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Solution conformational preferences of glutaric, 3-hydroxyglutaric, 3-methylglutaric acid, and their mono- and dianions

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Conformational preferences of glutaric, 3-hydroxyglutaric and 3-methylglutaric acid, and their mono- and dianions have been investigated with the aid of NMR spectroscopy. In contrast to succinic acid, glutaric acid displays essentially statistical conformational equilibria in polar and non-polar solutions of high and low hydrogen-bonding ability with no clear evidence for intramolecular hydrogen-bonding interactions. The acid ionization constant ratios, K_1/K_2, in D_2O and DMSO of glutaric, 3-hydroxyglutaric, and 3-methylglutaric acids also indicate that intramolecular interactions are much less important than, or indeed insignificant, for shorter-chain acids. FTIR studies on 3-methylglutaric acid indicate some preference for either association with solvent or dimerization, depending on the solvent, rather than intramolecular hydrogen bonding. Copyright © 2008 John Wiley & Sons, Ltd.

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INTRODUCTION

Following discovery of unexpected conformational preferences of succinic acid and its mono- and dianion in water and other solvents, a natural extension is towards longer-chain diacids.[1] To this end, the conformational preferences of glutaric acid, 3-hydroxyglutaric acid, and 3-methylglutaric acid have been investigated with the aid of NMR spectroscopy. Additional data were obtained by $^1H\{^2H\}$ NMR spectroscopy on the couplings of *threo*-2,3-dideuteroglutaric acid and FTIR spectroscopy on the carbonyl stretching frequency of 3-methylglutaric acid.

Conformational preferences in solution are strongly linked to solvent properties. For 1,4 dicarboxylic acids, such as succinic acid, there are solvent-dependent and degree of protonation-dependent conformational equilibria between gauche and *trans* conformers, where the gauche isomer is usually favored for the monoanionic state in poorly hydrogen-bonding solvents. As the chain length increases in a series of 1,*n*-dicarboxylic acids, the geometric constraints vary for approach of the two ends. The resulting changes in molecular geometry alter the energetic benefit of intramolecular hydrogen bonding because of steric, entropic, and stereoelectronic effects. Because changes in chain length are reasonably expected not to cause much difference in how the carboxylic and carboxylate ends are solvated, the important influences should be in the relative strengths of inter- and intramolecular interactions. In order for favorable intramolecular hydrogen bonding to occur, the donating carboxylic proton must be in the *E*-conformation relative to the carbonyl and also is more favorable when in the plane of the accepting carbonyl group with an angle θ close to 180° as shown in Fig. 1. This geometry preserves the n–π conjugation of the carboxyls and allows good stereoelectronic overlap between the O—H σ^* and the oxygen lone pair.[2] Still lower in energy would have the hydrogen in the *Z*-conformation, where hydrogen bonding internal to, as well as between carboxyl groups is maximized, but this precludes its approach to an acceptor at the far end of the chain of interest.[3] To explore the geometric feasiblity of intramolecular hydrogen bonding, computations were performed on glutaric acid in the gas phase at the HF/6-31G(d,p) level of theory using GAMESS.[4] As shown in Fig. 2, in the anti gauche–gauche conformation (here, syn and anti refer to the position of the carboxyl carbons relative to the plane of the methylene carbons), glutaric acid is capable of achieving the desired geometry while retaining backbone dihedral angles in the 58–59° range. However, calculations in the gas phase at this level of theory do not answer the question of whether this interaction is energetically favorable in the common solvents in which conformations are studied. Further computations were done on the monoanion at the B3LYP/6-31G(d,p) level of theory and using a PCM water solvent model. The computed geometry was similar to that shown in Fig. 2, with an O—H—O distance of 2.46 Å and an angle of 179°. The PCM solvent model, however, does not include any provision for solute–solvent hydrogen bonds that would compete with intramolecular interactions.

In addition to changes in hydrogen bonding, rotation about the C—C bonds will also alter the degree of electrostatic interactions, especially for the mono- and dianions, as the average distance between ends of the molecules changes.[5] Interactions between the two ends of the molecule, hydrogen bonding or otherwise, should perturb the distribution of conformations towards or away from those geometries that favor the interactions. Such perturbation will influence the vicinal

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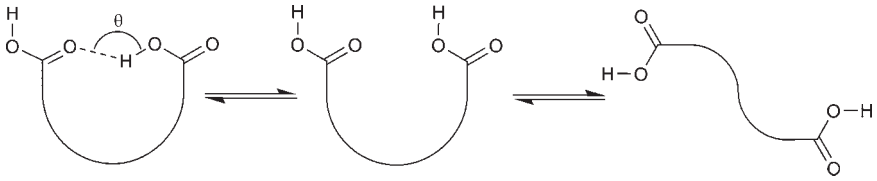

Figure 1. Intramolecular hydrogen-bonding geometries

proton couplings, while the interactions themselves will affect the relative acidities of the carboxylic acid groups so as to decrease pK_1 and increase pK_2 or the reverse.

In contrast to succinic acid, glutaric acid displays an essentially statistical conformational equilibrium in both protic and aprotic solutions of high and low polarity with no evidence for intramolecular interactions favoring hydrogen bonding. The acid ionization constant ratios, K_1/K_2, in DMSO of glutaric and 3-methylglutaric acid also indicate that intramolecular interactions are much less important than for shorter-chain acids. These results are in accord with prior studies showing a decrease in intramolecular interaction with increased chain length of Ω-hydroxy acids.[6]

EXPERIMENTAL RESULTS

Proton NMR spectra of glutaric acid were acquired in a variety of solvents with a range of polarities and known propensities to favor hydrogen bonding at concentrations of 0.25–3.36 M. Monoanion and dianion solutions were prepared from the appropriate tetrabutylammonium salts. The vicinal couplings between the protons α and β to the carboxylate carbons were obtained from the experimental spectra by simulation and iteration using gNMR.[7] The resulting data are tabulated along with the solvent dielectric constants for the diacid, monoanion, and dianion in Table 1.

The conformational equilibria of these glutaric acids and their anions are complicated relative to those of succinic acid by virtue of the greater number of degrees of freedom in the molecule. Instead of gauche and *trans* isomers, glutaric acid has syn gauche–gauche, anti gauche–gauche, gauche–*trans*, and *trans*–*trans* conformers. From the above data on glutaric acid and its anions, the most notable fact is that the fractions of gauche and *trans* conformers around any given methylene—methylene bond must be essentially equal because J_{13} and J_{14} are equal, where the

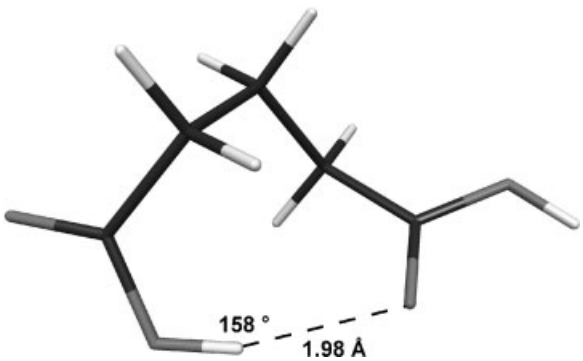

Figure 2. Calculated glutaric acid structure. The donating O–H bond is in the plane of the accepting COOH

J_{13} and J_{14} couplings are between the *threo* and *erythro* pairs of vicinal protons. Confirmation of the result with deuterium-decoupled proton NMR of *threo*-2,3-dideuteroglutaric acid was obtained in D_2O and DMSO as shown in Table 2. The diastereotopic methylene protons again show equal couplings to the proton on the β carbon.

Although the data so far are unable to show conclusively that the two ends of glutaric acid are completely independent, it seems unlikely that an interaction capable of driving such a preference would not also alter the gauche/*trans* balance in at least one of the solvents which have been investigated.

To resolve whether the ends are independent in 3-hydroxyglutaric acid, we assumed that they were independent and the ends of the molecule could be modeled with 3-hydroxybutyric acid. Thus, the methyl group of 3-hydroxybutyric acid is assumed to have steric bulk similar to that of the CH_2CO_2H group in 3-hydroxyglutaric acid, and on this basis, we assign the conformers, depicted in Fig. 3, the same probabilities as the ones calculated from analysis of the 3-hydroxybutyric acid NMR spectrum. If the two ends are independent this will imply that the probabilities of the 3-hydroxyglutaric conformers are products of the probabilities of the two ends. Using calculated J_{13} and J_{14} values for each of the conformers multiplied by its probability, a pair of couplings can be predicted and compared with the experimental value.

NMR spectra taken of 3-hydroxybutyric acid and sodium 3-hydroxybutyrate in D_2O and deuterated DMSO and the couplings were extracted from the spectra and used to derive rotamer populations via the Altona equation.[8] The percentages of **a**, **b**, and **c** in each solvent are listed in Table 3 along with the observed couplings. Two possible sets of populations are possible depending on how the couplings are assigned, the set with the higher fraction of **b** was chosen.

With these percentages in hand, we predicted percentages of the conformations shown in Fig. 4. As an example, $\mathbf{A} = \mathbf{b} \times \mathbf{b}$, $\mathbf{B} = \mathbf{b} \times \mathbf{c}$, etc. By summing the products of the predicted percentages by the predicted couplings of each conformer, a pair of predicted couplings is obtained. To perform this process on the hydroxyglutarate monoanion, one end was assigned the percentages of the hydroxybutyric acid and the other end was assigned hydroxybutyrate percentages. The predicted couplings and deviations from experimental values are shown in Table 4.

In any case, the agreement between prediction and experiment decreases as the carboxylic acid groups are deprotonated. Two factors can account for this divergence, electrostatic repulsion and indirect interaction via the hydroxyl group as shown in Fig. 5. The O—H bond of the hydroxyl group is capable of acting as a hydrogen-bond donor, however it can interact with only one acceptor at a time. Thus, if conformer **b** of one end of the molecule is stabilized by intramolecular hydrogen bonding to the hydroxyl in DMSO, the other end is destabilized away from **b** as shown in Fig. 5. The net effect is the average of the

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Table 1. Substituted glutaric acid couplings grouped as to being in protic or aprotic solvents

Compound		Glutaric		3-Methylglutaric		3-Hydroxyglutaric	
Solvent	ε[a]	J_{13}	J_{14}	J_{13}	J_{14}	J_{13}	J_{14}
Acid							
D_2O	78.5	7.42	7.42	7.8	7.9	4.26	8.76
MeOD	32.6	7.33	7.33				
EtOD	24.3	7.33	7.33				
i-PrOD	18.3	7.26	7.26				
t-BuOD	12.1	7.33	7.33				
DMSO	46.7	7.33	7.33	5.5	7.5	4.90	8.05
Dioxane	7.6	7.47	7.47	5.5	6.75		
THF	2.21	7.33	7.33	5.5	9.5	4.95	7.9
Monoanion							
D_2O	78.5	7.4	7.4	5.0	9.5	4.70	8.50
MeOD	32.6	7.6	7.6				
EtOD	24.3	7.39	7.39				
i-PrOD	18.3	7.24	7.24				
t-BuOD	12.1	6.78	6.78				
DMSO	46.7	6.99	6.99	5.12	7.62	6.27	6.13
Dianion							
D_2O	78.5	7.59	7.59	6.1	8.3	4.80	8.61
DMSO	46.7	7.31	7.31	5.56	8.42	5.82	7.18

[a] Dielectric constant.

Table 2. *threo*-2,3-Dideuteroglutaric acid coupling constants in D_2O and DMSO at 0.05 and 0.005 M concentrations

Solvent	ε[a]	J_{13}	J_{23}	J_{35}
Acid				
D_2O	78.5	7.18	7.18	6.98
DMSO 0.05 M	46.7	7.28	7.28	7.03
0.005 M		7.09	7.09	7.09
Monoanion				
D_2O	78.5	7.65	7.65	6.74
DMSO 0.05 M	46.7	7.17	7.17	7.18
0.005 M		7.12	7.12	7.42
Dianion				
D_2O	78.5	7.61	7.61	6.35
DMSO 0.05 M	46.7	7.16	7.16	7.68
0.005 M		7.11	7.11	7.74

[a] Dielectric constant.

Table 3. 3-Hydroxybutyric acid couplings and conformations calculated via the Altona equation

Solvent	J_{13}	J_{14}	% **a**	% **b**	% **c**
Acid					
D_2O	4.64	8.42	17	62	21
DMSO	5.86	7.32	18	48	34
Anion					
D_2O	6.36	7.24	13	47	40
DMSO	3.79	8.91	20	69	11

hydrogen bonding and the steric repulsion. This effect should become stronger as the carboxyl groups are deprotonated and become better hydrogen-bond acceptors.

The ionization constants in DMSO involved comparison with acids of known strength, the relative strengths of the acid and monoanion of glutaric acid can be determined by NMR of mixtures of glutarate and reference acids.[9] In the case of glutaric

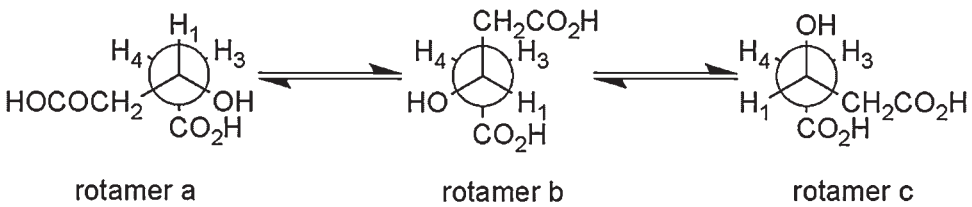

Figure 3. Conformations of one end of 3-hydroxyglutaric acid. 3-Hydroxybutyric acid is taken to be similar, with methyl replacing CH_2CO_2H

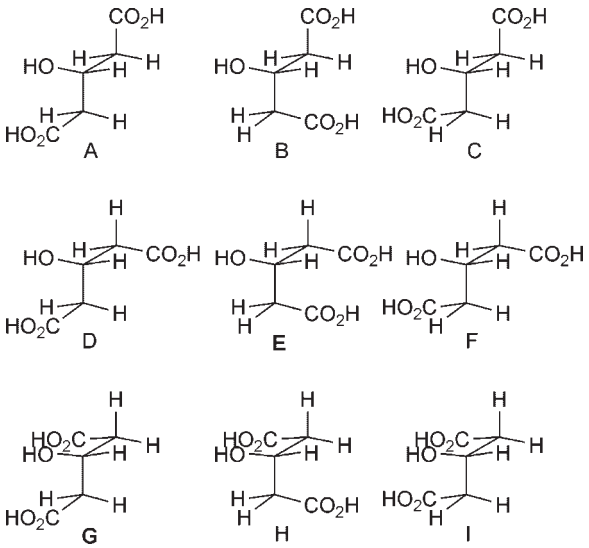

Figure 4. 3-Hydroxyglutaric acid conformations. Note that symmetry requires that B = D, C = G, and F = H

acid, the pK_a data give a pK_1 of 10.4 and a pK_2 of 14.0 for a K_1/K_2 of 7×10^3. With 3-methylglutaric acid, the measured pK_1 and pK_2 of 10.6 and 15.9 were obtained for a K_1/K_2 of 2×10^5, while 3-hydroxyglutaric acid showed a pK_1 of 10.1 and a pK_2 of 14.1 for a K_1/K_2 of 10^4. In D_2O, 3-hydroxyglutaric acid pK_1 and pK_2 were 4.08 and 5.03 for a K_1/K_2 of 10^1. Glutaric acid and 3-methylglutaric acid have previously had an aqueous K_1/K_2 measured as 10^1 as well.[10] For all acids, the ratios are much lower than the K_1/K_2 reported by Choi[9] for succinic acid in DMSO. For comparison, *trans*-1,4-cyclohexanedicarboxylic acid by the same procedure gave a pK_1 of 12 and a pK_2 of 14 for a K_1/K_2 of 10^2. This difference in ratio is like that of fumaric acid where neither intra- nor intermolecular hydrogen bonding is important and the K_1/K_2 ratios reflect the second ionization occurring with unfavorable negative charge interactions.[5]

The NMR spectra of the deuterated diacid show carboxyl protons in DMSO solution but not in water, where intermolecular exchange is expected to be rapid. With the monoanion, the carboxyl protons are not visible in either solvent. The conformational preferences of the molecule did not change with a 10-fold reduction in concentration, which suggests that dimeric or higher intermolecular hydrogen bonding does not play a significant role in determining the conformation of glutaric acid in DMSO solution or that the acid is present only as the dimer at both concentrations.

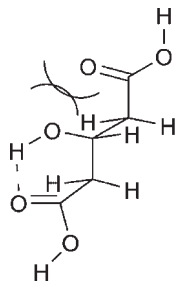

Figure 5. Hydrogen bonding on only one side at a time

To resolve this ambiguity, FTIR spectra were taken of the carbonyl frequencies of 3-methylglutaric acid in THF and DMSO (Table 5). These frequencies depend on the hydrogen bonding of the carboxylic acid, with dimers reported at approximately 1710 cm^{-1} in CCl_4, solvent-associated monomer at 1735 cm^{-1} in THF or dioxane, and unassociated monomeric acid at 1758 cm^{-1} in CCl_4 by Nakanishi and Solomon.[11] Solvent-associated and dimeric carbonyl stretching frequencies of 1717 and 1713 cm^{-1}, respectively, were reported for lauric acid in DMSO by Picquart *et al.*[12] Our FTIR data suggest that, in DMSO and THF, the acid is hydrogen bonded to solvent oxygen atoms at concentrations between 0.01 and 0.1 M. Any intramolecular H-bonding effect should be weaker in solvents such as water, which are capable of competitively acting as H-bond donors as well as H-bond acceptors in providing solvation.[1b] Previous infrared spectroscopic studies in CCl_4 by Takasuka *et al.*[13] have shown that formation of cyclic dimers is favored in glutaric acid over intramolecular hydrogen bonding, with the free carboxylic acid present at low concentrations. This suggests that other solvents capable of disrupting glutaric acid dimers will also prevent the appearance of intramolecular hydrogen bonding.

Table 4. 3-Hydroxyglutaric couplings predicted from 3-hydroxybutyric conformational equilibria and RMS deviations from experiment

	Calculated		Experimental		
Solvent	J_{13}	J_{14}	J_{13}	J_{14}	RMS dev. (Hz)
Acid					
D_2O	4.68	8.59	4.26	8.76	0.45
DMSO	5.88	7.35	4.90	8.05	0.98
Monoanion					
D_2O	5.57	8.04	4.70	8.50	0.98
DMSO	4.84	8.16	6.27	6.13	2.48
Dianion					
D_2O	6.43	7.37	4.80	8.61	2.05
DMSO	3.78	8.82	5.82	7.18	2.62

CONCLUSIONS

Intramolecular hydrogen bonding between the carboxylic acid groups in glutaric acid and its anions plays less of a role than in succinic acid and its anions, presumably because of the different geometric constraints placed on approach of the two functional groups. The change in the importance of intramolecular carboxyl-carboxylate hydrogen bonding manifests itself in a lack

Table 5. Carbonyl stretching frequency of 3-methylglutaric acid

Solvent	Dielectric constant	Peak (cm^{-1})
THF 0.1 M	2.21	1733.3
0.01 M		1734.4
DMSO 0.1 M	46.7	1715.3
0.01 M		1711.6

of perturbation of the conformational equilibrium away from a statistical mixture, lower values of K_1/K_2 than reported for succinic acid, as well as IR carbonyl stretching frequencies that match better with a lack of intramolecular hydrogen bonding. Intramolecular interaction between carboxylate and hydroxyl groups is possible in 3-hydroxyglutaric acid and may perturb the conformational equilibrium away from what would be predicted in its absence. However, the perturbation is mediated via interactions of vicinal groups rather than direct interactions of the respective carboxylate groups.

EXPERIMENTAL

Glutaconic acid and other chemicals were used without further purification.

Infrared spectra were taken on an FTIR spectrometer with background subtraction of absorptions from air in the beam path. NMR spectra were recorded using either a 300 MHz or 600 MHz NMR spectrometer with signal lock on the deuterated solvent and referenced to either TMS, DSS, or residual solvent protons. An exception was the acquisition of the deuterium-decoupled spectra, which were acquired without a signal lock.

threo-2,3-Dideuteroglutaric acid

trans-Glutaconic acid (0.943 g, 7.2 mmol) was dissolved in deuterium oxide and evaporated *in vacuo* three times followed by dissolution in and evaporation of ethan(ol-d). The acid was then dissolved in 30 ml of ethan(ol-d) in a round-bottom flask equipped with a magnetic stirrer and reflux condenser. Wilkinson's catalyst (0.073 g, 0.08 mmol) was added and the solution stirred while the apparatus was purged with deuterium gas. Under balloon pressure of deuterium, the reaction mixture was heated to slightly less than reflux with vigorous stirring for 2.5 h. The mixture was allowed to cool under deuterium before concentration *in vacuo*. The residue was taken up in 10 ml of deionized water and filtered through a short plug of celite. The remaining solids were rinsed with 5 ml of deionized water, filtered, and combined. The combined filtrate was concentrated *in vacuo* with residual water removed azeotropically with ethanol. The remaining material (0.955 g, 7.1 mmol, 98%) spontaneously crystallized and was not further purified. The proton NMR spectrum (500 MHz, D_2O) gave peaks at 1.865 ppm (ddm, 6.8, 6.4 Hz, 1H), 2.418 ppm (m, 1H), 2.438 ppm (d, 7.33 Hz, 2H). The proton decoupled ^{13}C NMR spectrum (126 MHz, D_2O) gave peaks at 178 ppm (s), 32.83 ppm (s), 32.57 (t, 20.0 Hz), 19.36 ppm (t, 20.1 Hz).

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REFERENCES

[1] a) L. N. Williams, K. A. Petterson, J. D. Roberts, *J. Phys. Chem. A* **2002**, *106*, 7491–7493; b) D. J. Price, J. D. Roberts, W. L. Jorgensen, *J. Am. Chem. Soc.* **1998**, *120*, 9672–9679.
[2] For an NBO treatment of hydrogen bonding and its stereoelectronic ramifications, see A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *88*, 899–926.
[3] a) L. Turi, J. J. Dannenberg, *J. Phys. Chem.* **1993**, *97*, 12197–12204; b) C. Rovira, J. J. Novoa, *J. Chem. Phys.* **2000**, *113*, 9208–9216.
[4] M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis, J. A. Montgomery, *J. Comput. Chem.* **1993**, *14*, 1347–1363.
[5] a) N. Bjerrum, *Z. Phys. Chem.* **1923**, *106*, 219–242; b) J. G. Kirkwood, F. H. Westheimer, *J. Chem. Phys.* **1938**, *6*, 506–512; c) F. H. Westheimer, J. G. Kirkwood, *J. Chem. Phys.* **1938**, *6*, 512–517.
[6] C. Alemán, J. Casanovas, D. Zanuy, H. K. Hall, Jr. *J. Org. Chem.* **2005**, *70*, 2950–2956.
[7] *gNMR 4.1, I.*, Adept Scientific: Litchworth, Herbs, **1999**.
[8] a) C. Altona, R. Francke, R. de Haan, J. H. Ippel, G. J. Daalmans, A. J. A. Westra Hoekzema, J. van Wijk, *Magn. Res. Chem.* **1994**, *32*, 670–678; b) C. Altona, J. H. Ippel, A. J. A. Westra Hoekzema, C. Erkelens, M. Groesbeek, L. A. Donders, *Magn. Res. Chem.* **1989**, *27*, 564–576.
[9] P. J. Choi, K. A. Petterson, J. D. Roberts, *J. Am. Phys. Org. Chem.* **2002**, *15*, 278–286.
[10] I. Jones, F. G. Soper, *J. Chem. Soc.* **1936**, 133–137.
[11] K. Nakanishi, P. H. Solomon, *Infrared Absorbtion Spectroscopy* (2nd edn). Holden-Day, XXXX, **1977**; 214–216.
[12] M. Picquart, T. Lefèvre, G. Lacrampe, *Applied Spectrosc.* **1995**, *49*, 1268–1274.
[13] M. Takasuka, T. Saito, M. Yamakawa, *J. Chem. Soc. Perkin Trans. 2* **1991**, 1513–1516.