Kinetics of ionisation of carbon acids in non-aqueous media: detritiation of [2-$^3H_1$]diethyl malonate by heterocyclic bases[1]

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This paper is dedicated to Professor Arthur N. Bourns

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To investigate proton transfer processes in non-aqueous media, two procedures have been developed of general applicability for the measurement of detritiation rates of carbon acids. One method is a variation of an existing solvent extraction procedure but with inclusion of a trace of trifluoroacetic acid, while the other involves the simple modification of a gas chromatograph so as to function as a radio-gas chromatograph. They have been established by studying the detritiation of [2-$^3H_1$]diethyl malonate in six different solvents (dimethylformamide, dimethyl sulfoxide, sulfolane, hexamethylphosphortriamide, tetrahydrofuran, ethanol) as catalyzed by various heterocyclic bases (substituted pyridines, imidazoles, benzimidazoles, pyrrole, pyrazole, purine, adenosine). The results are discussed in terms of solvation effects and catalyst structure. An approximate Brønsted correlation is found to exist between log k_B^T for detritiation determined in DMSO and the pK_a of the conjugate base measured in water at 25°C.

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Dans le but d'étudier les processus de transferts protoniques dans des milieux non-aqueux, on a développer deux méthodes d'application générale pour mesurer les vitesses de détritiation d'acides carboniques. Une des méthodes est une variation d'une procédure existante d'extraction par les solvants impliquant l'inclusion d'une trace d'acide trifluoroacétique; par ailleurs, l'autre implique une modification simple d'un chromatographe en phase gazeuse de façon à le faire fonctionner comme une chromatographe en phase gazeuse radio. On a établi la validité de ces méthodes en étudiant la réaction de détritiation du malonate de diéthyle [$^3H_1$-2] qui a été effectuée dans six solvants différents (diméthylformamide, diméthylsulfoxyde, sulfolane, hexaméthylphosphoretriamide, tétrahydrofuranne et éthanol) et catalysée par diverses bases hétérocycliques (pyridines substituées, imidazoles, benzimidazoles, pyrrole, pyrazole, purine, adénosine). On discute des résultats en fonction d'effets de solvatation et de structure du catalyseur. On a trouvé qu'il existe un corrélation approximative de Brønsted entre le log k_B^T pour la réaction de détritiation effectuée dans le DMSO et le pK_a de la base conjugée, mesuré dans l'eau, à 25°C.
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Proton transfer from one atom to another is a fundamental process in chemistry, present in the elementary steps of many reactions (1). In acid, base and enzyme catalyzed reactions, proton transfer between catalyst and substrate is often a key step in the mechanism (2, 3). In many organic reactions in particular, proton transfer from carbon plays a central role and has led to an appreciation of the factors governing the kinetic and thermodynamic properties of carbon acids (4, 5). However, despite an awareness of the importance of the solvent in proton transfer reactions (6) this is a relatively unexplored area. This may be due in part to the fact that the most widely used method of measuring the rates of such reactions, namely halogenation, cannot be readily adapted to non-aqueous conditions.

Hydrogen isotope exchange is particularly suited for studying proton transfer from carbon acids under a variety of conditions, for example as catalyzed by acids, bases and metal ions (7–12), but in the past such investigations have also been largely limited to aqueous media. In this paper we report on the development of two procedures which have general applicability for measurement of detritiation rates of carbon acids in non-aqueous media.

The first method is a variation of an existing extraction procedure with the difference that the exchange is carried out in the presence of a trace amount (0.01% v/v) of trifluoroacetic acid. This addend serves as a source of exchangeable protium in the system (*vide infra*), but does not alter the properties of the solvent to a measurable degree.

The second procedure takes advantage of the fact that commercial gas chromatographs usually have two flame ionisation detectors, a variable post-column splitter and dual pen recorder, and by attaching a second electrometer capable of measuring currents down to 10^{-12}–10^{-14} A, it is possible to use the second ionisation chamber as a radiation detector (13). Such a simple modification converts the instrument to a radio-gas chromatograph with good sample throughput, ideal for measuring the decrease in the tritium radioactivity of a labelled carbon acid. This method is particularly useful when no satisfactory solvent extraction procedure is available.

Both procedures have been established through investigating the detritiation of [2-$^3H_1$]diethyl malonate, which was previously studied only in aqueous media. In the present study, six different solvents have been employed, namely dimethylformamide (DMF), dimethyl sulfoxide (DMSO), sulfolane, hexamethylphosphortriamide (HMPT), tetrahydrofuran (THF), and ethanol. The catalysts used are heterocyclic nitrogen bases, namely substituted pyridines, imidazoles, benzimidazoles, pyrrole, pyrazole, purines, and adenosine. Because a solvent extraction procedure could be established for all the different solvent systems, the large majority of the experimental results were obtained using the first procedure.

Experimental

Materials

Stringent precautions were employed to ensure high solvent purity and the elimination of water from the experimental systems. Sulfolane

[1]Hydrogen exchange studies, Part 16: for Part 15, see ref. 12.

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was purified by heating the solvent (2 L) to 210°C in the presence of polyethylene sulfone (20 g) and anhydrous potassium fluoride (10 g); the mixture was then stirred for 24 h under a constant stream of dry nitrogen so as to remove any volatile impurities prior to distillation under reduced pressure. Dimethyl sulfoxide was partially frozen, the remaining liquid decanted off, and the solvent distilled under reduced pressure before storing over Linde type 4A molecular sieve. Dimethylformamide was stored in a similar manner prior to distillation under reduced pressure. Tetrahydrofuran was refluxed over lithium aluminum hydride prior to distillation and storing over calcium hydride. Ethanol was refluxed in the presence of magnesium turnings and iodine for 3 h before the fraction that distilled at 78.4°C/760 mm was collected.

All the organic bases used, with the exception of 6-aminobenzimidazole, were obtained commercially and their purity checked prior to use; this compound was prepared by the catalytic hydrogenation of 6-nitrobenzimidazole using a 5% Pd/C catalyst in methanol.

Tritiation procedure

Diethyl malonate was tritiated by adding freshly distilled material (1 mL) to a small ampoule containing sodium carbonate (0.3 g) and dioxane (0.5 mL); after adding tritiated water (5 μL, 50 Ci mL^{-1}) the ampoule was sealed and left at room temperature for 72 h. The tritiated substrate was isolated by extraction into chloroform (10 mL), which was washed with water (10 mL) and dried over anhydrous Na_2SO_4. After removing the solvent by carefully passing N_2, the tritiated product was taken up in a small volume (100 μL) of $CDCl_3$, a trace of internal standard (TMS) was added and the sample subjected to both ^1H and ^3H nmr analysis.

Kinetic measurements

Method 1

To a known volume (usually 50 mL) of the base solution thermostatted in a constant temperature bath at 50.0°C was added 5 μL of trifluoroacetic acid followed by 10 μL of a stock solution of the labelled diethyl malonate. At given time intervals, aliquots (2 mL) of the solution were withdrawn and injected into tubes containing 10 mL of 0.1 *M* hydrochloric acid and 10 mL of liquid scintillator (3.4 gL^{-1} of 2,5-diphenyl oxazole in toluene). After shaking, most of the toluene layer was extracted and dried over anhydrous Na_2SO_4 before counting 5 mL samples on a Beckman LS 100 scintillation counter. Normally the reaction was followed to more than 90% completion. The rate constants k^T obtained from the plots of $\log_{10}$ (radioactivity) against time (slope = $-2.303k^T$) agreed to within ± 2–3%; dividing k^T by the base concentration (usually in the range 10^{-1}–10^{-3} *M*) gave the second-order rate constant (k_B^T).

In the case of hexamethylphosphortriamide at 50°C there was evidence of catalysis by the solvent. For this reason the results reported for this solvent are limited to 25.0°C.

Method 2

For the radio-gas chromatography procedure (13) the main differences were that the radioactivity of the diethyl malonate was some 10–100 times higher and that the volume of reaction mixture was some ten times smaller than in the solvent extraction method. As mentioned previously the advantage of the method is that it is no longer dependent on our ability of achieving a satisfactory extraction procedure; it is only required to quench the reaction (using 0.1 *M* HCl), inject a sample into the radio-gas chromatograph, and integrate the diethyl malonate radioactivity signal. In the present investigation a 10% OV17 on chromosorb 80–100 mesh column at an oven temperature of 145°C was employed.

In both methods 1 and 2 the base concentration was varied at least ten-fold. In the case of imidazole catalysis where both methods were used the k_B^T values were 0.0224 ± 0.0005 for the solvent extraction procedure and 0.0220 ± 0.001 for the radio-gas chromatographic method.

Results and discussion

Investigation of proton transfer processes in non-aqueous media, while offering insight on solvation effects, also brings into focus the nature of the base to be used for proton abstraction. There is clearly less emphasis on the use of the lyate ion of the solvent compared with hydroxylic media, although work by Bordwell (14, 15), Ritchie (16), and Streitwieser (17, 18) in particular, has shown that the use of the methylsulfinyl anion and the cyclohexylamide anion in dimethyl sulfoxide and cyclohexylamine, respectively, has given forth a wealth of information on kinetic and thermodynamic acidities of carbon acids. However, it appears much less probable that comparable investigations would be undertaken in solvents such as DMF, HMPT, or THF with their lyate ion counterparts. One is hence led to investigate the efficacy of all types of bases when studying proton transfer in non-aqueous media. The goals of such studies will be to determine kinetic and thermodynamic acidities of carbon acids in different media, and to obtain information on inherent properties of the bases, unmasked by solvent effects, thus to improve the understanding of solvent effects on proton transfer processes.

In this first study, we have chosen to investigate the catalytic properties of a range of heterocyclic nitrogen bases, in various solvents, for the abstraction of the acidic proton from diethyl malonate.

The heterocyclic bases were chosen partly as a result of a parallel interest in the kinetic acidities of the C-2(H) proton in compounds such as the imidazoles and benzimidazoles (12, 19) and the equivalent C-8(H) position in purines, and partly because of the opportunity they afforded of investigating structural factors not frequently made available in this kind of study. Thus imidazole, benzimidazole, purine, and pyrrole are all examples of π-excessive N-heteroatoms where the nitrogen is in an electron releasing environment (=CH—NH—CH=). In pyrrole, however, the nitrogen atom contributes its lone pair of electrons to the π-system, completing an aromatic sextet, and

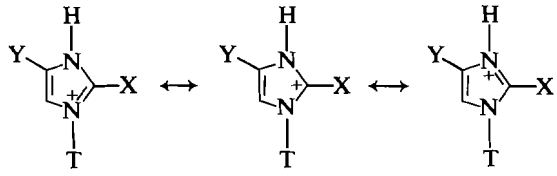
TABLE 1. Rates of detritiation of [2-$^3H_1$]diethyl malonate in dimethyl sulfoxide at 50°C by heterocyclic bases

Base	pK_a (H_2O, 25°C)	Ref.	$10^4k_B^T$ (M^{-1} s^{-1})
1. Imidazole	7.18	20	224
2. 1-Me imidazole			119
3. 2-Me imidazole	8.13	21	1680
4. 1,2-diMe imidazole			1140
5. 2-Et, 4-Me imidazole	8.57[a]	21	4390
6. 1-Benzyl, 2-Me imidazole			495
7. 2,4,5-Triphenyl imidazole			0.36
8. 4-NO_2 imidazole			No detritiation
9. Benzimidazole	5.53	22	22.3
10. 2-Me benzimidazole			130
11. 2-Phenyl benzimidazole			3.7
12. 2-NH_2 benzimidazole			1470
13. 6-NH_2 benzimidazole			158
14. 6-NO_2 benzimidazole			0.37
15. Pyridine	5.47	23	2.14
16. 2-Me pyridine	6.07	24	6.80
17. 3-Me pyridine	5.80	24	3.54
18. 4-Me pyridine	6.10	24	7.48
19. 4-Benzyl pyridine			3.74
20. 2-Acetyl pyridine			No detritiation
21. Adenine	4.20	25	13.8
22. Adenosine	3.50	25	2.88
23. Pyrazole	2.57	26	0.037
24. Pyrrole			No detritiation
25. Purine	2.60	27	No detritiation

[a]Refers to the structurally similar 2,4-dimethylimidazole.

thus rendering the substance only very weakly basic. The pyridines, on the other hand, are examples of π-deficient heterocycles; here nitrogen has dual character, attracting π-electron density from the ring while making available an unshared electron pair towards a proton.

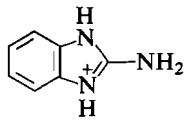
The results on the detritiation of [2-$^3H_1$]diethyl malonate in DMSO are given in Table 1. Analysis of these results reveals the following trend in kinetic basicities: imidazole > benzimidazole > pyridine > pyrazole > pyrrole, purine. However, within each group there are considerable rate variations. Thus in imidazole itself methyl substitution can lead to both rate retardation and rate acceleration, an observation that can be accounted for in the following way. In dimethyl sulfoxide the protonated base formed will be highly solvated and the insertion of electron donating groups X and Y at C-2 and C-4 will stabilise the charge to some degree via the resonance contributions **1***b* and **1***c*:



1*a* **1***b* **1***c*

This would lower the transition state energy for proton abstraction, leading to an increase in reaction rate. On the other hand, bases containing an —N—H group will be highly coordinated to the sulfoxide oxygen, so that N-alkylation will remove this mode of stabilisation, leading to a rate reduction even though the substituent may be electron donating. This would explain why the rate for 1-methylimidazole is lower than that for the parent compound, opposite to what is expected on the basis of pK_a data in water. It would also explain the less than expected rate enhancement for 1,2-dimethylimidazole as well as for 1-benzyl-2-methylimidazole compared with 2-methylimidazole. Steric hindrance in approach of the base (F-strain) is probably the main factor causing the slow rate for 2,4,5-triphenylimidazole.

Introduction of an amino group in both benzimidazole and purine has an accelerating effect, possibly because the amino group is itself able to act as the base in proton abstraction. An alternative possibility[2] is that of a guanidine-like structure whose high basicity is the result of a stabilized conjugate acid, i.e.,



2

No detritiation of the substrate was observed with the π-excessive bases pyrrole and purine, and to this list can be added indole, thymidine, and uridine.

It is interesting that an approximate Brønsted correlation exists between log k_B^T and pK_a (H_2O, 25°C) for the twelve bases for which pK_a data are available, despite the fact that k_B^T refers to DMSO and K_a to the aqueous state. The graph (Fig. 1) covers some 5 pK_a units and only the points for adenine and adenosine deviate significantly. This suggests that any solvation

[2]The authors thank a referee for this suggestion.

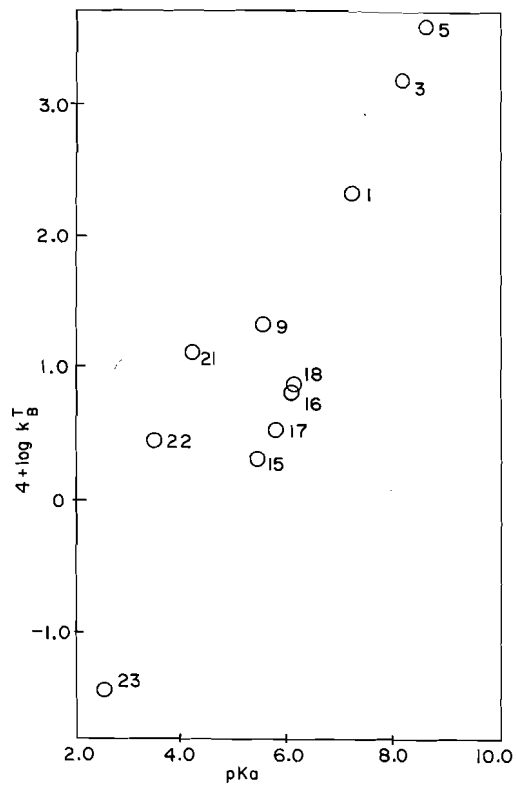


FIG. 1. Brønsted plot for detritiation of [2-$^3H_1$]diethyl malonate by heterocyclic bases: k_B^T values in DMSO at 50°C, K_a values in H_2O at 25°C (Table 1).

type arguments will hold for both media. More importantly, the observation of a Brønsted correlation is in accordance with the proposal that proton transfer is the rate-determining step.

Results on the variation of solvent in detritiation of diethyl malonate using the four imidazole-type bases are given in Table 2. It is seen that the rates vary within relatively narrow limits on solvent change, though the highest rate is generally observed in DMSO. Also noticeable is the regular trend observed for each catalyst, with the possible exception of 1-methylimidazole in tetrahydrofuran, the solvent with the lowest dielectric constant. In this case the possibility of some kind of association causing the unusually low rate cannot be ruled out.

The detritiation of diethyl malonate by the heterocyclic bases represents a reaction between two neutral molecules and hence differential effects of solvents would be expected to be at a minimum, as is borne out in the present investigation. Nevertheless it is somewhat surprising that the vastly different properties of some of the solvents, such as dimethyl sulfoxide, tetrahydrofuran, and ethanol, is not reflected in a wider range of rates.

The reaction mechanism followed in this hydrogen isotope exchange must differ from what operates in hydroxylic media leading to regeneration of base and unlabelled carbon acid, since solvents such as THF contain no exchangeable hydrogen. Radio-gas chromatographic analysis of a reaction mixture showed that the only radioactive peak present not arising from the diethyl malonate originated from the trifluoroacetic acid. Consequently we favour the following scheme in which the trifluoroacetic acid acts as the proton donor towards the carbanion formed on triton abstraction, generating unlabelled carbon acid and the neutral base via the equilibria in reactions [2] and [3]:

TABLE 2. Rate data for detritiation of [2-$^3H_1$]diethyl malonate with imidazole-type catalysts in various solvents at 50.0°C[a]

Base	Solvent					
	DMSO	DMF	Sulfolane	HMPT[b]	THF	EtOH
Imidazole	(224)[a]	(132)[a]	(89.8)[a]	(48.1)[a]	(108)[a]	(145)[a]
	1.00	1.00	1.00	1.00	1.00	1.00
1-Me imidazole	0.53	0.40	0.18	0.20	.057	0.46
2-Me imidazole	7.5	6.68	7.10	8.11	7.43	4.50
2-Et, 4-Me imidazole	19.6	15.0	13.4	15.8	8.44	8.14

[a]The data given in parentheses are the actual $10^4 k_B^T$ values (M^{-1} s^{-1}) for imidazole catalysis at 50°C (25°C for HMPT). The remaining data are the relative rate constants with respect to imidazole as the reference standard.
[b]At 25.0°C, the extrapolated rate constant for imidazole catalysis at 50°C being 164×10^{-4} M^{-1} s^{-1}.

[1] $RT + B \rightarrow R^- + BT^+$

[2] $R^- + CF_3COOH \rightleftharpoons RH + CF_3COO^-$

[3] $CF_3COO^- + BT^+ \rightleftharpoons CF_3COOT + B$

It is emphasized that the addition of only a trace quantity of trifluoroacetic acid (0.01% v/v) is required, since the substrate is present in extremely small concentration and the properties of the solvent medium are thereby unchanged. The kinetic data thus provide a valid measure of the solvent effect on the proton transfer (10, 13).

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