NMR conformational study of the neutralisation of *meso*- and *rac*-2,3-dimethyl- and 2,3-diethylsuccinic acids in aqueous solution

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The conformational behaviour of the *meso* and *racemic* isomers of aqueous 2,3-dimethyl- (**1**) and 2,3-diethylsuccinic acids (**2**) has been investigated at different degrees of titration. The changes of both the vicinal coupling constant between methine protons and the ^{13}C chemical shifts have been determined and discussed in terms of the relative content of conformers in the conformational equilibrium.

It was found for the *meso* forms that different amounts of staggered conformers explain the observed changes of NMR parameters. However, for *rac*-**1** and -**2** the NMR data give evidence that besides staggered conformers, a conformer with a non-staggered conformation due to formation of an intramolecular hydrogen bond also has to be taken into consideration. At half-degree of titration this conformer strongly prevails for *rac*-**2** and seems to exist in reasonable amounts for *rac*-**1**. This is in accordance with the different K_1/K_2 ratio of both acids.

Introduction

The dissociation behaviour of 2,3-dialkylsuccinic acids is the subject of many investigations.[1] It is characteristic that the ratio between the first and second dissociation constants of these acids depends on their configuration and on the steric requirements of the alkyl substituents. Whereas $\Delta pK = pK_2 - pK_{s1}$ is smaller than three for the *meso* isomers (**m**) it is up to 9.5 for the *racemic* isomers (**r**) depending on the alkyl substitution and solvent.[2] The main reason for these small K_2-values of *rac*-2,3-dialkylsuccinic acids is the formation of an intramolecular hydrogen bond in the monoanion. NMR spectroscopic evidence for the formation of intramolecular hydrogen bonds was obtained for monoanions of dicarboxylic acids in dimethyl sulfoxide solution from the extreme downfield-shifted signal of the hydrogen-bonded proton.[3] From isotope shifts on the ^{13}C spectra of ^{18}O-labelled dicarboxylic acids it was concluded that the hydrogen bond is asymmetric in aqueous solution but symmetric in non-polar solvents.[4] This difference was attributed to the disorder of the aqueous environment.

The hydrogen bond is stabilised by bulky alkyl substituents as can be concluded from increasing ΔpK values.[1] Such bulky groups reduce the conformational mobility of the molecule and can stabilise conformers with carboxyl groups in a *gauche*-position. However, they introduce steric strain in the molecule, which should be reduced in the preferred conformation of the monoanion with an intramolecular hydrogen bond. Such a conformer should deviate from a staggered arrangement of substituents.

NMR spectroscopy has become the preferred method to obtain information on the conformational equilibrium of dicarboxylic acids at different degrees of titration (α).[3-10] In this way, the conformational equilibrium of 2,3-dimethylsuccinic acid (**1**, R = H) and its dianion in aqueous solution was also investigated.[8,9] However, only the staggered rotamers **I**–**III** of *meso*- and **IV**–**VI** of *rac*-2,3-dialkylsuccinic acids, respectively, were considered in the conformational equilibrium and their content was estimated by analysing vicinal proton–proton coupling constants (Table 1, footnotes *c* and *d*).

Non-staggered conformations have never been taken into consideration to explain the changes of coupling constants as does seem reasonable especially for the racemic diastereoisomer.

Therefore, the aim of this paper is to investigate the conformational behaviour of the diastereoisomers of **1** and 2,3-diethylsuccinic acid (**2**, R = CH_3) in the course of neutralisation with respect to ^1H and ^{13}C NMR evidence for the formation of a non-staggered conformer with an intramolecular hydrogen bond in *aqueous* solution. With respect to **1** it is a reinvestigation of the results published in refs. 8 and 9. By including **2** the steric effect of the alkyl substituent is considered.

It was shown for **1** and 2-ethyl-3-methylsuccinic acid[10] that the relative populations of staggered rotamers can be estimated for these acids from the ^{13}C chemical shifts taking into account ^{13}C chemical shift changes depending on the relative arrangement of γ-substituents (γ-effect). However, ^{13}C chemical shifts at different degrees of titrations were not published. Since proton–proton coupling constants cannot be obtained for alternating copolymers containing 2,3-dialkyl substituted succinic acid units, the understanding of ^{13}C chemical shift changes during titration gives an additional opportunity to analyse the conformational behaviour of these polymers.[11]

Results and discussion

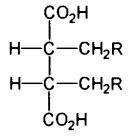
Estimation of conformer populations

The ^1H spectra of **1** and **2** are of the $A_3XX'A'_3$ and $A_3RSXX'R'S'A'_3$ type, respectively, where the methylene protons R and S of **2** are diastereotopic. Selective decoupling of the methyl group signal of **2** was used to simplify the spin system to the RSXX'R'S' type. Coupling constants and chemical shifts were obtained by spectrum simulation. Table 1 summarises the vicinal coupling constants for both acids and their dianions.

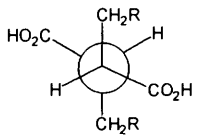
From the $^3J_{HH'}$ ($\equiv {}^3J_{XX'}$) values it is clear that besides configuration, the alkyl substituent also influences the conformational equilibrium. The percentages of the conformers with antiperiplanar methine protons can be estimated using the simple formula (1) where P_{anti} indicates the population of

$$P_{anti} = \frac{{}^3J_{HH'} - J_g}{J_t - J_g} \qquad (1)$$

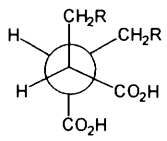
this conformer (**I** or **IV**), $^3J_{HH'}$ the experimental coupling constant, J_g and J_t the coupling constants of the corresponding conformers with methine protons in *gauche* and *trans* position, respectively.



1m: R = H
2m: R = CH_3



I



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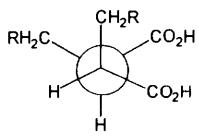

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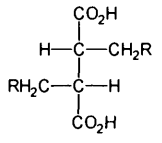
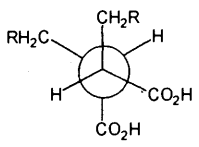
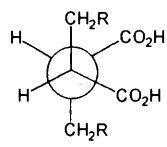


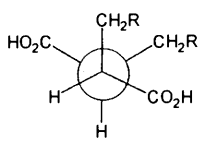
1r: R = H
2r: R = CH_3



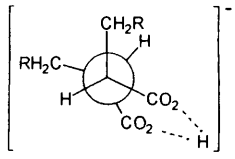
IV



V



VI



VII

Table 1 Vicinal proton–proton coupling constants of the diastereoisomers of **1** and **2** in acid and dianionic form, calculated $^3J_{XX'}$ values for the staggered conformers of **1m** and **1r**[a] and estimated populations (in %) of conformers **I**–**VI**

Compound	Solvent	$^3J_{XX'}$/Hz	P_I	$P_{(II+III)}$	Compound	Solvent	$^3J_{XX'}$/Hz	P_{IV}[b]	P_V[b]	P_{VI}[b]
1m[c]	D_2O	7.1	47	53	**1r**[d]	D_2O	8.8	66	17	17
	NaOD	10.95	92	8		NaOD	6.5	37	16	47
2m	D_2O	9.8	78	22	**2r**	D_2O	9.8	78	11	11
	NaOD	10.9	91	9		NaOD	8.3	59	10	31
conf. **I**		11.64			conf. **IV**		11.64			
conf. **II** (≡**III**)		3.15			conf. **V**		2.50			
					conf. **VI**		3.79			

[a] Calculated using eqn. (5) in ref. 12, group electronegativities: $\chi(H) = 2.08$, $\chi(CH_3) = 2.32$, $\chi(CO_2H) = 3.15$,[14] bond angle H–CH–CH = 106° for all conformers calculated from X-ray data of **1r**.[15] [b] Calculated assuming $P_{VI}/P_V = 1$ for the acid form and $P_{VI}/P_V = 3$ for the anionic form. [c] Literature data: D_2O: $^3J_{HH'}$ = 6.2 Hz,[8] 5.93 Hz,[9] P_I = 50%,[8] 49%,[9] NaOD: $^3J_{HH'}$ = 10.2 Hz,[8] 10.13 Hz,[9] P_I = 80%,[8] 91%.[9] [d] Literature data: D_2O: $^3J_{HH'}$ = 8 Hz,[8] 7.77 Hz,[9] P_{IV} = 70%,[8] 68%,[9] P_V = 10%,[8] NaOD: $^3J_{HH'}$ = 7.4 Hz,[8] 6.23 Hz,[9] P_{IV} = 55%,[8] 52%,[9] P_V = 30%.[8]

J_g and J_t of the conformers **I**–**VI** could not be determined experimentally and for this reason calculations were carried out using the simplified multiparametric Karplus equation of Imai and Osawa[12] (Table 1). Although the calculated *trans* coupling (^3J_t) of 11.64 Hz is similar to values assumed by other authors,[8,9] the *gauche* couplings are larger (^3J_g = 2.5–3.8 Hz *vs.* 1 Hz[8,9]). However, the vicinal coupling of 4.4 Hz for the methine protons of *cis*-cyclohexane-1,2-dicarboxylic acid with a **II**-like conformation supports these values. The different $^3J_{HH'}$ values of **V** and **VI** result from the orientational dependence of the substituent effect on vicinal proton–proton couplings. The effect of the different alkyl groups on $^3J_{HH'}$ can be neglected (< 0.03 Hz). However, the ionisation of the carboxylic groups also influences $^3J_{HH'}$.[13] This cannot be quantified for lack of the $\chi(CO_2^-)$ value. An estimated decrease in group electronegativity of 0.5 units results in increasing $^3J_{HH'}$ for **I**–**V** (at most 0.4 Hz) and in a nearly unchanged value for **VI**. These changes are within experimental errors. Therefore, the $^3J_{HH'}$ values given in Table 1 were used to obtain estimations for the conformer equilibrium of both diastereoisomers of **1** and **2** in the acid and dianion form (Table 1).

For **1m** and **2m**, the conformers **II** and **III** are enantiomers having the same value for J_g. The conformers **V** and **VI** of the racemic isomers **1r** and **2r** are different. Whereas for the dianion **VI** should be preferred due to the electrostatic repulsion of the carboxylate groups, the situation is not so clear for the acid form.[7,8,16] As a compromise, the same population is assumed for both conformers in the acid form. The estimations were carried out with 'effective' values for J_g. For the acid forms $J_{g\,eff}$ = 3.15 Hz was used as an effective value assuming a ratio **VI**/**V** = 1. For the anionic forms $J_{g\,eff}$ = 3.47 Hz was calculated with **VI**/**V** = 3. The preference of **VI** with regard to **V** for the anions is in accordance with ^{13}C NMR results as shown in the further discussion. Nevertheless, for both cases variation of the **VI**/**V** ratio does not change the population of **IV** significantly. Only these populations should be compared.

Conformations of acids and dianions

The analysis of the calculated conformational equilibria of **1** and **2** (Table 1) clearly shows the conformational effect of different 2,3-alkyl substituents.

The relative populations of rotamers of **1** are in accordance with literature data.[8,9] For the *meso*-acids, the larger steric effect of the ethyl group results in an enhanced preference for the conformer with the lowest number of γ-*gauche* interactions (**I**). The content of **I** is larger than 90% for the dianions independent of the alkyl substituent due to the dominant electrostatic repulsion of the carboxylate groups.

However, for the racemic dianions, the conformers with a *gauche* arrangement of carboxylate groups (**IV**, **V**) are calculated to be more than 40% also if the **VI**/**V** ratio is other than 3. This seems to be unlikely and shows the limits of the staggered conformer concept. A more realistic treatment should assume distortions of the staggered conformers due to steric and electrostatic interactions. Nevertheless, both treatments show that on going from **1r** to **2r** the increasing steric strain of *gauche* alkyl groups results in a decrease of the dihedral angle between carboxylate groups. The larger $^3J_{HH'}$ value for **2r** may be due to a higher content of **IV** (Table 1). On the other hand, assuming **VI** to be the preferred conformer the larger $^3J_{HH'}$ is due to increasing

steric repulsion of the alkyl groups which results in a decrease of the proton–proton dihedral angle and so in increasing $^3J_{HH'}$.

Conformational changes during transition from acid to dianion

These conformational changes of the different configurations of **1** and **2** were followed by both vicinal methine–methine proton coupling constants (Fig. 1) and ^{13}C chemical shifts (Fig. 2). *Meso*- and *rac*-isomers show quite different changes of these NMR parameters.

The $^3J_{HH'}$ values of **1m** and **2m** at different degrees of titration are shown in Fig. 1(*a*). Only a slight increase is observed up to $\alpha = 1$. With the ionisation of the second carboxylic group the conformers **II**/**III** with synclinal carboxylate groups become destabilised by increasing electrostatic repulsion, and the content of rotamer **I** increases significantly. This is more distinctive for **1m** due to the lower **I** content in the acid form. The same behaviour was observed for succinic acid and methyl succinic acid.[5–7]

These conformational changes are also reflected in the ^{13}C chemical shifts. However, both the conformation and the ionisation of the carboxylic groups influence the $\delta(^{13}C)$ values. The latter effect can be assumed to be proportional to the degree of titration. Therefore, deviations from a straight increase of $\delta(^{13}C)$ are due to conformational changes. Because the conformational equilibrium of **2m** is only slightly changed in the range between $\alpha = 0$ and 1, the increase of ^{13}C chemical shifts [Figs. 2(*a*), (*c*) and (*e*)] is mainly due to the ionisation of the carboxylic group. Extrapolation to $\alpha = 2$ gives reasonable values of this effect for the different carbon signals: $\Delta\delta(C{=}O) = 4.8$, $\Delta\delta(CH) = 4$ and $\Delta\delta(CH_2) = 1$ ppm. The superposition of the chemical shift effects determined for the ionisation of aliphatic monocarboxylic acids[17] results in larger values (5.3, 5.6 and 2.3 ppm). Obviously, a simple addition of the electric field effects is not possible due to their orientational dependency.

The influence of different γ-*gauche* interactions on the methyl ^{13}C chemical shift of **1m** can be seen in Fig. 2(*a*). Considering the ionisation effect, there is a slight increase of $\delta(^{13}C)$ up to $\alpha = 1$ but a strong increase during the ionisation of the second carboxylic group. This is expected from the ^1H data because the greatly increasing amount of **I** is connected with going from a CH_3/CH_3 to a $CH_3/C{=}O$ γ-*gauche* effect. The latter effect is smaller[10] resulting in an increasing ^{13}C chemical shift for the methyl signals.

For the carboxylic groups the changes are smaller and also the effect on carbonyl chemical shifts [Fig. 2(*e*)]. As shown in ref. 10, the methine carbon shifts are larger for **I** than for **II**/**III**. This is in accordance with the experimental results [Fig. 2(*c*)].

All these ^{13}C chemical shift effects can also be observed for **2m** but to a lower degree due to the smaller changes in the conformer equilibrium. The unexpected increase of the ^{13}C chemical shift between $\alpha = 0.2$ and 1 cannot be explained. There is no correlation to the $^3J_{HH'}$ values. Formation of an intramolecular hydrogen bond at $\alpha = 1$ should result in an opposite effect assuming a decreasing dihedral angle between carboxylic groups in **II**/**III**. It can be concluded that no conformer with an intramolecular hydrogen bond appears in the course of neutralisation. The changes in NMR parameters of *meso*-2,3-dialkylsuccinic acids can be explained by an equilibrium of conformers **I**–**III**.

The NMR parameters of **1r** and **2r** are influenced in a more complicated manner by the titration of carboxylic groups.

The same values for the ^{13}C chemical shift changes due to the ionisation of the carboxylic groups as for the *meso* isomer were assumed despite different orientations of carboxylic groups in the preferred conformer of the acid forms. However, a more reasonable value cannot be determined for the racemic isomers.

At first the behaviour of **2r** due to the larger effects should be discussed.

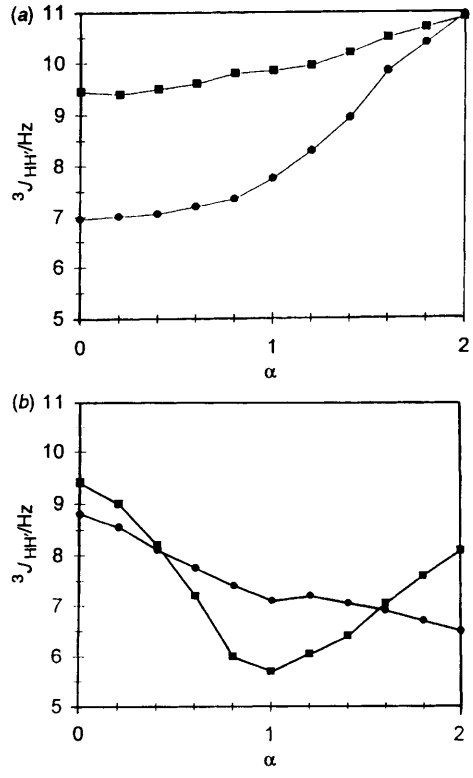


Fig. 1 Vicinal methine–methine proton coupling constants ($^3J_{HH'}$) for **1** (●) and **2** (■) as a function of degree of titration (α); (*a*) *meso* isomers, (*b*) *racemic* isomers

In the range of $0 < \alpha < 1$ a drastic change in conformation takes place. The value of $^3J_{HH'}$ becomes continuously smaller [Fig. 1(*b*)] whereas $\delta(CH_2)$ increases [Fig. 2(*b*)]. At half-degree of titration both values reach extrema. The coupling constant of 5.7 Hz at $\alpha = 1$ is larger than a *gauche* coupling but significantly smaller than a *trans* coupling constant. The change of $\delta(CH_2)$ has to be explained as a strong decrease of γ-*gauche* interactions between the methylene groups that exist in **IV**. The preference of conformer **V** seems to be in accordance with these facts. However, starting from a high amount of **IV** in the acid, the driving force of the conformational change from **IV** to **V** is not obvious. In both conformers the carboxylic groups are in synclinal arrangement and the number of γ-*gauche* interactions is larger for **V**.

This behaviour can be explained with an additional conformer **VII**. It is characterised by a distortion of the staggered arrangement of substituents caused by a strong intramolecular hydrogen bond which reduce the dihedral angle between the carboxylic groups. For maleic acid, a monopotassium salt was isolated and the crystal structure was determined.[18] In contrast to aqueous solution[4] a symmetrical hydrogen bond was found. This ion is considerably strained due to the C–C double bond. The strain would be completely relieved in a molecule with a C–C single bond if the carboxylic groups are tilted by 46° about their C–C bond so that the oxygens in the hydrogen bond lay on opposite sides of the plane of the carbons.[19] The formation of the intramolecular hydrogen bond leads to a change in the conformation from an 'open' one to a 'cyclic' arrangement.

The steric repulsion of alkyl substituents in the 2- and 3-positions can additionally reduce this angle. Therefore, it is reasonable to assume dihedral angles smaller than 160° between the protons and larger than 80° between the methylene groups.

The transition from **IV** to **VII** is a rotation of 20° or more. From the Karplus equation $^3J_{HH'}$ becomes an intermediate value between J_g and J_t as observed. The γ-*gauche* interaction

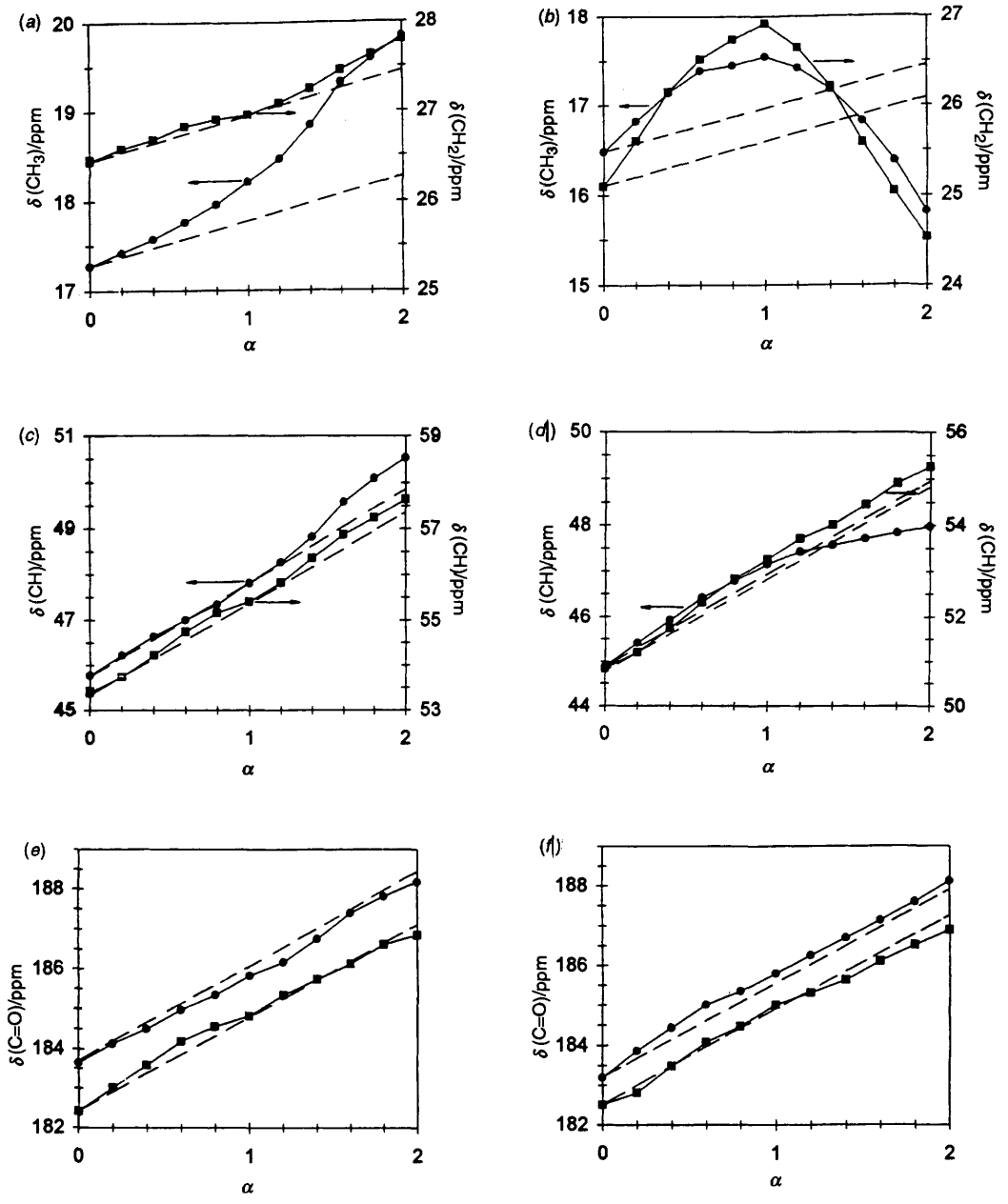


Fig. 2 ^{13}C chemical shifts for **1** (●) and **2** (■) as a function of degree of titration (α); (*a*, *c* and *e*) *meso* isomers; (*b*, *d* and *f*) *racemic* isomers. (*a*, *b*) methyl carbon of **1** and methylene carbon of **2**; (*c*, *d*) methine carbons; (*e*, *f*) carbonyl carbons. Broken lines represent the estimated chemical shift change only due to ionisation.

between methylene groups decreases resulting in downfield shift in accordance with the experiment. However, the expected upfield shift for the carbonyl carbons could not be observed [Fig. 2(*f*)]. Possibly this is due to chemical shift effects caused by hydrogen bond formation.

It should be mentioned that conformer **VII** of **2r** is characterised by a changed equilibrium of conformers around the CH–CH_2 bond. This can be concluded both from the ^1H chemical shift of the methylene protons and their couplings to the methine proton.† Whereas both values are different for the methylene protons R and S of acid and dianion, this difference disappears at α = 1. From examination of a model, it can be concluded that the methyl group is mainly antiperiplanar to the methine group both in acid and dianion, but in **VII** the conformer with the methyl group synclinal to methine and antiperiplanar to the carbonyl group is comparably populated due to reduced 1,4-diaxial interactions.

The effects on NMR parameters due to ionisation are less drastic for **1r**. Nevertheless, there are also hints on the formation of a monoanion with hydrogen bond. Up to α = 1, $^3J_{HH'}$ decreases with a slight minimum at half-degree of titration [Fig. 1(*b*)]. This minimum was also found by Morawetz and Choi.[9] The difference of $\delta(CH_3)$ at α = 0 and α = 1 is +0.5 ppm (corrected by −0.5 ppm for the ionisation of one carboxylic group). The same value for **2r** is $\Delta\delta(CH_2)$ = +1.3 ppm. This can be partly explained by the smaller γ-*gauche* effect of methyl groups. Taking into consideration the larger $^3J_{HH'}$ value of **1r** at α = 1 (7.1 Hz), the content of **VII** seems to be smaller than for **2r** and conformer **IV** with antiperiplanar protons exists in a reasonable amount at half-degree of titration. These effects can also be explained by a smaller decrease of the dihedral angle

† **2r** (α = 0): $^3J_{RX}$ = 3.8 Hz, $^3J_{SX}$ = 9.0 Hz, $\delta(H_R)$ = 1.76, $\delta(H_S)$ = 1.59; **2r** (α = 1): $^3J_{RX}$ = $^3J_{SX}$ = 7.1 Hz, $\delta(H_R)$ = $\delta(H_S)$ = 1.65; **2r** (α = 2): $^3J_{RX}$ = 4.1 Hz, $^3J_{SX}$ = 10.5 Hz, $\delta(H_R)$ = 1.54, $\delta(H_S)$ = 1.41.

between the carboxylic groups due to a less strong hydrogen bond. The steric strain due to synclinal alkyl groups is lower for **1r** than for **2r**.

The NMR results show that for **1r** the formation of a conformer with an intramolecular hydrogen bond is less distinct than for **2r**. This corresponds with the ratio of the first and second dissociation constants of both compounds. In water K_1/K_2 is 181 for **1r** and 1220 for **2r**[2] indicating the stronger hydrogen bond for **2r**.

The different behaviour of $^3J_{HH'}$ for **1r** and **2r** at $\alpha > 1$ results from the different steric requirements of the alkyl substituents and leads to different ratios of conformers **IV**–**VI** for the dianions (Table 1). The decrease of methyl and methylene carbon chemical shifts [Fig. 2(*b*)], respectively, indicates significant γ-*gauche* interactions in the preferred conformers (dianions of **IV** and, especially, **VI**).

Carbonyl chemical shifts seem to be less sensitive to different γ-interactions and so the effects on carbonyl chemical shifts are smaller [Fig. 2(*f*)]. The deviations from a straight increase cannot be explained by conformation effects alone.

As the $^3J_{HH'}$ values, the methine carbon chemical shifts, also reflect the different conformational behaviour of **1r** and **2r** at $\alpha > 1$ [Fig. 2(*d*)]. The content of **IV** is significantly smaller for the dianion of **1r** than for **2r** (Table 1) and, consequently, the δ(CH) value of **1r** is smaller then the value of **2r** as expected from ref. 10.

Conclusions

It has been shown that the analysis of conformation-dependent ^1H and ^{13}C NMR parameters confirms that aqueous *rac*-2,3-dialkylsuccinic acids form a non-staggered conformer with an intramolecular hydrogen bond at half-degree of titration. This can be concluded from characteristic changes of vicinal proton–proton coupling constants and ^{13}C chemical shifts. Therefore, it is not adequate[9] to discuss the changes in proton–proton couplings of these compounds during neutralisation only as an equilibrium of staggered conformers. For the *rac*-2,3-diethylsuccinic acid, the NMR-data at half-degree of titration clearly show evidence for the dominance of such a conformer. Also, for the corresponding methyl compound, it is reasonable to assume such a conformer exists in a distinct amount in the conformational equilibrium. This is in accordance with ionisation data.

For the *meso*-isomers no evidence of an intramolecular hydrogen bond was found at half-degree of titration. The conformational equilibrium can be characterised by different contents of staggered conformers.

Going from methyl to ethyl substitution results in significant differences in conformational equilibria. Conformers with a large number of γ-*gauche* interactions were more strongly destabilised, increasing the alkyl group.

Analysis of ^{13}C chemical shift changes during titration seems to be useful to obtain information on conformational equilibria of succinic acid derivatives like polymers whose proton-proton coupling constants cannot be determined. An extension of these investigations to polar but non-hydrogen-bonding solvents should result in enhanced effects due to the absence of interactions with other hydrogen-bonding molecules.

Experimental

Materials

meso- and *rac*-2,3-dimethylsuccinic acids were obtained from the Aldrich Chemical Co. They were purified as described in ref. 9. The 2,3-diethylsuccinic acids were kindly donated by Dr Zschoche. The melting points agree with those reported in ref. 20.

Spectroscopy

The NMR spectra were obtained using a Bruker AMX 300 spectrometer operating at 300.13 MHz for ^1H and 75.475 MHz for ^{13}C. Measurements were carried out with a 5 mm 1H/X-nuclei inverse probe to record both ^1H and ^{13}C spectra on the same sample at 300 K. The spectra had a final resolution of 0.067 Hz/Pt for ^1H and 1.1 Hz/Pt for ^{13}C, respectively. The spectra were referenced on a small amount of internal sodium [2,2,3,3-$^2H_4$]3-(trimethylsilyl)propionate [$\delta(^1H) = \delta(^{13}C) = 0$ ppm at $\alpha = 0$].

The proton spectra were simulated and iterated with the computer program WIN-DAISY (Bruker). This was done using the overall spectral band shapes. The absolute error of proton coupling constants is estimated to less than 0.3 Hz.

Titrations

Titrations were carried out directly in the NMR tube. The *racemic* acids were used as 0.5 mol dm^{-3} solutions in D_2O. Owing to lower solubility the concentrations of *meso* acids were 0.25 mol dm^{-3}. Self-dissociation at these concentrations can be calculated from the pK_1 values[1] and is at most 3% (for **2m**). Different degrees of titration were realised by adding in succession appropriate amounts of 1 mol dm^{-3} NaOD solution in D_2O with a syringe.

Acknowledgements

The author wishes to thank Professor G. Großmann (Dresden University of Technology) and Dr V. Steinert for many helpful discussions.

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Paper 5/00833F
Received 13*th February* 1995
Accepted 11*th May* 1995