,NH}$	0.9	
1,2,3-Triazole (2)	H-4	7.81$_5$	7.98
	H-5	7.85	7.98
	NH	16.90	16.37$_5$

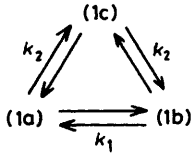
For this reason we undertook the present investigation in order to elucidate the kinetics of this dynamic process. The direct approach is the same used in a previous study on the tautomerism of triazenes,[16] which can be regarded to some extent as the acyclic counterparts of triazoles.

Results and Discussion

The ^1H n.m.r. spectra (100 MHz) of the ring hydrogens (H-3, H-5) of 1,2,4-triazole (1) in deuteriated tetrahydrofuran ([$^2H_8$]THF) show, below 10 °C, two bands of equal intensity (Figure 1). Their relative intensity remains the same in a different solvent (Me_2O–CD_3CN 1 : 1). At −70 °C the band upfield is further split into a pair of lines: the 300 MHz spectrum indicates that this splitting (0.9 Hz) is independent of the field whereas the larger separation increases (in Hz) by a factor of three. Accordingly, the spectrum was interpreted as due to a pair of non-equivalent protons (see also ref. 10) one of which is coupled with the NH proton (Table 1). The spectrum is consistent with the c_s symmetry of tautomer (1a) ≡ (1b) and not with the c_{2v} symmetry of (1c).

The coupled line could be assigned to H-5, on the grounds that this hydrogen is closer to NH than H-3. Although this assignment is not completely unambiguous, it leads to the same attribution as that based on the chemical shift.[10]

Despite the remarkably good signal to noise ratio (particularly at 300 MHz) we could not find any signal attributable to tautomer (1c). The population of the latter, if any, is thus ≤ 1%. In our opinion this finding is not compatible with the ^{15}N and ^{14}N studies [13,14] which indicate (in a polar solvent) a non-negligible presence of tautomer (1c). The possible explanations that can be put forward to settle this discrepancy seem all rather weak.



Scheme.

(i) The accidental degeneracy of the lines for H-3 and -5 in (1c), with those of (1a) is quite unlikely, particularly at 300 MHz.

(ii) The different solvents and the different temperatures required for a direct observation of the tautomers could, in principle, further reduce the population of (1c); nonetheless at least traces of the ' missing ' species should still be observable.

(iii) The rate constant for the hydrogen exchange between N-1 and -4 (k_2 in the Scheme) could be much higher than that between N-1 and -2 (k_1 in the Scheme). If so, the observed spectrum (Figure 1) should not be that of (1a) but the weighted average of (1a and c), a situation which would prevent the direct identification of (1c).

This, however, would mean that (1a) can interconvert into (1b) *via* (1c) (a 1,3 prototropic shift) and therefore no distinction between H-3 and -5 could be achieved, even when k_1 is negligible. This is contrary to the experimental observation.

Therefore, it seems to us that the report [13,14] of a non-negligible population of (1c) has to be taken very cautiously and could well be a consequence of the approximations involved in the method of determining the tautomer populations in an indirect rather than in a direct manner.

The kinetic study of the equilibrium between (1a and b) (autotropic tautomerism) was carried out by total line-shape

Table 2. Activation parameters for the annular tautomerism of 1,2-diazole,[4] 1,2,4-triazole (1), and 1,2,3-triazole (2) in deuteriated DMSO, [$^2H_8$]THF, and CD_2Cl_2 respectively. In the last the values refer to the transformation of the symmetric (2c) into the asymmetric (2a) ≡ (2b) tautomer. The equilibrium parameters (relative to the same transformation) are also given for 0.05M solutions of (2) in CD_2Cl_2 and in [$^2H_8$]toluene. The values for pyrazole were recalculated using the original data (Table 2) of ref. 4

	$\Delta H^{\ddagger}$ [a]	$\Delta S^{\ddagger}$ [b]	$\Delta G^{\ddagger}_{273}$ [a]	E_a [a]	log A
1,2-Diazole in DMSO	6.0 ± 0.4	−28 ± 1.5	13.6	6.5_5	7.0
1,2,4-Triazole (1) in [$^2H_8$]THF	5.8 ± 0.2	−29 ± 1	13.7	6.3	6.9
1,2,3-Triazole (2) in CD_2Cl_2	6.5 ± 0.4	−19 ± 2	11.7	7.0	9.0
	ΔH° [a]	ΔS° [b]	ΔG°_{273} [a]		
(2) in CD_2Cl_2 (0.05M)	−1.8	−8.6	0.55		
(2) in [$^2H_8$]Toluene (0.05M)	−2.9	−16.5	1.60		

[a] In kcal mol^{-1}. [b] In cal mol^{-1} K^{-1}.

analysis of the spectrum at various temperatures (Figure 1) and at different concentrations. No effect on the rate constant k_1 was observed when the concentration was modified. This supports the hypothesis of an intramolecular mechanism for the 1,2 autotropic shift and casts some doubt on the suggestion [6] that the mechanism involves two or more molecules. The Arrhenius plot is linear and does not display any of the unusual deviations reported [6] for the same process in an analogous system (pyrazole) and attributed to quantum tunnelling. On the other hand, our plot agrees with that of a subsequent study [2] on pyrazole itself, where no mention was made of such a deviation. The activation parameters we found for 1,2,4-triazole (1) are reported in Table 2.

The intramolecular mechanism and the absence of tautomer (1c) seem to rule out a 1,3 prototropic shift; accordingly, in the isomeric 1,2,3-triazole (2) one would expect that both *s*- and *v*-tautomers [(2a) = (2b) and (2c)] be detectable. In other words, if the process remains intramolecular, the very same mechanism (1,2 shift) that inhibits the existence of the *v*-tautomer (1c) in 1,2,4-triazole should produce the *v*-tautomer (2c) in 1,2,3-triazole.

The low-temperature 100 MHz spectra of (2) in CD_2Cl_2 were inconclusive to this respect, but the 300 MHz spectrum displayed (at −98 °C) three signals for the ring and two for the NH protons (Figure 2). They were obviously due to the presence of both tautomers, otherwise only a single NH signal [as happened in (1)] would have been observed.

The *v*-tautomer (2c) displays a single line for H-4 and -5 whereas the *s*-tautomer should give an AB spectrum. In our conditions, however, as the lines are quite broad (linewidth >10 Hz) J_{HH} cannot be observed (the expected value is 3—4 Hz). In consequence, the AB spectrum is reduced to a pair of lines. The intensity ratio (Figure 2) of the two NH signals (for a 0.05M solution in CD_2Cl_2 at −98 °C) is 2.3 : 1; accordingly, if the *v*-tautomer (2c) had been the more populated, the relative ratio of the three CH lines would have been 1 : 1 : 4.6. On the other hand, since the experimental ratio is *ca.* 2 : 2.3 : 2.3, the asymmetric (2a) ≡ (2b) *s*-tautomer is the more populated. Therefore, the intense NH signal downfield belongs to the *s*- and that upfield to the *v*-tautomer (Figure 2).

The slight difference in the linewidth of the two CH signals

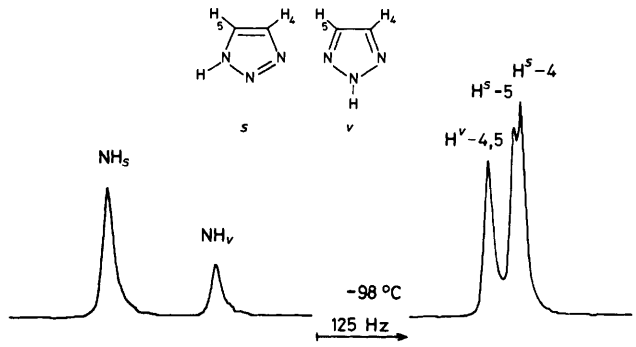


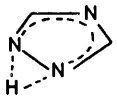
Figure 2. Spectrum (300 MHz) of 1,2,3-triazole (2) in CD_2Cl_2 (0.05M) at −98 °C. The signals of NH (left) and of H-4 and -5 (right) indicate a ratio between the *s*- and *v*-tautomer of 2.3. The ratio is reversed (*v* more stable than *s*) above −60 °C

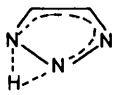
of (2a) (see Figure 2) suggests the assignment of the upfield (Table 1) to H-4 and of the downfield line to H-5. The latter in fact has, probably, an unresolved coupling with NH which further broadens the line of H-5.

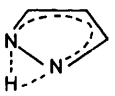
The relative intensities of the NH signals change dramatically on increasing the temperature and, for the 0.05M solution in CD_2Cl_2, the ratio is even reversed above −60 °C. The corresponding equilibrium parameters (Table 2) indicate that at 300 K the ratio *v* : *s* becomes 80 : 20, thus making (2c) the more stable of the two tautomers at room temperature, in this solution.

Since methylene dichloride is a solvent with a relatively high dielectric constant, the tautomeric ratio of (2) was also measured, at the same concentration, in a less polar solvent, [$^2H_8$]toluene. An analogous dependence of the ratio upon the temperature was observed. The thermodynamic parameters for the equilibrium are given in Table 2: they indicate that at 300 K the population of the *v*-tautomer (2c) in toluene is even higher (97%) than in a CD_2Cl_2 solution of equal concentration. It seems therefore that the asymmetric *s*-tautomer is much less stable, at room temperature, than the symmetric, despite its greater statistic factor (two identical forms rather than the single one of the more symmetric *v*-tautomer). These conclusions agree with a recent ^{15}N study on the J_{NH} couplings of (2) and its methyl derivatives in aqueous solutions.[17] On the other hand, they apparently contradict those of refs. 12 and 13, where concentrated solutions in chloroform and DMSO were investigated. This discrepancy could depend, in part, on the approximations of the indirect methods, but could also be a consequence of the decreased stability of the symmetric *v*-tautomer (2c) when the concentration is raised. For instance in CD_2Cl_2 we measured, at the same temperature (−80 °C), a *v* : *s* ratio of 1.1 in a 0.01M solution but of 0.68 in a 0.05M solution. This explains why so many contradictory reports appeared on the relative stability of these tautomers: very different ratios have to be expected if different concentrations are employed.

The rate constants for the 1,2 prototropic shift in (2) were found to be independent of the concentration, thus suggesting (contrary to the hypothesis of ref. 12) an intramolecular mechanism, as in the case of (1). The activation and equilibrium parameters are reported in Table 1. The values of $\Delta H^{\ddagger}$ are almost equal (within experimental error) to that of (1) and to that of pyrazole: [4] it is not unreasonable that the energy barriers for 1,2 prototropic shifts are similar in analogous molecules. The highly negative values of the activation entropies of (1), (2), and pyrazole [4] (Table 2) probably reflect the relatively low probability of reaching the ordered transition


(I)


(II)


(III)

states [of types (I)—(III), respectively] required for carrying on the intramolecular process.

Despite the difference in the solvent employed (THF and DMSO) $\Delta S^{\ddagger}$ for 1,2,4-triazole (1) is identical with that for 1,2-diazole (pyrazole):[4] actually these two molecules, with only two nitrogen atoms involved in the tautomeric process, are even more similar to each other than to 1,2,3-triazole (2). The different $\Delta S^{\ddagger}$ of the latter could therefore be typical of a tautomeric process involving three nitrogens, although we cannot rule out that the difference with respect to (1) and to pyrazole is mainly due to the different solvent (CD_2Cl_2).

Experimental

1,2,4-Triazole (1) was commercially available. 1,2,3-Triazole (2) was obtained by cycloaddition of trimethylsilyl azide to the trimethylsilyl ester of propiolic acid, followed by hydrolysis and decarboxylation.[18] Great care had to be taken in preparing the samples in that very often the tautomeric process was found to be catalysed by traces of impurity in the solvents. Various sources of [$^2H_8$]THF and CD_2Cl_2 had to be tested and purified, and only a few sources of the deuteriated solvents could be purified sufficiently for our purpose. Those we finally selected gave reproducible results, as well as the slowest observed rate constants. The n.m.r. samples were always degassed and sealed under vacuum (10^{-3} Torr): addition of BaO to the samples was found to be useful for eliminating the residual traces of acidic impurities in the solution.[16] THF was the only suitable solvent for the n.m.r. spectra of (1), in that various concentrations could be obtained even at low temperatures (−70 °C). The Me_2O–CD_3CN mixture only allowed a saturated solution of (1) to be examined. On the other hand THF was not suited for reaching the even lower temperatures required to study the tautomerism of (2), so that CD_2Cl_2 (and [$^2H_8$]toluene) had to be used.

The invariance of the rate constants of (1) with concentration (intramolecular process) was checked for 0.04, 0.08, and 0.2M solutions; in the case of (2) 0.01 and 0.05M solutions were employed. The rate constants best fitting the n.m.r. spectra of (2) were subsequently divided by two, to account for the statistical factor of the transformation of (2c) into (2a and b). The activation parameters (Table 2) of (1) resulted from measurements at 13 temperatures in the range −40 to +20 °C, those of (2) at seven temperatures between −79 and −41 °C. The equilibrium parameters for (2) in CD_2Cl_2 were obtained at nine temperatures between −98 and −41 °C and those in [$^2H_8$]toluene at four temperatures between −88 and −61 °C.

The 100 MHz spectra were taken on a Varian XL-100 where the temperature was monitored with a thermocouple inserted in the probe before or after each determination. The 300 MHz spectra were taken on the Bruker CXP-300 instrument of the 'Highfield NMR Service' of the Italian CNR: the temperature was measured by comparing the difference of the shifts of a sample of CH_3OH. Total line-shape analysis was carried out by means of a program written [19] for an Apple II personal computer connected to a plotter.

Acknowledgements

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References

1 Part 26, L. Lunazzi, G. Placucci, C. Chatgilialoglu, and D. Macciantelli, *J. Chem. Soc., Perkin Trans. 2*, 1984, 819.
2 G. P. Kreishman, J. T. Witkowski, R. K. Robins, and M. P. Schweizer, *J. Am. Chem. Soc.*, 1972, **94**, 5894.
3 M. Munowitz, W. W. Bachovchin, J. Herzfeld, C. M. Dobson, and R. G. Griffin, *J. Am. Chem. Soc.*, 1982, **104**, 1192.
4 J. Elguero, C. Martin, A. R. Katritzky, and P. Linda, 'The Tautomerism of Heterocyclics,' Academic Press, New York, 1976.
5 M. L. Roumestant, P. Viallefont, J. Elguero, and R. Jacquier, *Tetrahedron Lett.*, 1969, 495.
6 A. N. Nesmeyanov, E. B. Zavelovich, V. N. Babin, N. S. Kochetkova, and E. I. Fedin, *Tetrahedron*, 1975, **31**, 1461, 1463.
7 M. T. Chennon, C. Coupry, D. M. Grant, and R. Pugmire, *J. Org. Chem.*, 1977, **42**, 659.
8 W. M. Litchman, *J. Am. Chem. Soc.*, 1979, **101**, 545.
9 I. Elguero, A. Fruchier, and V. Pellegrin, *J. Chem. Soc., Chem. Commun.*, 1981, 1207.
10 L. T. Creagh and P. Truitt, *J. Org. Chem.*, 1968, **33**, 2956.
11 J. Elguero, C. Martin, and J. D. Roberts, *J. Org. Chem.*, 1974, **39**, 357.
12 M. Begtrup, *J. Chem. Soc., Chem. Commun.*, 1974, 702.
13 D. S. Wofford, D. M. Forkey, and J. G. Russel, *J. Org. Chem.*, 1982, **47**, 5132.
14 W. Witanowski, L. S. Stefaniak, H. Januszewski, Z. Grabowski, and G. A. Webb, *Tetrahedron*, 1972, **28**, 637.
15 W. M. Litchman, *J. Heterocycl. Chem.*, 1982, **19**, 1235.
16 L. Lunazzi, G. Panciera, and M. Guerra, *J. Chem. Soc., Perkin Trans. 2*, 1980, 52.
17 W. Von Philipsborn and R. Muller, personal communication.
18 L. Birkofer and P. Wegner, *Chem. Ber.*, 1967, **100**, 3485.
19 F. Parisi, Doctoral Thesis, University of Bologna, 1982.

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